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2010 SSAT PLENARY PRESENTATION

Perioperative Anti-Tumor Necrosis Factor Therapy Does Not Increase the Rate of Early Postoperative Complications in Crohn's Disease

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Abstract
Background There have been numerous studies with conflicting results regarding the use of anti-tumor necrosis factor (TNF) therapy and its relationship to postoperative outcome in Crohn disease. The aim of our study was to examine the rate of postoperative morbidity in patients receiving anti TNF therapy in the perioperative period.
Methods All patients undergoing surgery for Crohn disease from 2005 till 2008 were abstracted from a prospective database. Patients undergoing surgery which included a suture or staple line at risk for leaking were selected for the study. A retrospective review of medical records was performed. The study group comprised patients treated with perioperative anti TNF therapy (defined as treatment within 8 weeks preoperatively or up to 30 days postoperatively). The remainder of the patients did not receive perioperative anti TNF therapy. Patient characteristics, disease severity, medication use, operative intervention and 30-day complication were compared between the two groups.
Results Three hundred and seventy patients were selected for analysis in this study, of which 119 received perioperative anti TNF therapy and 251 did not. The groups were similar in baseline characteristics, perioperative risk factors and procedures. The group who received perioperative anti TNF therapy had a more severe disease overall as measured by the American College of Gastroenterology (ACG) categories of disease (50% severe fulminant disease in the perioperative anti-TNF therapy group versus 18% in the group that did not receive perioperative anti-TNF therapy, $p < 0.001$). There was no significant association of perioperative anti TNF therapy and any postoperative complications (27.9% in anti-TNF group versus 30.1% in no anti-TNF group, $p = 0.63$) nor intra-abdominal infectious complications (5.0% in anti-TNF group versus 7.2% in no anti-TNF group, $p = 0.44$). Univariate analysis showed that the only factors associated with an increase in postoperative intra-abdominal infections were age and penetrating disease.
Conclusions The use of anti-TNF therapy in the perioperative period is safe and is not associated with an increase in overall or infectious complications in Crohn disease patients undergoing surgery.

Keywords Crohn's disease · Anti-tumor necrosis factor · Postoperative complications · Infliximab

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Introduction

Despite advances in medical therapy for Crohn's disease, surgical intervention is required in up to two thirds of patients.[1,2] The most common indications for surgical resection are medically refractory disease or medication

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side effects.[1–8] Surgery is also indicated in the treatment of complications of the disease, such as hemorrhage, perforation, obstruction, and fistula formation. Therapy, medical or surgical, rarely results in cure from the disease and the primary objective is to restore the patient to health and well-being.

Medical therapy in Crohn's disease has undergone dramatic changes in the past decade.[1,3–8] The use of immunomodulators and anti-tumor necrosis factor (TNF) alpha therapy has become increasingly prevalent in this population. Past experience with perioperative steroids and the effect that immunosuppression has on postoperative outcomes have lead to the evaluation of the use of immunomodulators and biologic agents in the perioperative period. There has been recent interest in the effect of biologics on postoperative outcomes.[9–15] A number of studies have been published with conflicting results. A study form our institution, published in 2004 by Colombel et al. showed that early complications after elective abdominal surgery was not associated with immunosuppressive therapy.[9] Contrary to this, Appau et al. demonstrated that anastomotic complications were increased by the use of biologics in patient undergoing terminal ileal resection, and that diversion should be considered.[10]

Our aim was to report our experience since 2005 with the use of biologics in the perioperative period, and to study its effect on postoperative outcomes.

Material and Methods

A retrospective analysis was performed on all patients undergoing surgery for Crohn's disease from 2005 through 2009. Patients were identified from a prospective registry of patients undergoing surgery at the Division of Colon and Rectal Surgery, Mayo Clinic, Rochester. The study was approved by the Institutional Review Board of the Mayo Foundation.

Variables collected included demographic data, extent and severity of disease, and medications used in the perioperative period. The disease severity was stratified based on ACG categories of disease.[1] We also categorized patients according to whether or not they had penetrating complication of the disease (fistulae or abscess) at the time of operation. Medication specific variables included dose and duration of treatment with immunomodulators and steroids. In the case of biologic agents, the specific agent, dose, timing, and duration of therapy was documented.

Based on the perioperative use of anti-TNF therapy, patients were stratified into two groups: a group that received perioperative therapy with an anti-TNF biologic agent (defined as either treatment within 8 weeks preoperatively or within 4 weeks postoperatively) and a group that did not receive perioperative anti-TNF therapy. An 8-week wash-out period was selected based on the pharmacokinetics of these agents.[14,16–18] Using infliximab as an example; the half life is 8–10 days and most patients have detectable concentrations at 8 weeks, but not at 12 weeks.[6,14,16] The other anti-TNF biologics adalimumab and certolizumab pegol have similar kinetics.[17,18]

All operations were performed at a single institution. Details of the operations, including type of operation and mode (open, hand-assisted, laparoscopic) were analyzed. Since our aim was to study anastomotic complications, we included only operations resulting in some form of suture or staple line at risk. For example, patients undergoing a total proctocolectomy with end ileostomy were excluded, since there was no suture/staple line at risk. We also excluded patient undergoing emergency procedures and patients who had a proximal diversion. Postoperative complications were divided into infectious and non-infectious complications. We studied all postoperative complications, and segregated them into a category that includes infectious complications relating to the anastomosis and another category which includes overall complications. We did study infectious complications not relating to the anastomosis, such as wound infection,

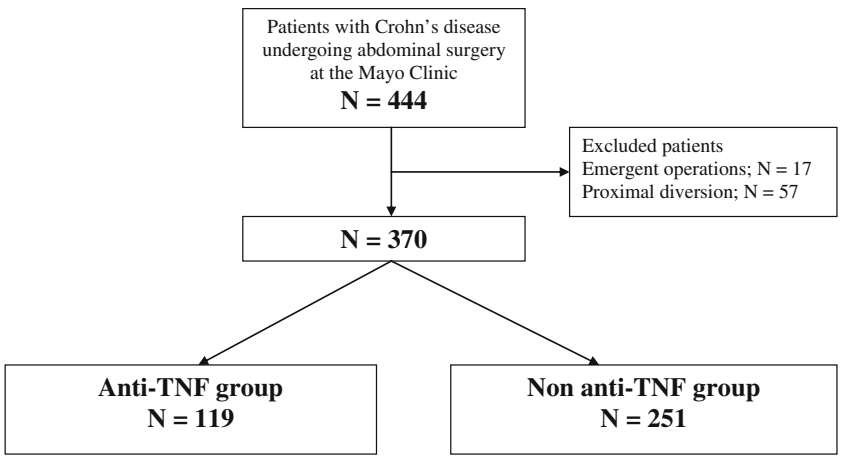

Fig. 1 Cohort identification

Table 1 Details of anti-TNF therapy in the perioperative period

	Number
Infliximab	69
5 mg/kg every 8 weeks	37
7.5 mg/kg every 8 weeks	5
10 mg/kg every 8 weeks	13
Unknown dose	14
Adalimumab, 40 mg every 2 weeks	47
Certolizumab pegol, 400 mg every 4 weeks	3

pneumonia, urosepsis; however, these were included with the overall complications and not as a separate group.

Statistical Analysis

Descriptive statistics are reported as median and range or as number and percentage as appropriate. Univariate assessment of one or more complications (any complication and separately intra-abdominal abscess/anastomotic leak) within 30 days of the procedure were made using logistic regression, results reported as an odds ratio and 95% confidence interval.

The alpha-level was set at 0.05 for statistical significance.

Results

Between January 2005 and February 2009, 444 patients underwent surgery for Crohn's disease. Of those, 370 patients fulfilled inclusion criteria to be included in the study (Fig. 1). The study group, which included patient receiving anti-TNF within 8 weeks preoperatively or 30 days postoperatively (n=119) were compared with those who received no anti-TNF alpha therapy (n=251). The details of anti-TNF therapy for the 119 patients are shown in Table 1.

The demographic characteristics for the two patient groups are shown in Table. 2. There were no significant differences between the two groups in baseline patient-related demographic variables such as age, gender, ASA status, BMI, etc. Disease-specific data is shown in Table 3. A greater proportion of patients in the perioperative anti-TNF group had severe disease according to the ACG criteria. In contrast, a greater proportion of patients who did not receive perioperative treatment with an anti-TNF agent were receiving steroid therapy. Other disease-specific risk factors, such as the presence of penetrating disease and the use of other immunosuppressants were similar in the two groups.

All operations were performed electively, and as specified in the inclusion criteria, none of the patients had a diversion performed. Operations were performed either laparoscopically, hand-assisted, or open. The distribution amongst the groups is shown in Table 4. Conversion rates from hand-assisted or laparoscopic cases to open cases were similar in the two groups.

The overall complications rate for the entire study cohort was 28.6%. The overall complication rate was 30.3% in the anti-TNF therapy group versus 27.9% in the no anti-TNF therapy group (P=0.63) Univariate analysis showed that the rate of overall complications was increased with age and higher American Society of Anesthesiology class. This analysis is shown in Table 5. Figure 2 shows the complications observed in each group.

The rate of intra-abdominal abscess or anastomotic leaks for the entire cohort was 2.4%. There was no statistically significant difference in intra-abdominal infectious complications between the two groups (1.99% in the perioperative anti-TNF therapy group versus 3.36% in no perioperative

Table 2 Baseline characteristics

	Anti-TNF group N=119	Non-anti-TNF group N=251	Total N=370	P value
Gender (n (%))				0.68
Male	52 (44)	104 (41)	156 (42)	
Female	67 (56)	147 (59)	214 (58)	
Mean age in years (range)	38.2 (17–66)	43.3 (17–77)	41.7 (17–77)	0.001
ASA (n (%))				0.99
1	7 (6)	14 (6)	21 (6)	
2	97 (82)	205 (82)	302 (82)	
3	15 (13)	32 (13)	47 (13)	
BMI (n (%))				0.93
<18	5 (4)	13 (5)	18 (5)	
18–24	65 (55)	126 (50)	191 (52)	
25–29	34 (29)	75 (30)	109 (29)	
30–34	9 (8)	24 (10)	33 (9)	
>OR=35	6 (5)	13 (5)	19 (5)	

ASA American Society of Anesthesiologists class,
BMI Body mass index

Table 3 Disease-specific characteristics

	Anti-TNF group *N*=119	Non-anti-TNF group *N*=251	Total *N*=370	*P* value
Duration of Crohn's disease in years, median (range)	11.9 (0–40)	11.8 (0–46)	11.9 (0–46)	0.93
Location of disease (*n* (%))				0.02
Small bowel	49 (41)	143 (57)	192 (52)	
Colon	19 (16)	29 (12)	48 (13)	
Small bowel and colon	50 (42)	75 (30)	125 (34)	
Other	1 (1)	4 (2)	5 (1)	
ACG severity of disease (*n* (%))				<0.01
Remission	21 (18)	33 (13)	54 (15)	
Mild–moderate	25 (21)	87 (35)	112 (30)	
Moderate–severe	10 (8)	73 (29)	83 (22)	
Severe–fulminant	60 (50)	45 (18)	105 (28)	
Steroid dependant	3 (3)	13 (5)	16 (4)	
Penetrating disease (*n* (%))				0.23
No	72 (60)	168 (67)	240 (65)	
Yes	47 (40)	83 (33)	130 (35)	
Steroid (*n* (%))				0.01
No	82 (69)	137 (55)	219 (59)	
Yes	37 (31)	114 (45)	151 (41)	
Immunosuppressant (*n* (%))				0.23
No	87 (73)	168 (67)	255 (69)	
Yes	32 (27)	83 (33)	115 (31)	

ACG American College of Gastroenterologists classification of disease severity

Table 4 Surgical procedure data

	Number (%)			*P* value
	Anti-TNF group *N*=119	Non-anti-TNF group *N*=251	Total *N*=370	
Mode				0.64
Open	70 (59)	136 (53)	206 (56)	
Hand-assisted	8 (7)	22 (9)	30 (8)	
Laparoscopy-assisted	41 (34)	93 (37)	134 (36)	
Procedure				0.34[a]
Abdominal colectomy	61 (51)	132 (68)	193	
Ileocecectomy	29	75	104	
Right hemicolectomy	14	35	49	
Transverse colectomy	1	2	3	
Left hemicolectomy	2	2	4	
Sigmoid colectomy	9	10	19	
Subtotal colectomy with ileorectostomy	6	8	14	
Small bowel resection	26 (22)	69 (27)	95	
=1	22	60	82	
>1	4	9	13	
Stricturoplasty	13 (11)	15 (6)	28	
Stoma reversal	12 (10)	25 (10)	37	
Other	7 (6)	10 (4)	17	

[a] The P value is an overall value testing the difference in regards to procedure (categorized ad colectomy, small bowel resection, stricturoplasty, stoma reversal, or other) between the anti-TNF group and the non-anti-TNF group

Table 5 Complications

	Number	Intra-abdominal abscess/anastomotic leak			Overall complications		
		N (%)	OR (95% CI)	*P* value	*N* (%)	OR (95%CI)	*P* value
Age, per 5 years	370	–	1.2(0.96-1.5)	0.12	–	1.14 (1.1–1.2)	<0.001
ASA class 1	21	0 (0)	0.0	0.33	4 (19)	1.0 (ref)	
ASA class 2	302	7 (2.32)	1.0 (ref)		78 (25.8)	1.5 (0.5–4.5)	0.49
ASA class 3	47	2 (4.26)	1.9 (0.4–9.3)	0.44	24 (51.1)	4.4 (1.3–15.2)	0.018
Non-penetrating disease	240	1 (0.42)	1.0 (ref)		71 (29.6)	1.0 (ref)	
Penetrating disease	130	8 (6.15)	15.7 (1.9–127)	0.01	35 (26.9)	0.9 (0.5–1.4)	0.59
ACG, remission	54	0 (0)	0.0	0.07	13 (24.1)	1.0 (ref)	
ACG, mild–moderate	112	4 (3.57)	1.0(ref)		33 (29.5)	1.3 (0.6–2.8)	0.47
ACG, moderate–severe	83	0 (0)	0.0	0.03	24 (28.9)	1.3 (0.6–2.8)	0.53
ACG, severe–fulminant	105	4 (3.81)	1.1 (0.3–4.4)	0.93	31 (29.5)	1.3 (0.6–2.8)	0.47
ACG, steroid-dependent	16	1 (6.25)	1.8(0.2–17)	0.61	5 (31.3)	1.4 (0.4–4.9)	0.57
No anti-TNF	251	5 (1.99)	1.0 (ref)		70 (27.9)	1.0 (ref)	
Anti-TNF	119	4 (3.36)	1.7 (0.5–6.5)	0.43	36 (30.3)	1.1 (0.7–1.8)	0.64
No steroid	219	7 (3.20)	1.0 (ref)		64 (29.2)	1.0 (ref)	
Steroid	151	2 (1.32)	0.4 (0.1–2.0)	0.27	42 (27.8)	0.9 (0.6–1.5)	0.77
No immunosuppressant	255	7 (2.75)	1.0 (ref)		77 (30.2)	1.0 (ref)	
Immunosuppressant	115	2 (1.74)	0.6 (0.1–3.1)	0.56	29 (25.2)	0.8 (0.5–1.3)	0.33
Open	203	7 (3.45)	1.0		61 (30)	1.0 (ref)	
Hand-assisted	30	1 (3.33)	1.0 (0.1–8.1)	0.97	11 (36.7)	1.4 (0.6–3.0)	0.46
Laparoscopy-assisted	134	1 (0.75)	0.2 (0.03–1.7)	0.15	33 (24.6)	0.8 (0.5–1.2)	0.28

anti-TNF therapy groups, P=0.44). A univariate analysis showed that the only factors that predicted intra-abdominal infectious complications were age and the presence of penetrating disease (Table 5). The odds ratio for having an intra-abdominal infectious complication in the penetrating disease group was 15.6 (P=0.001).

We further analyzed the subgroup of nine patients who developed an abdominal abscess or anastomotic leak. Eight out of the nine patients had penetrating disease. The procedures were equally distributed amongst the patients in a similar manner to the overall cohort with three patients receiving an ileocecal resection, three undergoing a small bowel resection, two stoma reversals, and one sigmoid colectomy. Three patients in this subset received perioperative anti-TNF therapy.

Discussion

In our study, we did not find an association between perioperative anti-TNF therapy and postoperative complications. In contrast to Appau et al., we did not limit our inclusion

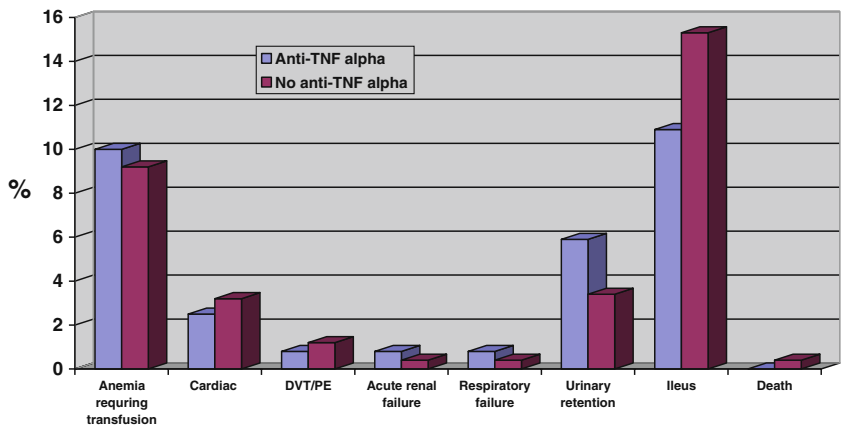

Fig. 2 Postoperative non-infectious complications

criteria to one operation (ileocecal resection), but rather included all procedures that resulted in a suture or staple line at risk of leaking. Such expanded inclusion criterion may be more representative of the real world and have the advantage of increasing the sample size and the statistical power of the study. Our study does not support the practices now utilized by some centers of delaying surgery for patients with Crohn's disease who have received anti-TNF therapy within 8–12 weeks of operation. Similarly, our data do not suggest that the early use of anti-TNF therapy in the early postoperative setting is contraindicated, and provide some additional safety data supporting that the evolving use of anti-TNF therapy to prevent postoperative recurrence.[5] In addition, our data do not support the practice of creating a defunctionalizing proximal stoma solely because the patient receives perioperative anti-TNF therapy.

The effect of perioperative anti-TNF therapy on postoperative outcomes, especially septic complications, has been a topic of increasing interest, and many publications have addressed this issue.[9–15] These studies have yielded conflicting results. We previously reported an initial early experience through 2004 at Mayo Clinic, showing no increase in early septic or overall complications among patients undergoing surgery for Crohn's disease who received perioperative therapy with infliximab.[9] However, in patients with ulcerative colitis, were we did find that perioperative anti-TNF therapy with infliximab before proctocolectomy and ileal pouch anal anastomosis was associated with an increased risk of postoperative pouch-related infectious complications.[14] Kunitake et al. recently reported no increased risk of postoperative complications in patients with either Crohn's disease or ulcerative colitis who received perioperative anti-TNF therapy with infliximab prior to undergoing surgical resection.[11]

A recent study from the Cleveland Clinic reported that perioperative anti-TNF therapy with infliximab (defined as use within 3 months of surgery) was associated with increased postoperative sepsis, abscess, and readmissions in 60 patients with Crohn's disease undergoing ileocolic resection.[10] The authors suggested that the use of a diverting stoma may protect against these complications. This study and other studies[9–12] are hampered by relative small sample sizes. In addition, they reported only on the use of the anti-TNF agent infliximab, and did not include patients who received perioperative anti-TNF therapy with other anti-TNF agents, such as adalimumab and certolizumab pegol.

Our study is the first to adjust for disease severity when evaluating postoperative complications in patients with Crohn's disease undergoing surgical resection. It is likely that patients receiving perioperative anti-TNF therapy would have more severe disease, when compared with patients who did not receive perioperative anti-TNF therapy, and failure to stratify for disease severity could have introduced an important bias into previous studies. Similarly, it is likely that patients with penetrating complications of Crohn's disease (fistula and abscess) may be at greater risk for postoperative complications. Our results demonstrate this to be the case, and in fact, penetrating Crohn's disease may be the most important factor for the development postoperative complications related to a suture or staple line.

Our study has limitations. Firstly, it is retrospective, and suffers therefore from potential selection bias. Second, although we have the largest sample size reported to date, the rate of intra-abdominal infective complications is very low (2.4%) thus introducing the possibility of a type II error. However, an advantage of this study is that we stratified for disease severity, presence of penetrating disease complications, and other potential risk factors. Most prior studies that reported an association between perioperative anti-TNF therapy and postoperative complications did not adjust for disease severity, and as a result, it is difficult to assess whether their findings were a true association with perioperative anti-TNF therapy, or whether perioperative anti-TNF therapy was simply a surrogate for disease severity.

Conclusion

In conclusion, we did not find an association between perioperative anti-TNF therapy and postoperative complications in patients with Crohn's disease undergoing surgery with an anastomosis or staple line at risk of leaking. Based on these findings, we do not recommend delaying operation or creation of a proximal diverting stoma in patients who have received anti-TNF therapy during the 8–12 weeks preceding surgery.

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Discussant

Dr. Liliana G. Bordeianou (Boston, MA): This is a very important presentation. I view it as a bucket of cold water thrown to stop an irrational brush fire set off not too long ago by a paper that showed doubling of surgical complications following exposure to infliximab in patients with Crohn's disease. As you know, that manuscript advocated diversion in all patients exposed to the drug, including those undergoing ileocecal resections. Your paper, on the other hand, shows that infliximab exposure does not alter surgical complications in a statistically significant fashion when controlling for disease severity. One of these papers is right and another is incorrect. A cumulative body of reports from other institutions is needed to get us to the truth. There is no question that in this debate negative papers are just as important as the positive ones.

I do have a few questions pertaining to your data. Can you please specify how many patients within your cohort were treated with inflximab before surgery and how many received the drug postoperatively? I am concerned that these two groups of patients may be different. The patients receiving infliximab prior to surgery are being treated for active disease. As such, they are sick, malnourished, anemic. On the other hand, the patients given infliximab after surgery are usually those who presumably don't have any evidence of postoperative complications, which are usually a contraindication to infliximab. Are you concerned that by combining these two groups together you are perhaps obscuring the effect of preoperative infliximab on outcomes? A subset analysis of these two groups may be helpful here.

My second question is in regards to the statistical analysis used in the paper. During this presentation at least, you have only shown us results obtained on univariate analysis. Have you constructed a multivariable model accounting for steroids, other immune modulators, severity of disease, etc. to pinpoint effect of infliximab in this context further?

Closing Discussant

Dr. Basil Saad Nasir: The whole reason behind including patients who had infliximab postoperatively was to increase the subset of patients that we would examine. And yes, there is one particular weakness to this paper insofar as that patients who do get complication do not get the drug. However, this also does augment the point that we are trying to make, that even if you do get the drug, there's no increase in complications.

With regards to your second question, although we started off with a large number of patients, 370 patients, the leak rate was so low, it was 2.4%. There was really only nine patients that leaked. It's really hard to do a multivariate analysis when the numbers are that low. And that is, again, another downfall for this study, which is a good thing, because the patients don't leak as much. But it makes it harder to study. So I did not have an analysis for that.

Discussant

Dr. Yun Shin Chun (Philadelphia, PA): Did the interval between the last dose of infliximab and surgery make a difference—for example, patients who received the last dose of infliximab eight weeks versus one week before surgery?

Closing Discussant

Dr. Basil Saad Nasir: We didn't perform that analysis, so I can't comment to that. We only lumped patients into whether they got it eight weeks before or within the 8-week period or not, so I don't have the answer to that.

Discussant

Dr. Yun Shin Chun (Philadelphia, PA): And most of the patients in this study underwent right-sided resections?

Dr. Basil Saad Nasir: Yes, but that also included patients who underwent left-sided resection, small bowel resection, stricturoplasties, pretty much any operation that resulted in an anastomosis.

Discussant

Dr. Yun Shin Chun (Philadelphia, PA): So at your institution, if you have a more high-risk anastomosis, are you more likely to divert for somebody on infliximab?

Closing Discussant

Dr. Basil Saad Nasir: We actually were going to lump them up into high-risk versus low-risk anastomosis, but it was difficult to make that distinction—where do you draw the line? What's a high-risk anastomosis, what's a low-risk anastomosis? And then when I actually started to examine the data, it was hard to find objective data that said this kind of anastomosis was more likely to leak versus another. So because of that, we actually did not make that distinction. We figured that if the procedures were similar between the two groups that would be sufficient.

As far as whether you are likely to get diverted or not. I think you have to look at the big picture, and the decision to divert is not based on one thing or another. At our institution, I don't think anybody bases it on just anastomosis, unless it's somebody who has an IPAA, but that is a different situation altogether and different disease process.

Discussant

Dr. Mary Otterson (Milwaukee, WI): I think this is it's an important paper, because a lot of these patients, especially those with the small bowel Crohn's disease, are dependent on these medications to maintain their health and their life expectancy. If you have a child who develops Crohn's disease and is treated with standard therapy, their life expectancy-standard therapy like steroids, which is essentially no therapy, their life expectancy is 58 years.

So if you insist that some of these patients come off their medication before you operate on them, you may end up burning bridges for these patients medically. And I think it's an important paper, and I think that it's important to distinguish between ulcerative colitis, where people are suffering and dying, and stable, well-treated Crohn's disease, so I applaud your efforts.

Closing Discussant

Dr. Basil Saad Nasir: With regards to ulcerative colitis, there are papers out there that show worse outcomes, but we specifically only looked at Crohn's disease. And we obviously agree with what you said.

Discussant

Dr. Dave Larson (Rochester, MN): My only comment, addresses the question Dr. Chun asked a question about who do we divert. Obviously, penetrating disease is the one thing that Basil has shown that may increase risk. So a high-risk anastomosis is probably in that subset. And obviously, patients that are getting Remicade or Humira postop are likely getting Remicade and Humira preop as well.

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2010 SSAT PLENARY PRESENTATION

Elective Surgery for Diverticulitis is Associated with High Risk of Intestinal Diversion and Hospital Readmission in Older Adults

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Abstract
Purpose This study seeks to compare outcomes (in-hospital mortality, colostomy rates, and 30-day readmission rates) in older adult patients undergoing emergency/urgent versus elective surgery for diverticulitis.
Methods Data were derived from the 100% Medicare Provider Analysis and Review (MEDPAR) inpatient file from 2004–2007. All patients 65 years of age and above with a primary diagnosis of diverticulitis that underwent left colon resection, colostomy, or ileostomy were included. The primary outcome variable was in-hospital mortality. Secondary outcome variables included intestinal diversion, 30-day post-discharge readmission rates, discharge destination, length of stay, and total charges. Patients were grouped in two categories for comparison: emergent/urgent (EU) versus elective surgery, as defined by admission type. Multivariate analysis was performed adjusting for age (categorized by five groups), gender, race, and medical comorbidity as measured by Charlson Index.
Results Fifty-three thousand three hundred sixteen individuals were eligible for inclusion, with 23,764 (44.6%) in the elective group. On average, EU patients were older (76.8 vs. 73.9 years of age, $p<0.001$) and less likely to be female (65.4% vs. 71.1%, $p<0.001$). EU patients had higher in-hospital mortality (8.0% vs. 1.4%, $p<0.001$), higher intestinal diversion rates (64.2% vs. 12.7%, $p<0.001$), and higher 30-day readmission rates (21.4% vs. 11.9%, $p<0.001$) and the worse outcomes persisted even after adjustment for risk factors. Unadjusted and adjusted mortality rates dramatically increased by age, although the affect of age on mortality was more pronounced in the elective group where mortality rates ranged from 0.56% in patients 65–69 years old to 6.5% in patients 85+years old. The rates of ostomy and 30-day readmission generally increased with age, with worse outcomes noted particularly in the elective group.
Conclusions As expected, older adults undergoing emergent/urgent surgical treatment for diverticulitis have significantly increased risks of poor outcomes compared with elective patients. While advancing age is associated with a substantial increase in mortality, intestinal diversion and 30-day readmission after surgery for diverticulitis, this affect is especially evident among patients undergoing elective colectomy. Our data suggest that given the considerable risk of prophylactic colon resection in elderly patients with sigmoid diverticulitis, a reappraisal of the proper role of elective colectomy in this population may be warranted.

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Keywords Diverticular disease · Sigmoid diverticulitis · Elderly · Surgical outcomes · Prophylactic colectomy

Introduction

Diverticular disease is a common medical condition which accounts for over 300,000 hospitalizations yearly in the USA[1] and incurs a tremendous cost to the health care system. Half of all Americans older than 60 years have diverticulosis of the colon, and almost 60% of those aged 80 years and older are affected. It is estimated that up to 25% of these patients will develop signs and symptoms of acute diverticulitis.[2] The decision to proceed with emergency surgical intervention in patients who present in extremis with acute diverticulitis is fairly straightforward. However, there is controversy regarding indications for performing elective colectomy in patients who were managed non-operatively during an acute diverticulitis episode. Several large studies have been published recently which seem to favor observation versus operation.[3–6] However, there is little to guide the care of older adults, the population most likely to have this problem.

Diverticulitis is a multifaceted clinical problem for which there is surprisingly little evidence to guide treatment. There are no prospective studies or registries such as in cancer (SEER) or transplant (UNOS) to follow the natural history of this disease, which frequently has an indolent course with low rates of recurrences over extended periods of time.[7–9] Although the more recent large studies have attempted to remedy this, they have limitations. In particular, no outpatient information was collected despite the fact that much of diverticulitis is treated in an outpatient setting. In addition, diverticulitis can present with varying levels of severity and the management is highly dependent on physician judgment. It is likely that the older patients with diverticulitis may be regarded as too high risk to undergo surgery, and are not being managed according to the published practice parameters. As such, there is controversy about the optimal way to manage elderly patients with diverticular disease.

The current practice guidelines for treatment of sigmoid diverticulitis, devised by the Standards Committee of The American Society of Colon and Rectal Surgeons, have recently been revised. The guidelines state that the decision to offer elective surgery after acute diverticulitis should be made on a case-by-case basis.[2] The previous recommendations by this group, based largely on data published one or more decades ago, included prophylactic colectomy after one or two episodes of uncomplicated diverticulitis and after one episode of complicated diverticulitis.[10] There is general consensus that younger patients (age <50 years) are more likely to have recurrent episodes, and ultimately to need emergency surgery. However, there are no specific recommendations for managing older and very old patients with diverticulitis. The goal of this study is to examine the differences in outcomes for emergency and elective surgery in elderly patients with diverticulitis in order to clarify the role of prophylactic colectomy in this group of patients.

Methods

We used data from the 100% Medicare Provider Analysis and Review (MEDPAR) inpatient files which contains records for all claims for inpatient services provided to Medicare beneficiaries For this analysis, we examined inpatient claims from January 1, 2004 through December 31, 2007 Because patients covered by Medicare are assigned unique identifying numbers, we were able to link their records across time to track readmissions.

Our analytic cohort was defined as follows: beneficiaries were included if they were 65 years of age and older and had a primary admission diagnosis of diverticulitis defined as International Classification of Diseases 9 (ICD-9) code 562.11 (diverticulitis without hemorrhage) or 562.13 (diverticulitis with hemorrhage), and they had left colon resection (ICD-9 procedure codes: 45.71, 45.75, 45.76, 45.79, 45.8, 48.62, 48.63), colostomy (ICD-9 procedure codes: 46.03, 46.1x, 48.62), or ileostomy (46.01, 46.2x). Individuals with a concurrent diagnosis of colorectal cancer identified by ICD-9 diagnosis codes 153.2, 153.3, 154.0, 154.1, 154.2, 154.3, or 154.8 were excluded. We compared outcomes for individuals having emergent/urgent (emergent) surgery relative to those having elective (elective) surgery. Individuals were categorized based on the admission-type field associated with the hospitalization for the surgery.

The primary outcome was in-hospital mortality. Secondary outcomes were intestinal diversion (colostomy or diverting ileostomy) procedure (ICD-9 procedure codes 46.01, 46.03, 46.10, 46.11, 46.13, 46.14, 46.20, 46.21, 46.22, 46.23, 46.24, or 48.62), readmission to an acute care hospital within 30-days of hospital discharge, discharge destination from index admission, length of stay and total charges. For this study, readmission excluded admissions to rehabilitation hospitals as well as the admissions associated with discharge from the index hospital directly to a short-term general hospital, a federal hospital, another type of institution for inpatient care or a long-term care hospital. Independent variables included type of admission: emergent vs. elective patient, gender, race, burden of comorbid disease, as measured by the Charlson Index[11] and age categorized into five groups, 65 to 69, 70 to 74, 75 to 79, 80 to 84, and 85+years old.

We examined characteristics of individuals in the elective and emergency surgery groups using Student *t*

tests and Wilcoxon rank-sum tests, for continuous variables, and chi square tests for dichotomous variables. The odds for in-hospital death in the two surgical groups of interest was examined using multivariable logistic regression adjusting for age (categorized in five groups), gender, race, and medical comorbidity. All analyses were conducted using Stata, version 8.0 (Stata Corp, College Station, Texas).

Results

We identified 53,676 patients meeting eligibility criteria. Of these, 109 were excluded due to missing data on admission type and 46 were excluded due to missing data on race. Also, 204 individuals with a concurrent diagnosis of colorectal cancer were excluded. The final analytic cohort included the remaining 53,316 individuals. Among these, 29,552 (55.4%) had emergent surgery and 23,764 (44.6%) had elective surgery. Patients treated with emergent surgery were older (76.8 vs. 73.9 years, $p<0.001$) and less likely to be female (68.7% vs. 71.7%, $p<0.001$) than those who had elective surgery. Emergently treated patients had higher Charlson scores than electively treated patients (mean score 1.02 vs. 0.69, $p<0.001$), suggesting a greater burden of comorbid medical illness. (Table 1)

Compared with electively treated patients, those emergently treated had higher rates of in-hospital mortality (8.0% vs. 1.4%, $p<0.001$). They also had a higher ostomy rate (64.2% vs. 12.7%, $p<0.001$) than patients undergoing elective surgery. Patients treated emergently were readmitted within 30 days to inpatient settings at a higher rate than patients undergoing elective surgery (21.4% vs. 11.9%, $p<0.001$). On average, emergently treated patients were hospitalized longer (14.5 vs. 8 days, $p<0.001$) and incurred higher hospital charges ($86,909 vs. $43,904, $p<0.001$) (Table 2).

The lowest mortality rates were in the youngest, electively treated individuals who had in-hospital morality rates less than 1%. In contrast, emergently treated individuals over the age of 85 years had an in-hospital morality rate of 15%. Mortality dramatically increased with advancing age in both the emergency and the elective groups, although the affect of age on mortality was more pronounced in the elective group where mortality rates ranged from 0.56% in the youngest age group to 6.5% in the oldest (Fig. 1). Calculation of the predicted mortality rates by age group, adjusted for gender, race, and comorbidity did not differ significantly from the unadjusted rates.

An interaction between age and admission type was observed wherein the odds of in-hospital mortality in the two admission type groups converged with advancing age. Emergently treated individuals patients aged 85 years and older had nearly five times the odds of in-hospital mortality as emergent/urgent patients aged 65 to 69 (OR 4.8, 95% CI 4.1–5.6). Among patients undergoing elective procedures the difference in the odds of mortality was even greater: electively treated patients aged 85 years and older had 12 times greater odds of in-hospital death compared with electively treated patients aged 65 to 69 years (OR 12.4, 95% CI 8.4–18.4).

Although the rates of ostomy and 30-day readmission generally increased with age, the differences across age groups were not as dramatic as observed for mortality. Once again, with advancing age, there were worse outcomes, particularly in the elective group (Figs. 2 and 3). The unadjusted rates of intestinal diversion in the elective group ranged from less than 10% in the youngest age group to almost 30% in the oldest.

Among all electively treated patients, 85.5% were discharged to home without or without contracted care services and 11.4% to skilled nursing or other inpatient facilities. Among patients treated on an emergent basis, 50% were discharged home without or without contracted care services and 36% to skilled nursing or other inpatient facilities. As with the other outcomes, older age was associated with reduced rates of discharge to home. In the electively treated individuals aged 65–69, 94.7% of patients were discharged to home and 4.1% to skilled nursing or other inpatient facilities compared with 47.2% and 41.7%, respectively, in the over 85 years group (Fig. 4).

In multivariable logistic regression models adjusting for risk factors including age, gender, race and Charlson score, patients treated emergently had significantly greater odds ratio for mortality (OR=4.28, 95% CI 3.86–4.75), intestinal diversion (OR=11.26, 95% CI 10.76–11.78) and readmission to inpatient care within 30 days of discharge (OR 1.84, 95% CI 1.75–1.93) relative to individuals treated electively. There was a non-linear increase in odds of mortality, as demonstrated by fourfold greater odds comparing the oldest age group with the youngest (Table 3).

Discussion

The role and timing of elective colectomy for recurrent sigmoid diverticulitis in the elderly remains controversial. As the population of developed nations continues to age, the number of people for whom diverticulitis surgery is considered will likewise continue to increase. As such, it is imperative that the risks associated with surgery be critically evaluated to help determine optimal strategies for the management of this complex disease process.

This study sought to identify factors predictive of poor outcomes after surgery for diverticulitis among patients over 65 years of age covered by Medicare. To our

Table 1 Patient demographics

	Emergent/Urgent *N*=29,552	Elective *N*=23,764	*p* Value
Female	20,145 (65.4%)	13,982 (71.1%)	<0.001
Black	2,405 (5.2%)	717 (3.1%)	
Age, mean (SD)	76.8 (7.2)	73.9 (5.9)	<0.001
Age by category			
65–69 years	5,680 (19.2%)	6,841 (28.8%)	
70–74	6,607 (22.4%)	7,046 (29.7%)	
75–79	6,715 (22.7%)	5,583 (23.5%)	
80–85	5,951 (20.1%)	2,998 (12.6%)	
85 and up	4,599 (15.6%)	1,296 (5.5%)	<0.001
Charlson Index, mean (SD)	1.02 (1.46)	0.69 (1.12)	<0.001

knowledge, this is the first and the largest study to evaluate outcomes after colectomy for sigmoid diverticulitis that focuses on the population of older adults.

We found, as expected that outcomes were markedly worse (in-hospital mortality, need for intestinal diversion, 30-day readmission rate, length of stay, and total charges) in patients undergoing emergency colectomy for sigmoid diverticulitis compared with those operated on electively, even after adjusting for all variables. Although advancing age is associated with a substantial increase in mortality and morbidity in both groups, these poor outcomes are more pronounced among patients undergoing elective colectomy.

A recent paper by Etzioni et al.[12] reviewed the patterns of admission and treatment for diverticulitis from 1998 to 2005 using the nationwide inpatient sample. They reported results very similar to ours: worse overall outcomes (e.g., in-hospital mortality, likelihood of requiring a colostomy, increased length of stay) in the emergency group and in older patients. Their emergent and elective surgical mortality rates of 12.4% and 3.1%, respectively, in patients aged 75 years and older undergoing surgery for diverticulitis is comparable to our finding of mortality rates of 10.36% and 2.4% in the same groups. The slightly worse outcomes noted in their study can possibly explained by inclusion of uninsured and Medicaid patients, as many previous reports have identified lack of adequate insurance to be predictive of poor outcomes after surgery.[13–15]

The central question of this study regards whether elective surgery for diverticulitis is beneficial in all elderly patients, or whether there are subsets of patients for whom the benefit may be marginal or perhaps even non-existent. It is clear that the management of patients who require emergency operation for acute complicated diverticulitis leaves little room for debate. These patients require immediate surgical intervention, and pre-operative decision-making is limited. However, it is in non-emergent patients that the need for a critical appraisal of the surgical risks and outcome predictors assumes paramount importance. In addition to the risks of the surgery, which include the possibility of receiving an ostomy, it is also worth noting that resection is not curative in all patients, with a recurrence rate following surgery estimated at 2.6–10%.[16–18] In addition, some studies have suggested that prophylactic colectomy may not even result in improvement of pre-operative symptoms or might even lead to worsening of symptoms in some cases.[19,20]

In the recent years, the literature suggests a trend away from elective surgery in recurrent disease. Although more papers are suggesting nonoperative management may be clinically appropriate and cost-effective, this is not mirrored by general clinical practice. Etzioni et al.'s paper[12] found that the overall incidence rates of elective operations for diverticulitis increased by 38% over the years of the study; although the rates in individuals aged 65–74 years of age

Table 2 Unadjusted outcomes

	Emergent/Urgent		Elective		*p* Value
	N=29,552	Mean (SD)	*N*=23,764	Mean (SD)	
In-hospital mortality	2,351 (8.0%)		329 (1.4%)		<0.001
Ostomy	18,863 (64.2%)		3,006 (12.7%)		<0.001
30-day readmission*	5,821 (21.4%)		2,799 (11.9%)		<0.001
Length of stay (days)		14.5 (10.2)		8.0 (6.2)	<0.001
Total charges ($)		86,909 (94,986)		43,904 (49,523)	<0.001

* Only patients discharged alive were eligible for readmission

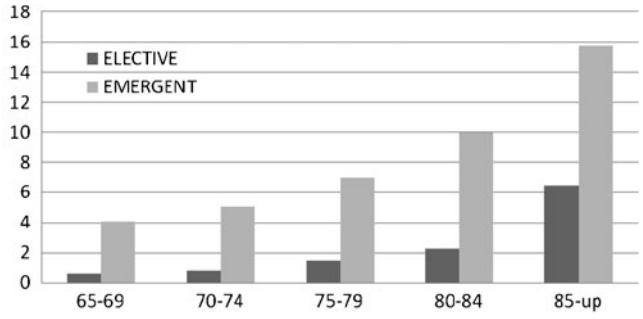

Fig. 1 Unadjusted mortality rates by age group

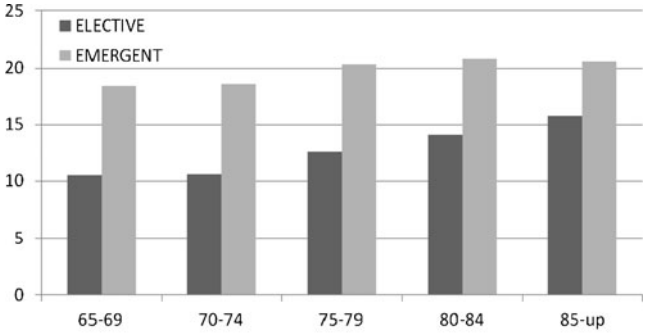

Fig. 3 Unadjusted 30-day readmission by age group

increased slightly, they actually decreased in those aged 75 years and above. This trend was seen in our study as well. There was a more even age-distribution among patients operated on emergently than there was among electively operated patients, in whom the younger age ranges were more heavily represented. A possible explanation for this is that the emergency group likely includes patients thought to be too high risk to be offered elective surgery.

While many studies suggest that elderly patients can generally tolerate major abdominal surgery well,[21–24] our results indicate that, as age increases, the risks of mortality and morbidity increase considerably. Interestingly, the rate at which mortality increases with age is not linear, and actually accelerated with age. This finding persisted even after adjustment for comorbidity and other patient variables. This underscores the potentially diminishing returns for elective operation with increasing age.

Our findings are very similar to a recent retrospective population-based cohort study using a Washington State hospital discharge database by Masserweh et al.[25] In this study, the authors demonstrated an association of increased frequency of complications, as well as mortality, with advancing age in patients undergoing common abdominal operations. This study included colectomy (for all diagnoses, including both elective and emergency) and demonstrated unadjusted mortality rates (9.4% total 90-day mortality: 17.6% in patients aged 85 years and older) which were quite similar to those found in our study (8% in-hospital emergency mortality: 15.74% among patients 85 years and older undergoing emergency surgery). In their study, advancing age was associated with dramatic increases in 90-day mortality rates, and this effect was accentuated in the presence of a postoperative complication. The authors concluded that the elderly are less capable of adapting to intraoperative stress or postoperative complications. Despite the number of studies that suggest abdominal surgery is safe in the elderly, the concepts of frailty and disability are widely recognized as predictors of outcome in elderly patients[26,27] and are another possible explanation for our findings. Nevertheless, such factors remain nebulous and are exceedingly difficult to account for, no less quantify, when relying on administrative databases.

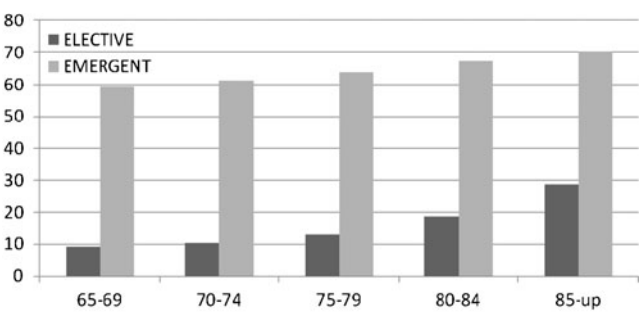

Fig. 2 Unadjusted ostomy rates by age group

The surgical treatment of patients requiring emergency intervention for diverticulitis has traditionally involved sigmoid resection and colostomy, with the option for restoration of intestinal continuity at a later date, particularly in patients who present in critical condition or with fecal peritonitis. Nevertheless, current trends indicate an evolution toward a broader acceptance of primary anastomosis, even in cases of severe disease[28,29] - partially

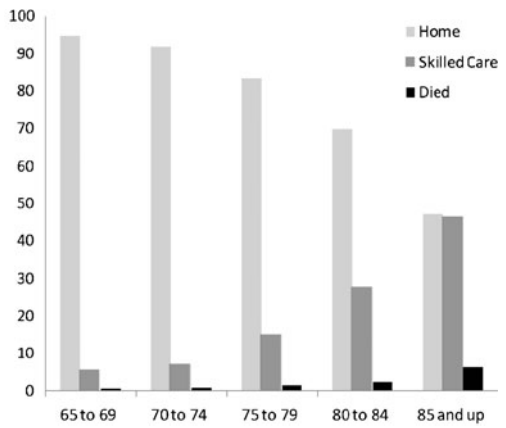

Fig. 4 Discharge destination in patients undergoing elective surgery. Home=discharge to home with or without in-home health assistance. Skilled Care=skilled nursing facility, long term care, other inpatient facility, inpatient rehabilitation, hospice, psychiatric hospital

Table 3 Adjusted odds of in-hospital mortality

	In-hospital death OR (95% CI) *N*= 53,316	Intestinal diversion OR (95% CI) *N*= 53,316	30-day readmission[a] OR (95% CI) *N*= 50,636
Emergent/ Urgent	4.28 (3.86–4.75)	11.26 (10.76–11.78)	1.84 (1.75–1.93)
Age			
70–74 years	1.30 (1.11–1.52)	1.10 (1.03–1.16)	1.03 (0.96–1.11)
75–79	1.97 (1.69–2.29)	1.27 (1.20–1.35)	1.21 (1.13–1.30)
80–84	2.97 (2.57–3.45)	1.60 (1.50–1.71)	1.33 (1.24–1.44)
85 up	5.42 (4.69–6.27)	1.99 (1.84–2.14)	1.46 (1.34–1.59)
Charlson Index	1.20 (1.17–1.22)	1.12 (1.10–1.14)	1.10 (1.08–1.11)
Male gender	1.34 (1.24–1.58)	1.09 (1.05–1.14)	1.01 (0.96–1.07)
Black race	1.40 (1.23–1.58)	0.79 (0.72–0.87)	1.40 (1.26–1.55)

Note: reference group is 65–69 years, white and female

[a] Only live discharges eligible

negating what was once seen by patients as a serious advantage in considering prophylactic colon resection for diverticular disease: i.e., the chance to avoid eventual emergency operation and colostomy in favor of the much lower likelihood of colostomy during elective resection. The likelihood of requiring intestinal diversion (colostomy or protective ileostomy) during an elective operation has been variously reported to be between 2.9% and 10.7%[12,30,31] but was surprisingly high in our patients—12.7% overall, 16.7% in those 75 years and older and 21.7% in those 80 years and older. The functional and emotional impact of a colostomy—especially if permanent cannot be ignored. The implications with respect to the utilization of health care resources are significant. Moreover, colostomy reversal carries considerable risk of further adverse post operative outcomes.[32,33]

This study has several limitations. Firstly, we used administrative billing data. It has been well documented that claims-based databases, which are constructed primarily for reimbursement rather than research purposes, are inherently susceptible to errors due to missing or inaccurately entered codes.[34]However, it is not unreasonable to assume that coding errors ought to be randomly distributed across all categories and would seem unlikely to alter the validity of our findings. Administrative databases do not include detailed clinical history or laboratory values, nor do they document information on physical disabilities, all of which might have provided additional insight as to the overall lack of physiologic reserve in these patients. Secondly, the 30-day readmission rate includes admissions for any condition, and may capture admissions not specifically related to the index admission. Finally, because our study only included patients who are enrolled in Medicare, the results of this study may not be generalizable to all patients over 65 years old. Medicare data has an inherent flaw in that blacks are under-represented. In a previous study by our group[15], lack of adequate health insurance and black race was found to be a powerful predictor for disease severity and mortality after surgery for diverticulitis. It is possible, therefore, that uninsured elderly black patients may have worse outcomes than presented here.

We found that elective surgery for diverticulitis is far from a benign procedure, especially in the very old, who had a marked increase in morbidity and mortality. These risks should be kept in mind by surgeons when considering offering prophylactic colectomy to the geriatric population. In the few studies that have analyzed this problem in this particular subset of patients, the risk of recurrence following an episode of diverticulitis—and ultimately the need for emergency surgery—may not be as high as had previously been thought. Such factors may warrant a reassessment of the cost-benefit calculation in offering prophylactic colectomy to elderly patients with diverticular disease. In a retrospective cohort study using a Kaiser Permanente Discharge Abstract Database in Southern California, Broderick-Villa et al.[4], found that of all the patients that required emergency colectomy for acute diverticulitis, only 3.4% of them were over the age of 79 years. In addition, the authors observed a significantly lower recurrence rate for those patients under 50 years compared with those 50 years or older. Similarly, Anaya and Flum[3] performed a retrospective cohort study using a statewide hospital administrative database and found that the predicted probability of emergency colectomy and/or colostomy decreased with increasing age, including those patients who had multiple admissions for recurrent diverticulitis.

In conclusion, many considerations in the management of diverticular disease in elderly patients await further elucidation. The precise risk that an elderly individual with

diverticulitis will subsequently develop an acute emergency requiring surgical intervention remains ill-defined. Nevertheless, our study suggests that the risk of elective colon resection in elderly patients is considerable. Recognition of this fact, along with an increasing body of data suggesting that diverticular disease among the elderly may in fact follow a more benign natural history than previously thought, suggests that a reappraisal of the proper role of elective colectomy in elderly patients with diverticulitis may indeed be warranted.

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Discussant

Dr. Bridget N. Fahy (Houston, TX): I congratulate Dr. Lidor and her colleagues for a really important study. I do surgical oncology, and I think second only to breast,

diverticulitis is the biggest moving target that any of us are facing right now. So I really applaud you for focusing on a very important topic. And I have a couple of questions.

Did you have any information about the time from which the patients were admitted to the time that they went to their operation? It may have been that that emergent group had failed IV antibiotics for a while and had a percutaneous drainage that failed to resolve thereafter, so on and so forth.

And my second question is, you mentioned, particularly in the paper, which is very nicely written, about thethat marked difference in mortality, particularly in the elective group. And I'm wondering if you can comment on why you think that the that mortality was even more pronounced than what you saw in the emergency group.

Closing discussant

Dr. Anne O. Lidor: For the first question, we broke our patients into two groups: an elective group and an emergency/urgent group. The elective group included patients who had a primary diagnosis of diverticulitis, were admitted on an elective basis, and had their surgery on the same day as their admission.

The emergency/urgent group included patients that were classified as having an emergency admission or an urgent admission. That would actually include patients who came in with fecal peritonitis and went right to the operating room, but it also includes patients that were admitted and failed intravenous antibiotics or some other type of therapy prior to going to the operating room.

As far as the second question: the emergency group likely includes patients that were thought to be too high risk to have been offered elective surgery and are only presenting as emergencies, which leads to uniformly worse outcomes across the board. The patients in the elective group are obviously a highly selected group of patients, because those are patients that, by definition, are already thought to be healthy enough to undergo surgery. Therefore I think that the most likely explanation for the more pronounced effect noted in the elective group is secondary to multiple factors that you can't adjust for, such as lack of physiologic reserve, or inability to cope with intraoperative or postoperative stress. That's actually very hard to account for when you are looking at a claims-based database.

Discussant

Dr. Shimul A. Shah (Worchester, MA): I guess the question that I have would be, how do we know that a 12% intestinal diversion rate in the elderly people is actually high? Maybe in this age group that would be expected as well as a high of 30% readmission rate for the elective group. Maybe those are normal numbers.

Closing discussant

Dr. Anne O. Lidor: If you look in the literature, the reported range for an ostomy during an elective colectomy ranges anywhere from 2% to 10.5%. So even if we look at all comers, almost 13%, that's already higher than what is in the literature.

One thing that I should mention, however, is that it's a little bit difficult using this database to clarify which of those patients actually got their ostomies at the time of their initial operation and which patients received an ostomy during a subsequent operation during the same admission. That is, let's say you did the operation, you weren't happy with the anastomosis, and you gave them a diverting ostomy; but it also includes patients on whom you did the surgery, they may have leaked while they were still in the hospital, and went back to the operating room and got an ostomy. So it's a little bit hard to look at that as a strict number.

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2010 SSAT POSTER PRESENTATION

Single-Incision Versus Hand-Assisted Laparoscopic Colectomy: A Case-Matched Series

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Abstract
Background Single-incision laparoscopic colorectal surgery is an emerging modality. We incorporated this technique as an alternative to hand-assisted laparoscopic surgery. We investigated intraoperative and short-term outcomes following single-incision laparoscopic colectomy compared with hand-assisted laparoscopic colectomy.
Methods Between July and November 2009, single-incision colorectal procedures were performed and matched to hand-assisted procedures based on five criteria: gender, age, body mass index, pathology, and type of procedure. Demographic, intraoperative, and postoperative data were assessed.
Results Twenty-four pairs of patients with a mean age of 55.1 years and mean body mass index of 28.5 kg/m^2 were matched. The majority of cases (79.2%) were right hemicolectomies. The ranges of incision length were 2–6 cm (single incision) and 5–11 cm (hand-assisted). Mean operating time was significantly longer for single-incision procedures (143.2 min) compared with hand-assisted procedures (112.8 min), $p<0.0004$. There was no significant difference in the groups regarding conversions or intraoperative complications ($p<0.083$ and $p<1.0$, respectively). Mean length of stay for the single-incision approach (2.7 days) was significantly shorter compared with the hand-assisted approach (3.3 days), $p<0.02$.
Conclusion Single-incision laparoscopic colectomy is a safe and feasible alternative to hand-assisted laparoscopic surgery. Although the technique required longer operative time, it resulted in smaller incision size and significantly shorter length of hospitalization.

Keywords Colectomy · Single-incision laparoscopic surgery · Hand-assisted laparoscopic surgery · Matched-case analysis · Feasibility

Abbreviations

AR	Anterior rectosigmoidectomy
ASA	American Society of Anesthesiologists
BMI	Body mass index
EBL	Estimated blood loss
HALS	Hand-assisted laparoscopic surgery
IL	Incision length
LN	Lymph node
LOS	Length of hospital stay
OT	Total operative time
RH	Right hemicolectomy
SILC	Single-incision laparoscopic colectomy
TC	Total colectomy

This work was presented in poster format at the May 2010 SSAT Meeting during Digestive Disease Week in New Orleans, Louisiana.

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Introduction

Single-incision laparoscopic surgery is an emerging modality, first reported for gynecologic surgery in 1992[1] and

7 years later for general surgery.[2] Slow to achieve widespread acceptance, this technique has recently experienced resurgence in its use, including increasing application for minimally invasive colorectal surgery. Single-incision laparoscopic colectomy (SILC) has been described through case reports and small case series.[3–7] Considered safe and feasible,[8,9] the single-incision technique results in improved cosmesis with the potential for decreased pain and fewer incisional hernias.[4,7,10,11]

Hand-assisted laparoscopic surgery (HALS) was first described in 1996 for colorectal surgery[12] and was initially used as a bridge to facilitate completion of a minimally invasive procedure for surgeons with limited laparoscopic experience. This technique allows the surgeon to use tactile feedback to identify various structures in order to complete the operation in a shorter period of time[13,14] and with lower conversion rate compared with conventional laparoscopic surgery (CLS).[15,16] Hand-assisted laparoscopic surgery has since gained widespread acceptance, as it has resulted in reduced operative times yet comparable short-term benefits compared with CLS.[13–16]

Single-incision laparoscopic colectomy has yet to be compared with other minimally invasive modalities to evaluate its potential benefits and limitations. The purpose of this study was to assess whether the proven short-term benefits and outcomes of minimally invasive technique are maintained with the SILC approach. We report the first known case-matched series of SILC compared with HALS colectomy in regards to safety, efficacy, and patient outcomes.

Material and Methods

This study was approved by the Institutional Review Board. Twenty-four single-incision laparoscopic colorectal procedures performed between July and November 2009 were matched to 24 hand-assisted laparoscopic colorectal procedures based on five matching criteria: gender, age, body mass index (BMI), pathology (benign or malignant), and type of procedure (right hemicolectomy (RH), total colectomy (TC), or anterior rectosigmoidectomy (AR)). Demographic data including age, gender, BMI, and American Society of Anesthesiologists (ASA) score were collected. Intraoperative parameters including umbilical incision length (IL), estimated blood loss (EBL), total operative time (OT), and lymph node extraction (malignant cases only) were tabulated and analyzed. Single-incision laparoscopic colectomies that required conversion were analyzed within the SILC group. Postoperative outcomes including length of hospital stay (LOS), 30-day complications, and perioperative mortality were assessed.

Surgical Technique

Each procedure was performed by one of two board-certified colorectal surgeons (E.M.H. and T.B.P.) after obtaining informed consent. The SILS™ Port Multiple Instrument Access Port (n=13, Covidien, Mansfield, MA), GelPOINT® (n=9, Applied Medical, Rancho Santa Margarita, CA), or GelPort® (n=2, Applied Medical) was utilized for the SILC procedures. The GelPort® (Applied Medical) was utilized for all HALS procedures. Standard non-articulating laparoscopic instruments were utilized for all procedures.

Our SILC technique has previously been reported.[9,17] Patients undergoing RH were placed in the supine position. Patients undergoing AR or TC were placed in the lithotomy position. The single-incision device was inserted through a 2.5 cm transumbilical incision (Fig. 1a). The direction of dissection (medial-to-lateral or lateral-to-medial) was performed at the discretion of the operating surgeon. For each patient, the specimen was extracted through the transumbilical single incision after placement of an Alexis® wound retractor (Applied Medical, Rancho Santa Margarita, CA). Resection was achieved following extracorporealization. The anastomosis for RH was performed extracorporeally while the anastomosis for AR or TC was performed intracorporeally with the use of a 29 mm EEA stapler (Ethicon Endo-Surgery, Inc., Cincinnati, OH).

Our HALS approach began with insertion of a laparoscopic port for initial entry into the peritoneum. Once pneumoperitoneum was achieved, an umbilical or Pfannenstiel incision was made, through which the GelPort® hand-assist device was placed. The initial incision for the hand port was 5 cm in length and was extended up to 8 cm as necessary depending on the surgeon's hand size and the depth of the patient's abdominal wall. In addition to the hand-assist device, two 5 mm trocars were utilized for RH (Fig. 1c) and three 5 mm trocars were placed for AR and TC (Fig. 1b). A 12 mm trocar was placed through the hand-assist device in all cases. The operation proceeded in a similar approach as the SILC procedure.

Statistical Analysis

Data analysis was performed using Intercooled Stata version 9.2 (Stata Corporation, College Station, TX). Categorical data, summarized as percentages, were compared with the chi-square test. For quantitative data, paired two-tailed Student's t test was performed with significance level of alpha=0.05. Results are presented as mean± standard deviation.

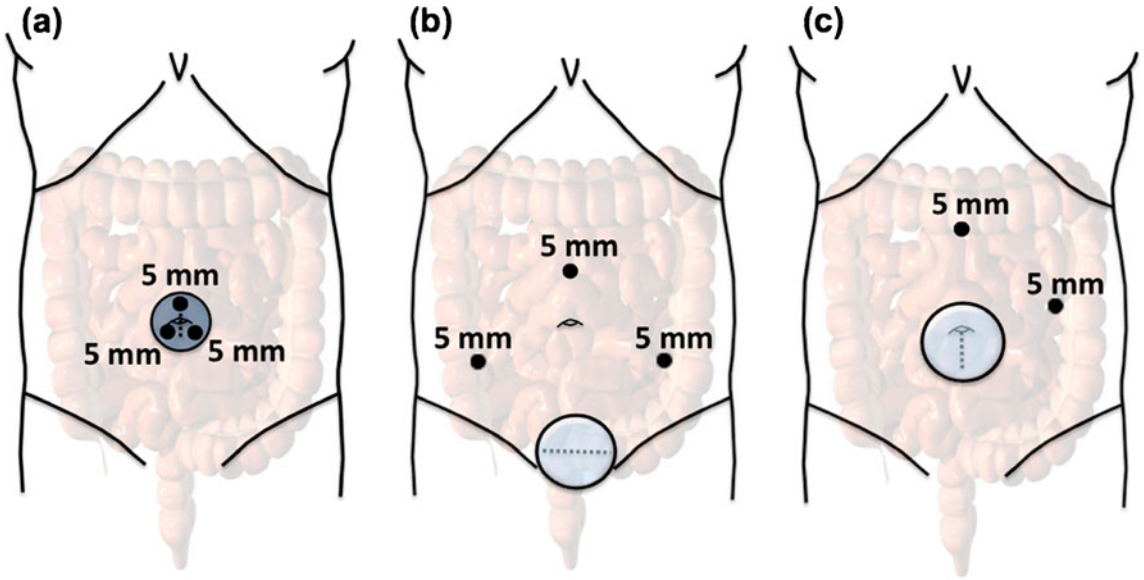

Fig. 1 **a** Single-incision laparoscopic colectomy: three 5 mm trocars placed through transumbilical single-access port. **b** Hand-assisted laparoscopic anterior rectosigmoidectomy or total colectomy: three 5 mm trocars placed through abdomen, a 12 mm trocar and hand placed through hand-assist device. **c** Hand-assisted laparoscopic right hemicolectomy: two 5 mm trocars placed through the abdomen, one 12 mm trocar and hand placed through hand-assist device

Results

Twenty-four SILC and HALS cases each were paired together based on five matching criteria: gender (n=12 male, p<1.0), age (54.1±8.6 years in the SILC group and 56.0±11.1 years in the HALS group, p<0.36), BMI (28.5±7.2 kg/m^2 in the SILC group and 28.5±6.0 kg/m^2 in the HALS group, p<0.95), pathology (n=15 (62.5%) cases for benign disease and n=9 (37.5%) cases for malignant disease, p<1.0), and surgical procedure (n=19 (79.2%) RH, n=3 (12.5%) AR, and n=2 (8.3%) TC, p<1.0), see Table 1. Ten patients (41.7%) in the SILC group and 12 patients (50%) in the HALS group had prior abdominal surgery (p<0.49). The median ASA score for both the SILC and HALS groups was 2.

The mean IL was 3.3±1.1 cm in the SILC group with a range of 2–6 cm (based on n=21 patients for whom IL was recorded). The mean incision length for the HALS group was 6.6±2.1 cm with a range of 5–11 cm (based on n=17 patients for whom IL was recorded) and this was significantly greater than that of the SILC group, p< 0.00001. The EBL in the SILC and HALS groups was 62.5±37.6 mL and 90.6±60.6 mL, respectively (p<0.06). The mean OT for the SILC group (143.2±37.2 min) was significantly longer compared with that of the HALS group (112.8±44.8 min), p<0.0004. There were no conversions to open colectomy in either group. Three patients in the SILC group (12.5%) required conversion to another MIS technique (two HALS and one multiport laparoscopy) for completion of the procedure while no conversions were required for the HALS cases, p<0.083. No intraoperative complications were encountered in either group. For the malignant cases, LN extraction in the SILC and HALS cases was 24.6±12.3 and 18.6±5.7, respectively (p<0.22), see Table 2. There were no significant differences between surgeons with respect to EBL, OT, and intraoperative complication rate.

The LOS in the SILC group was significantly shorter compared with that in the HALS group (2.7±0.8 days compared with 3.3±1.1 days, p<0.02). Two postoperative complications (8.3%) were encountered in the SILC group (anastomotic bleeding and wound infection) and none were encountered in the HALS group, p<0.15. No patients required reoperative intervention. One perioperative death was encountered in a patient following palliative SILC right hemicolectomy as a result of complications from metastatic disease. There were no significant differences between surgeons with respect to LOS, postoperative complication rate, and perioperative mortality.

Discussion

Single-incision laparoscopic technique was first reported in the gynecologic surgical literature in 1992 for a supracervical hysterectomy with bilateral salpingo-oopherectomy[1] and in the general surgical literature in 1999 for a single-incision cholecystectomy.[2] In the last 2 years, however, advancements

Table 1 Summary of demographic information

Characteristic	SILC (n=24)	HALS (n=24)	p value
Gender[a]	12 male/12 female		NS, $p<1.0$
Age[a] (years)	54.1±8.6	56.0±11.1	NS, $p<0.36$
BMI[a] (kg/m^2)	28.5±7.2	28.5±6.0	NS, $p<0.95$
Pathology[a]	15 benign (62.5%)/9 malignant (37.5%)		NS, $p<1.0$
Type of procedure[a]			
Right hemicolectomy	19 (79.2%)		NS, $p<1.0$
Anterior rectosigmoidectomy	3 (12.5%)		NS, $p<1.0$
Total colectomy	2 (8.3%)		NS, $p<1.0$
ASA score	2.3±0.6	2.3±0.5	NS, $p<0.77$
Previous abdominal surgery (%)	10 (41.7%)	12 (50%)	NS, $p<0.49$

ASA American Society of Anesthesiologists, *HALS* hand-assisted laparoscopic surgery, *NS* not significant, *SILC* single-incision laparoscopic colectomy

[a] Characteristics used as matching criteria

in instrumentation and port devices have revived interest in this approach. The adaptation of the single-incision approach has recently emerged for colorectal surgery in the form of case reports[4,7,10,11,18] and small case series.[8] These reports have indicated improved cosmesis as the primary benefit,[4,7,8,10,11] with additional benefits and potential limitations having yet to be elicited. We previously demonstrated safety and feasibility of the technique in a cohort of unselected patients undergoing single-incision right colectomy.[9] In order to further investigate outcomes, we undertook a matched-case analysis comparing the single-incision approach with hand-assisted laparoscopic surgery.

Hand-assisted laparoscopic surgery represents a modification of conventional laparoscopic surgery, designed to help overcome several of the technical challenges of CLS.[13,14,16] HALS allows surgeons to use a hand for dissection or retraction, thereby providing direct tactile feedback during a procedure. In addition, it allows surgeons to maintain a minimally invasive approach and retain the short-term benefits of laparoscopic surgery, including short length of stay, small incision, and reduced perioperative complications.[14,16] Compared with open surgery, the smaller incision used for HALS may contribute to fewer incisional hernias and faster recovery.[13]

In this series, the incision length for patients in the SILC group was significantly smaller in comparison to the incision length for patients in the HALS group ($p<0.00001$). In all SILC cases, the initial incision length was 2.5 cm. In 16 patients (76.2%), the incision was extended by 1 cm or less at the time of specimen extraction. In five cases (23.8%), the IL was extended by 1–2.5 cm beyond the initial incision, for extraction of a bulky specimen (n=4) or exchange of the SILS™ device for a GelPort® due to dislodgement (n=1) in a patient with large abdominal girth. Other reports have described similar incision lengths, ranging from 2–3.5 following the SILC procedure.[4,7,8,10,11,18] Although it may be expected that the absence of multiple trocar-site incisions and an overall smaller extraction-site incision following SILC would result in improved cosmesis, we did not directly assess the

Table 2 Intraoperative parameters, pathology, and postoperative outcomes

Category	Parameter	SILC (n=24)	HALS (n=24)	p value
Intraoperative	Umbilical incision length (cm)	3.3±1.1 (range, 2–6)[a]	6.6±2.1 (range, 5–11)[b]	[c], $p<0.00001$
	Conversion (%)	12.5%	0.0%	NS, $p<0.083$
	EBL (mL)	62.5±37.6	90.6±60.6	NS, $p<0.06$
	OT (min)	143.2±37.2	112.8±44.8	[c], $p<0.0004$
	Complications (%)	0.0%	0.0%	NS, $p<1.0$
Pathology	LN extraction (n=9)	24.6±12.3	18.6±5.7	NS, $p<0.22$
Postoperative	LOS (days)	2.7±0.8	3.3±1.1	[c], $p<0.02$
	Complications (%)	8.3%	0.0%	NS, $p<0.15$

EBL estimated blood loss, *HALS* hand-assisted laparoscopic surgery, *LN* lymph node, *LOS* length of stay, *NS* not significant, *OT* total operative time, *SILC* single-incision laparoscopic colectomy

[a] n=21

[b] n=17

[c] Significant difference

patients' perceptions of their incisions. Establishing a validated questionnaire to address this outcomes measure will be an important consideration when comparing SILC to established MIS procedures. In addition to the known benefit of improved cosmesis, we believe that a smaller single incision provides the potential for diminished postoperative pain.

On average, the SILC technique required 30 min longer to complete compared with the HALS technique. We did not utilize flexible (articulating) instruments as they were not readily available, would have added additional cost, and were not required to complete the procedure. With more complex procedures and advances in technology, utilization of such instrumentation may be warranted. Since the surgeons in this series only recently adopted the SILC technique, it is plausible that the SILC OT may diminish with increased experience. It is further noted that the HALS cases in this study were completed after each surgeon had gained competence with the technique. In addition, previous studies have found HALS to require shorter OT compared with CLS.[15] Thus, one may expect similar findings when comparing HALS to SILC.

For each technique, the postoperative complication rate and perioperative mortality rate were low. For one patient in the SILC group, a postoperative flexible sigmoidoscopy revealed bleeding at the ileorectal anastomosis and an endoscopic clip (Olympus, Center Valley, PA) was placed across the anastomosis at the site of bleeding. A second patient in the SILC group experienced a wound infection that was managed with local wound care. No postoperative complications were encountered in the HALS group. A single postoperative mortality occurred in the SILC group - a 52 year-old female with extensive pulmonary and hepatic metastatic disease who underwent a palliative resection for cecal obstruction. Her operation was completed in 100 min without any adverse events; however, her postoperative course was complicated by respiratory failure, for which supportive care was voluntarily withdrawn.

We analyzed the pathology results for the nine patients in each group (37.5%) with malignant disease to assess the adequacy of the oncologic resections. Neither technique hindered the ability to extract an adequate number of lymph nodes, as evidenced by a median lymph node extraction of 19 in the SILC group and 17 in the HALS group. These values exceeded the median values of 10 and 12 reported for laparoscopic technique in national randomized studies comparing open to laparoscopic approach for colectomy[19–21]. To further enumerate additional parameters such as single-incision site ("port-site") recurrence, long-term follow up will be required.

Mean length of hospital stay following SILC and HALS was 2.7 and 3.3 days, respectively ($p<0.02$). Although statistically significant, we did not evaluate whether this reduction in LOS resulted in an economic benefit, an important consideration for future studies, following the single-incision technique. Both groups were placed on identical postoperative recovery pathways, which included early feeding and ambulation, absence of a nasogastric tube, early removal of Foley catheter, and additional quality measures. Patients were discharged following evidence of bowel activity, either passage of flatus or bowel movements, and absence of abdominal strain or distention. The significant difference between the two groups may be attributed to diminished pain from decreased trauma and incision size with SILC, leading to earlier return of bowel function. In reports comparing HALS to CLS, patients were likely to experience more pain[14–16] and early postoperative bowel obstruction[14] with the HALS technique. It should be noted, however, that these parameters were not primary outcomes of this study.

Conversion was required in three SILC cases. In one patient, lengthening of the incision for specimen extraction resulted in inability to reestablish pneumoperitoneum with the SILS™ device, and thus the GelPort® was introduced to complete the procedure with hand-assisted technique. The second conversion to HALS was required for additional mobilization of the transverse colon for a tension-free ileocolic anastomosis. In the third conversion, two auxiliary ports were placed outside of the single incision to facilitate primary suture closure of colorectal anastomosis following a positive air insufflation test. Conversion to open technique was not required for these three cases, which reflects the ability to maintain a minimally invasive platform and avoid the negative outcomes associated with open conversions, such as prolonged LOS[22] and increased postoperative morbidity.[23]

Many of the SILC cases involved lysis of adhesions before proceeding to mobilization of the colon and these procedures were able to be completed safely through a single incision. In a study of 430 CLS colorectal procedures, adhesions were determined to be a specific indication for conversion, accounting for 30% of conversions to open technique.[24] Given that 50% of patients undergoing HALS and 41.7% of patients undergoing SILC had undergone previous abdominal surgery, the results of this study indicate that surgeons should not be dissuaded from using either minimally invasive approach to perform colectomy in such patients.

Conclusion

Single-incision laparoscopic colectomy can be utilized for surgical resection of benign or malignant disease of the colon. When compared with hand-assisted laparoscopic surgical technique, single-incision laparoscopic colectomy resulted in smaller incision length and shorter length of

hospital stay at the expense of longer operative time. Furthermore, single-incision procedures that prove to be complex can be salvaged with hand-assisted or multiport technique rather than conversion to an open approach. With increased adoption of the single-incision technique, shorter operative times and fewer conversions may be realized.

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2010 SSAT PLENARY PRESENTATION

Hepatectomy is Superior to Thermal Ablation for Patients with a Solitary Colorectal Liver Metastasis

Suzanne Claire Schiffman · Matthew Bower · Russell E. Brown · Robert C. G. Martin · Kelly M. McMasters · Charles R. Scoggins

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Abstract
Introduction Hepatic resection is the mainstay of treatment for solitary colorectal liver metastases (mCRC); however, some patients are not ideal candidates. The aim of this study was to compare outcomes for patients with solitary mCRC who underwent resection or ablation.
Methods A retrospective review of a hepatobiliary database identified patients with solitary mCRC. Patients who were treated with hepatectomy were compared to patients who underwent thermal ablation.
Results The median follow-up time was 25.9 months. Ninety-four patients (67.1%) underwent resection whereas 46 patients (32.8%) underwent ablation. Of the resected patients, most (60%) required a major hepatectomy. Tumor ablation was a significant predictor of overall survival (p=0.002, OR 3.75, 95% CI 1.696–8.284). Overall, the median disease-free survival was 55.2 months for patients undergoing resection vs. 42.6 months for ablated patients (p=0.073). Median overall survival was 112.7 months for patients undergoing resection vs. 50.2 months for patients undergoing ablation (p=0.005).
Conclusion Patients with solitary hepatic colorectal cancer metastases should be considered for hepatic resection as this provides superior survival when compared to thermal ablation.

Keywords Colorectal liver metastases · Radiofrequency ablation · Hepatectomy

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Introduction

Colorectal cancer remains one of the leading causes of cancer-related death in the USA. Approximately 25% of patients with colorectal cancer present with concomitant liver metastases and an additional 50% will develop metastatic disease within 5 years.[1] The management of patients with liver metastases from colorectal cancer (mCRC) is a therapeutic challenge and requires a multidisciplinary treatment plan. Surgical resection is the treatment of choice for patients with mCRC. Survival data demonstrate that with modern multidisciplinary regimens, 25–60% of resected patients are alive at 5 years.[2–7] The goal of surgery is the removal of all of the metastatic tumors with an acceptable resection margin. Some studies have demonstrated that smaller margins may not affect survival and that complete removal of tumor with a minimal margin may be acceptable when technically impossible to obtain a larger margin.[8–10]

Despite improvements in surgical techniques, many patients with hepatic metastases are not amenable to surgical resection.[11,12] The major factors precluding resection are the anatomical location of the tumor, insufficient functional hepatic reserve, prohibitive medical co-morbidities, or the presence of extrahepatic metastases.[13] In addition, surgery may not be indicated in patients with multiple bilobar metastases, lesions involving the portal vein, hepatic artery, or vena cava, or in patients with portal vein thrombosis.[14]

Recent studies have demonstrated that patients who do not undergo surgical therapy will rarely survive long-term.[12,15] Despite improvements in chemotherapy, medically treated patients with mCRC continue to have a poor prognosis with a median survival of approximately 21 months.[2] The most common cause of death is progression of liver disease with subsequent liver failure. Because control of the liver disease is so important, recent efforts have been placed on developing additional regional therapies, such as radiofrequency ablation (RFA), for patients with unresectable mCRC. RFA uses thermal energy produced by a radiofrequency generator to destroy tumors and (hopefully) a surrounding rim of normal parenchyma.[1,3,4,16] Selected studies regarding RFA report 5-year survival rates ranging from 14% to 27%.[1,3,5,15–17]

Although hepatectomy is the mainstay of treatment for solitary mCRC, some patients are not ideal candidates for resection. Furthermore, RFA seems to have a more favorable complication profile. These factors have led the way for thermal ablation to become an increasingly popular alternative to liver resection for patients with mCRC. Despite its attractiveness, RFA may be inferior to resection,[3] and may be administered to patients who are otherwise good resection candidates. Because of these issues, we sought to compare outcomes for patients whose solitary mCRC was either resected or ablated.

Materials and Methods

This study was a retrospective review of a prospectively collected hepatobiliary database at the University of Louisville. Institutional review board approval was obtained prior to the initiation of this study. Consecutive patients with a solitary colorectal metastasis to the liver who underwent surgical therapy from March, 1995 to May, 2009 were identified and included in this analysis. Tumors were regarded as resectable if the anticipated hepatic parenchymal transection plane yielded a tumor-free margin while preserving adequate hepatic remnant. In addition, patients with extrahepatic metastases were excluded from this analysis. Patients with prohibitive medical co-morbidities were not resected. All patients who underwent RFA were considered to have unresectable disease, and all of the ablations were performed surgically. Systemic chemotherapy was administered at the discretion of the medical oncologist.

All adverse events were recorded per standards and terminology set forth by the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events, Version 3.0. Adverse events were recorded during the hospital stay and for 30 days following each treatment and were graded according to the standard five-point grading scale. Major complications were defined as grade 3 or higher. Operative mortality was defined as patient death within 90 days of operation. Synchronous metastases were defined as mCRC occurring within 1 year of CRC diagnosis. Metachronous metastases occurred greater than 1 year following CRC diagnosis. A negative margin (R0) was defined as microscopically tumor free, whereas as microscopically positive margin was defined as R1.

Patients who were treated with hepatic resection were compared to patients who underwent thermal ablation using Fischer's exact, Chi square, and the *t* test where appropriate. Statistical analysis was performed using JMP 4.0 and SPSS version 16 software. Continuous variables were compared using the student's *t* test and categorical variables were compared with chi-square test. Survival was plotted using the method of Kaplan–Meier and compared using the log-rank test. A p value<0.05 was considered a significant difference. Survival (in months) was measured from date of initial diagnosis until death. Cox regression was used to determine independent predictors of outcome. Multivariate analysis was performed with Cox proportional hazards model.

Results

One hundred forty consecutive patients with a solitary hepatic mCRC were identified. The median follow-up time was 25.9 months. The median age was 60.9 years, and the study population was comprised of 72 men (51.4%) and 68 women (48.6%). Eight patients (5.7%) reported alcohol use and 39 patients (27.9%) reported tobacco usage. The median body mass index was 26.9 kg/m2 (range 17.5–46.1 kg/m2). Eleven patients (7.9%) had a family history significant for colon cancer and an additional 28 patients (20%) reported a family history of any type of cancer. The past medical history was significant for pulmonary disease (n=10), cardiac disease (n=25) and diabetes (n=21).

The location of the primary tumor was heavily weighted to the left colon, with the sigmoid colon (34.3%) being the most common site, followed by the ascending colon (20.7%), rectum (20%), and cecum (15.7%). The majority of patients had advanced primary tumors, with 79.3% T3

Table 1 Characteristics of the primary and metastatic tumors

	Number	Percentage (%)
Hepatic resection		
Right hepatectomy	29	30.51
Left hepatectomy	12	12.6
Left lateral segmentectomy	10	10.5
Central liver resection	3	3.2
Extended left hepatectomy	3	3.2
Extended right hepatectomy	13	13.7
Right posterior segementectomy	5	5.3
Segment/wedge resection	20	21.1
1 segment	13	13.7
2 segments	3	3.2
Wedge	3	3.2
Caudate	1	1.1
CRC tumor depth		
T1	2	1.4
T2	11	7.9
T3	111	79.3
T4	12	8.6
Unknown	4	2.9
CRC location		
Ascending colon	29	20.7
Cecum	22	15.7
Descending colon	6	4.3
Rectum	28	20.0
Sigmoid colon	48	34.3
Transverse colon	5	3.6
Unknown	2	1.4
CRC nodal status (N1)	83	59.30
Preoperative chemotherapy	82	58.60
Synchronous	65	46.40

tumors, and 83 patients (59.3%) had tumor-positive lymph nodes at the time of initial CRC resection. Sixty-five patients (46.4%) presented with synchronous metastatic disease. (Table 1)

The hepatic metastases were resected in 95 patients (67.8%), while 45 patients (32.1%) underwent thermal ablation. Of the resected patients, most (60%) required a major hepatectomy. Eighty-two patients (58.6%) received prehepatectomy or preablation chemotherapy. While there was no standardization of chemotherapy regimens used, the majority of patients (65%) received 5-fluoroucil- and oxaliplatin-based regimens for a median of 3.2 months prior to hepatic resection/ablation. The most common anatomic hepatic resection performed was a right hepatectomy (30.5%), followed by segmental resection (20%), extended right hepatectomy (13.7%), left hepatectomy (12.6%), and left lateral segmental resection (10.5%). The majority of resected patients (88.3%) had an R0 resection and the median margin obtained in patients was 1.7 cm. (Table 1)

When comparing the resected and ablated patients, there were no significant differences in gender (p=0.632), age (p=0.992), use of prehepatectomy chemotherapy (p=0.702), primary tumor nodal status (p=0.368) or synchronous vs. metachronous metastases (p=0.627) between the two groups. Resected patients had significantly larger metastatic tumor sizes than ablated patients (5.6 vs. 3.85 cm, respectively; p=0.004; Table 2).

Overall, the median disease-free survival (DFS) was 55.2 months for patients undergoing resection compared to 42.6 months for ablated patients (p=0.073; Fig. 1). The median overall survival (OS) was 112.7 months for patients undergoing resection compared to 50.2 months for patients undergoing ablation (p=0.005; Fig. 2). There were no significant predictors of recurrence on univariate analysis. Age, T stage, N stage, margin status, tumor size, thermal ablation, and use of prehepatectomy (or ablation) chemo-

Table 2 Demographics and tumor characteristics of patients undergoing hepatic resection compared to patients undergoing thermal ablation

	Ablation	Hepatic Resection	p value
Gender	53.3% male	50.5% male	0.632
Age	62.1 years	60.6 years	0.992
Preoperative chemotherapy	60.00%	57.90%	0.702
Liver tumor size	3.9 cm	5.6 cm	0.004
CRC tumor nodal status (N1)	53.30%	62.10%	0.368
CRC tumor depth			0.11
T1	0	2	
T2	2	9	
T3	38	73	
T4	3	9	
Unknown	2	2	
Metastatic diagnosis (synchronous)	42.20%	48.10%	0.627

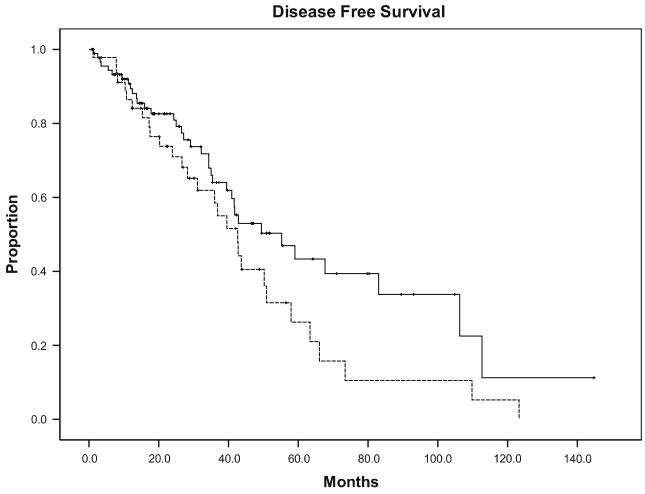

Fig. 1 Kaplan–Meier curves depicting disease-free survival for patients undergoing hepatic resection compared to thermal ablation (P=0.073). *Solid line,* hepatic resection; *dotted line,* thermal ablation

therapy did not impact recurrence (Table 3). Shorter overall survival was predicted by tumor ablation on multivariate analysis (p=0.002, OR 3.75, 95% CI 1.696–8.284). Age, T stage, N stage, margin status, tumor size, and use of prehepatectomy chemotherapy did not impact overall survival (Table 4).

At median follow-up, 16 patients (35.6%) in the ablation group developed an intrahepatic local recurrence. Of these, five (11.1%) were located at the margin. In the hepatic resection group, 12 patients (12.6%) developed an intrahepatic local recurrence (p=0.026). Two patients (2.1%) demonstrated a recurrence at the resection margin. There was no a significant difference in the extrahepatic recurrence rate between the ablation and resection groups (20% vs. 18.9%, respectively; p=0.2; Fig. 3).

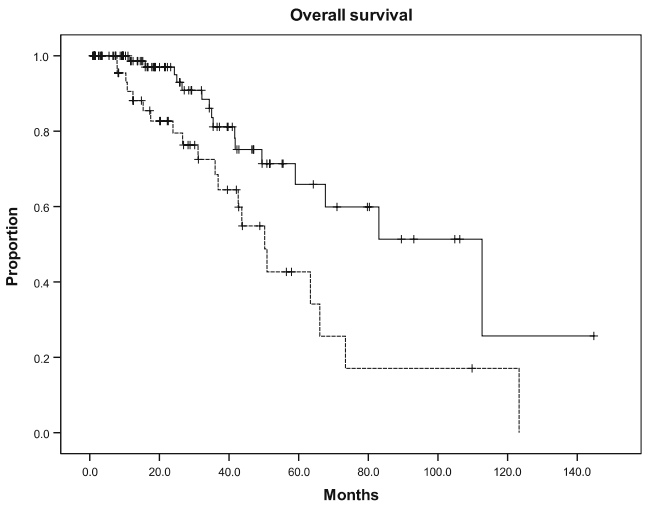

Fig. 2 Kaplan–Meier curves depicting overall survival for patients undergoing hepatic resection compared to thermal ablation (P=0.005). *Solid line,* hepatic resection; *dotted line,* thermal ablation

There were no differences in the rate (p=0.35) or severity (p=0.14) of complications between the resected and ablated patients. Of the patients undergoing resection, 46 patients (48.4%) sustained a complication of any grade. Twenty-three (50%) of the complications were major (grade 3 or greater). Of the patients undergoing RFA, 18 patients (40%) sustained a complication of any grade. Of these, 12 (66.7%) were major complications. There were two postoperative deaths (2.1%) in the hepatic resection group. One patient had an extended right hepatectomy for a 6-cm synchronous metastasis. He did receive prehepatectomy chemotherapy. He presented with recurrent disease approximately 2 years later and underwent caudate resection. The patient developed peritonitis secondary to a small-bowel perforation and underwent exploratory laparotomy with small-bowel anastomosis 19 days after the caudate resection. Shortly thereafter, he developed an intrabdominal abscess and sepsis and subsequently expired. The other patient presented with a 5.5-cm metachronous lesion and also underwent an extended right hepatectomy. He did not receive neoadjuvant chemotherapy. The patient sustained a cardiac arrest 4 days following resection and expired (Table 5). Both patients were reported to have normal liver parenchyma. There were no deaths following thermal ablation.

Discussion

We sought to determine whether there is a difference in outcomes for patients with solitary hepatic colorectal cancer metastases who undergo either resection or ablation. Our data demonstrate that tumor resection is superior to thermal ablation. As such, we believe that resection of colorectal cancer liver metastases remains the treatment of choice for solitary liver lesions. Because some patients are not suitable candidates for hepatectomy, investigators have sought "less-invasive" methods of treating liver tumors. One of the most popular of these methods is thermal tumor

Table 3 Predictors of recurrence

Factor	Univariate p value
Treatment type (RFA vs resection)	0.07
Liver tumor size	0.092
CRC nodal status (N1)	0.20
Age	0.557
Gender	0.544
T stage	0.663
Primary location	0.910
Margin	0.569
Preoperative chemotherapy	0.749

Table 4 Predictors of survival

Factor	Univariate p value	Hazard ratio	95% CI
Treatment type (RFA vs resection) *	0.006	2.5	1.3–4.8
Age	0.407		
Gender	0.558		
T stage	0.995		
Primary location	0.946		
Margin	0.330		
Liver tumor size	0.975		
Preoperative chemotherapy	0.414		
CRC nodal status (N1)	0.842		

*$p<0.05$

ablation, usually radiofrequency ablation. Recently, RFA has been proposed as an alternative to resection in patients with metastatic colorectal cancer. In one study, Oshowo et al. demonstrated comparable 3-year survival rates between resected and ablated patients with solitary liver metastases (55% vs. 53%, respectively).[4] It is noteworthy that RFA was only utilized in patients who were considered unsuitable for surgical resection. This selection bias is also present within our study, as we have a strong bias toward surgical resection, reserving ablation for patients who are deemed unsuitable for tumor resection.

The current study found longer DFS in patients undergoing resection compared to ablated patients (55.2 vs 42.6 months; $p=0.07$ respectively). Many factors have been associated with a higher risk of recurrence following treatment of mCRC. The factor described most often is tumor size. Interestingly, in this study the patients undergoing hepatic resection had significantly larger tumor size than the patients undergoing RFA. A recent study has shown that the incidence of local recurrence increases 33% following RFA for lesions greater than 3 cm.[2] Aloia et al. analyzed patients with solitary colorectal liver metastases and compared recurrence patterns following hepatectomy and ablation. They determined that RFA was associated with a very high local failure rate (37%) regardless of tumor size and was associated with shorter DFS and OS.[5] In the current study, we demonstrated a significantly higher local recurrence rate in the patients undergoing ablation compared to the patients undergoing resection (35.6% vs. 12.6%). The local recurrence rate after RFA in this study is comparable to the rates demonstrated in the recent literature.[5,16] Unfortunately, retreatment of a local recurrence by RFA is often impossible or followed by a high failure rate.[5,18] As such, we believe that operable patients with resectable mCRC should be offered resection.

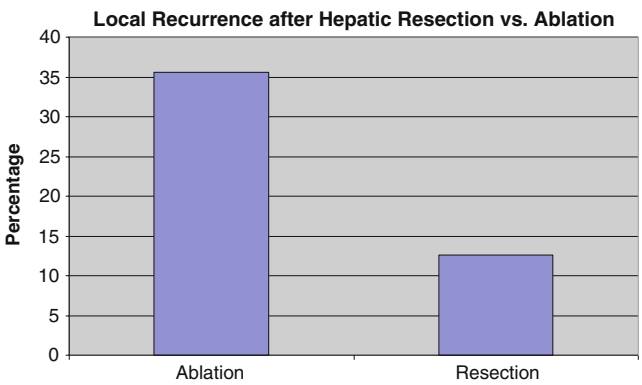

Fig. 3 Local (intrahepatic) recurrence after hepatic resection compared to thermal ablation ($p=0.026$)

We found no difference in primary tumor characteristics, including depth, nodal status, time of mCRC diagnosis, or preoperative chemotherapy, in patients undergoing resection compared to ablated patients. Despite this similarity in traditional predictors of survival, resection yielded a significantly better outcome. The only statistically significant predictor OS was treatment type (resection or ablation). The differences in DFS and OS between resected and ablated patients cannot be explained by differences in patient demographics or characteristics, primary tumor characteristics, hepatic tumor characteristics, or other perioperative factors. This demonstrates oncologic superiority of resection over ablation.

Abdalla et al. performed a retrospective review of patients with mCRC who received resection, RFA, or both. They showed 65% survival rate with surgery compared to 22% survival rate with RFA alone at 4 years. Interestingly, they found a 36% survival rate with surgery+RFA at 4 years. These data show that RFA alone or in combination

Table 5 Complication grade following hepatic resection or thermal ablation

Complication grade	Ablation (n)	Resection (n)
1	5	3
2	7	20
3	5	17
4	1	4
5	0	2

with surgery does not provide a survival rate comparable to surgical resection for patients with mCRC. RFA was used to treat solitary tumors in locations where a margin negative resection was not possible. There was a highly significant survival difference in patients with solitary tumors treated with resection versus RFA ($p=0.025$).[3] These data support our findings that the median OS of patients with a solitary mCRC lesion undergoing hepatic resection was significantly longer then the OS of those undergoing RFA.

There are limitations to the current study. First, it is a retrospective study with inherent bias. Second, our group maintains a bias toward resection, and we thus introduce selection bias when selecting the operative approach. Next, the sample size may not be substantial enough to detect a true difference in the DFS. Finally, the patients in this study did not receive identical chemotherapy treatments; therefore no meaningful conclusions may be drawn from those data.

Conclusion

In conclusion, suitable patients with solitary hepatic colorectal cancer metastases should be considered for hepatic resection as this provides superior survival when compared to thermal ablation. The present study advocates for the aggressive resection of solitary mCRC, as RFA is associated with a shorter DFS and OS.

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Discussant

Dr. Kaye M. Reid Lombardo (Rochester, MN): Thank you for trying to shed some insight into this very important question. More and more patients are being referred directly for ablation, as opposed to seeing the surgeon ahead of time. I do want you to clarify one of the statements you made. Were these patients in the ablative group unresectable initially or resectable? I thought you said they were unresectable.

Closing Discussant

Dr. Suzanne C. Schiffman: They were unresectable.

Discussant

Dr. Kaye Reid Lombardo (Rochester, MN): So it's kind of hard to compare them to patients who are initially resectable. Also, during the time period that you studied, FOLFOX was introduced somewhere midway between that. So I'm not sure how much impact the type of chemotherapy had on the actual overall survival. The role really of ablation is to provide local controls. So I also want you to comment on how many patients actually benefited from the ablation locally, as opposed to just having recurrence anywhere else.

Closing Discussant

Dr. Suzanne C. Schiffman: As you pointed out, there is, of course, a selection bias in this study in that the patients selected for RFA were considered to be unresectable. All of our RFAs were done by surgeons either open or laparoscopically. There is also a referral bias in that we may not have seen some of these patients until after they have received neoadjuvant therapy and were referred to us later by the medical oncologists.

In the current study we demonstrated a significantly higher local recurrence rate in the patients undergoing ablation as compared to the patients undergoing resection (35.6% vs. 12.6%). There was no difference in the extrahepatic recurrence rate in the patients who were ablated compared to the patients who were resected.

We did not have a standardized chemotherapy regimen for these patients. Approximately 60% of the resected patients and 60% of the ablated patients received chemotherapy. The most common regimen was FOLFOX; but again, it was not standardized, so I don't know that we can make an accurate comparison or draw any meaningful conclusions about chemotherapy with this patient group.

Discussant

Dr. Margo Shoup (Baltimore, MD): I have a couple of questions for you. One is, you talked about ablation. How many of these had microwave and how many had radiofrequency? Was there a difference in recurrence in those two? My other question is, I saw you had two deaths. And both of these patients underwent extended right hepatic lobectomies. I hope it's your practice to get away from doing this operation, if possible, because it looks like two out of eleven people died.

Closing Discussant

Dr. Suzanne C. Schiffman: All of the ablation patients in this series underwent radiofrequency ablations. I did not include microwave ablations in this population, although our group has moved towards doing more microwave ablations rather than radiofrequency ablations.

These patients that underwent the extended right hepatectomies may not have been ideal operative candidates. Perhaps, more extensive preoperative evaluation was necessary. One patient expired after an unanticipated cardiac event and the other due to sepsis from an abdominal abscess.

Discussant

Dr. Jonathan Critchlow (Boston, MA): The patients with solitary mass who had just local resection alone was quite small, 20%. And a large number of them had very large procedures. I was wondering whether this is consonant with the general situation of doing large resections for solitary lesions?

Closing Discussant

Dr. Suzanne C. Schiffman: Likely it was due to the anatomic location of the tumor. In our practice, we usually attempt to get a 1-centimeter margin, if possible, but we'll settle for a few millimeters.

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2010 SSAT PLENARY PRESENTATION

Insulin, Leptin, and Tumoral Adipocytes Promote Murine Pancreatic Cancer Growth

Patrick B. White · Eben M. True · Kathryn M. Ziegler · Sue S. Wang · Deborah A. Swartz-Basile · Henry A. Pitt · Nicholas J. Zyromski

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Abstract
Background Obesity accelerates development and growth of human pancreatic cancer. We recently reported similar findings in a novel murine model of pancreatic cancer in congenitally obese mice. The current experiments were designed to evaluate the effects of diet-induced obesity on pancreatic cancer growth.
Methods Thirty C57BL/6J female mice were fed either control 10% fat (n=10) or 60% fat diet (n=20) starting at age 6 weeks. At 11 weeks, 2.5×10^5 PAN02 murine pancreatic cancer cells were inoculated. After 6 weeks, tumors were harvested. Serum adiponectin, leptin, insulin, and glucose concentrations were measured. Tumor proliferation, apoptosis, adipocyte content, and tumor-infiltrating lymphocytes were evaluated.
Results The diet-induced obesity diet led to significant weight gain (control 21.3±0.6 g; diet-induced obesity 23.1±0.5 g; p=0.03). Mice heavier than 23.1 g were considered "Overweight." Tumors grew significantly larger in overweight (1.3± 0.3 g) compared to lean (0.5±0.2 g; p=0.03) mice; tumor size correlated positively with body weight (R=0.56; p<0.02). Serum leptin (3.1±0.7 vs. 1.4±0.2 ng/ml) and insulin (0.5±0.2 vs. 0.18±0.02 ng/ml) were significantly greater in overweight mice. Tumor proliferation, apoptosis, and tumor adipocyte volume were similar. T and B lymphocytes were observed infiltrating tumors from lean and overweight mice in similar number.
Conclusion These data show that diet-induced obesity accelerates the growth of murine pancreatic cancer.

Keywords Pancreas cancer · Diet-induced obesity · Mouse model · Insulin · Leptin

Introduction

Obesity has become a major worldwide health problem.[1] Pancreatic cancer is a devastating malignancy with an annual mortality that approaches its incidence.[2] Combined, obesity and pancreatic cancer constitute a particularly lethal combination. Over the past decade, numerous epidemiologic and clinical studies have shown that obesity not only is an independent risk factor for developing pancreatic cancer, but is also associated with poorer survival in patients with resected pancreatic cancer.[3,4] However, the mechanisms underlying this association between obesity and pancreatic cancer remain unclear.

We recently reported a novel, in vivo murine model of pancreatic cancer in obesity.[5] In this model, congenitally obese mice developed larger tumors, more metastases, and had significantly increased mortality compared to lean wild-type animals. The congenital obesity model is convenient, but has several limitations including significant immune perturbation, a condition that affects pancreatic cancer.[6,7] The diet-induced model of obesity is appealing, however, because of its closer approximation of the human obese situation as well as its potential application to other

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tumor systems (such as human xenografts). The current study was therefore undertaken to evaluate the effects of diet-induced obesity on the growth of murine pancreatic cancer.

Materials and Methods

Animals and Diets

All experiments were carried out with the approval of the Indiana University Animal Care and Use Committee. Thirty lean C57BL/6J female mice were obtained at 6 weeks of age from Jackson Laboratory (Bar Harbor, ME) and housed in standard conditions. After 1 week of acclimation, animals were randomly divided into two groups: ten control mice were assigned to a 20% protein, 70% carbohydrate, and 10% fat diet and 20 diet-induced obesity (DIO) mice were assigned to a 20% protein, 20% carbohydrate, and 60% fat diet (Research Diets, Inc., New Brunswick, NJ, D12450B and D12492, respectively)

Tumor Model

PAN02 cells were a kind gift from David Linehan, MD, Washington University, St. Louis, MO. Cells were cultured in Roswell Park Memorial Institute-1640 medium (Cellgro, Herndon, VA) and supplemented with 10% fetal bovine serum (Valley Biomedical, Winchester, VA), 1% penicillin/streptomycin, and 1% glutamine (Cellgro). At 11 weeks of age, all mice had 2.5×10^5 PAN02 cells suspended in 150 μl of phosphate-buffered saline injected subcutaneously into the right flank. Mice were monitored daily; mouse weight and tumor size were measured weekly with a vernier caliper, with volume calculated as previously described: $V = 0.5236 \times l \times w \times h$.[8]

Tumor Procurement

After 6 weeks of tumor growth, mice were injected intraperitoneally with Bromodeoxyuridine Reagent 120 mg/kg (BrDU, Invitrogen, Carlsbad, CA) and sacrificed 2 h later by overdose of 1 ml/kg ketamine/xylazine solution (Sigma, St. Louis, MO). Tumors were carefully dissected from the surrounding tissue, weighed, and measured with vernier calipers. A portion of the tumor was immediately frozen in liquid nitrogen, and the remaining tumor was preserved in 10% formalin for subsequent histologic evaluation. Blood was collected by ventricular puncture, immediately centrifuged at 5,000 rpm for 10 min, and sera were preserved for subsequent analysis.

Biochemical Analysis

Enzyme-linked immunosorbent assay was used to determine serum concentration of adiponectin, leptin, and insulin (Millipore, Billerica, MA). Serum glucose concentration was determined by colorimetric assay (Stanbio Laboratory, Boerne, TX). The HOMA-IR index was calculated using the formula $IR = \text{insulin}/(22.5e^{-\ln\text{glucose}})$.[9]

Tumor Proliferation

Tumor proliferation was determined using the standard method of DNA incorporation of 5-bromodeoxyuridine (BrDU). A monoclonal BrDU antibody and streptavidin–biotin staining system were used per the manufacturer's instruction (Invitrogen, Carlsbad, CA). The number of positively stained cells per 10 high-powered fields (original magnification ×400) of formalin-fixed, paraffin-embedded tumor sections was recorded by three observers who were unaware of treatment protocol.

Tumor Apoptosis

The Apoptag peroxidase kit (Millipore) using terminal deoxynucleotidyl transferase was used to identify and quantify apoptosis in formalin-fixed, paraffin-embedded tumor sections. Three observers blinded to treatment group counted the number of positively stained cells in 10 high-powered fields per specimen.

Tumor Adipocyte Histology

Tumor adipocytes were evaluated by light microscopy. Three observers blinded to treatment arm estimated the percentage of tumor occupied by adipocytes in 10 high-powered fields per tumor specimen.

Tumor-Infiltrating Lymphocytes

Immunohistochemistry techniques were used to identify tumor-infiltrating lymphocytes (T cells and B cells). After blockade of endogenous peroxidase, slides were incubated with primary antibody against T cells (CD3 Envision+ Rabbit 1:80 Dako North America, Carpinteria, CA), and B cells (CD45/B220 1:50, BD Pharmingen, San Diego, CA). Secondary incubation was performed with biotin conjugated-donkey-anti-rat (1:100, Jackson Laboratory) and LSAB2-streptavidin (Dako). T and B lymphocytes were visualized using diaminobenzadine substrate (Dako). Two observers unaware of treatment protocol identified tumor-infiltrating lymphocytes in 10 HPF per specimen using a 0–4+ quantitative scale.

Statistics

Data are reported as mean±standard error of the mean (SEM). All statistical analyses were performed using the SigmaStat software package (Jandel Corp., San Rafael, CA). Student's *t* test, Mann–Whitney rank sum, and Pearson correlation were applied where appropriate. A p value<0.05 was accepted as statistically significant.

Results

Diet Consumption

Mice on both diets consumed an equivalent amount of diet per day (2.61 g/mouse/day on the control diet vs. 2.62 g/mouse/day for diet-induced obesity diet). Mice fed the control diet consumed on average 11.76 kcal/mouse/day while those on the DIO diet ate 18.32 kcal/mouse/day (p<0.001).

Mouse Weight

At 7 weeks of age, the control and DIO mice did not differ in weight (control 16.3±0.43 g vs. DIO 16.53±0.24 g; p=0.68). At sacrifice, the average weight of mice fed the control diet was 21.3±0.6 g and that of those on the DIO diet was 23.1±0.5 g (p=0.03). Since the primary goal of this study was to evaluate the influence of obesity on pancreatic cancer growth, further analysis was performed based on segregation into lean (weight <23.1 g, n=19) and overweight (weight ≥23.1 g, n=10). Therefore, mice heavier than the mean weight of the animals fed the DIO diet were categorized as overweight. One animal that was two standard deviations less than the average weight for both lean and overweight animals and was excluded from analysis. The average weight of lean mice was 21.2±0.2 g and the average weight of the overweight mice was 25.0±0.4 g (p<0.001; Fig. 1).

Tumor Growth

Tumors developed in 53% (10 of 19) of lean mice and 80% (8 of 10) of overweight mice (p=0.23). Tumors in overweight mice were significantly heavier than those growing in lean animals (1.3±0.3 g vs. 0.5±0.2 g, p=0.03; Fig. 2a). A significant positive correlation was observed between animal weight and tumor weight (R=0.56, p=0.02; Fig. 2b).

Biochemical Analysis

Circulating concentration of the adipokines adiponectin and leptin, glucose, insulin, and the HOMA-IR index are shown in Table 1. No difference was observed in circulating adiponectin or glucose between lean and overweight mice. In contrast, circulating leptin (p=0.05) and insulin (p=0.02) were significantly greater in overweight as compared to lean animals. Serum leptin correlated positively with mouse weight (R=0.64; p<0.01) The HOMA-IR was likewise greater in overweight compared to lean animals (5.63 vs. 1.76±0.33, p=0.04).

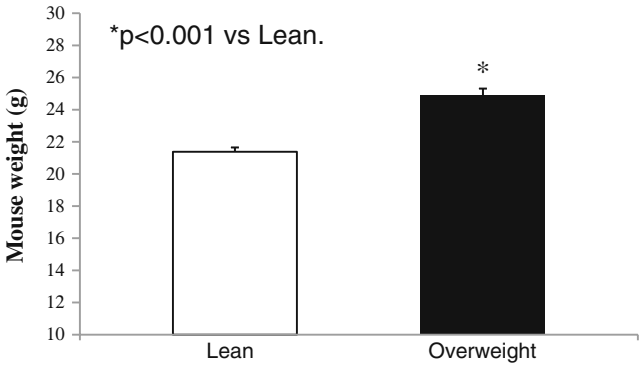

Fig. 1 Weight of lean (n=19) and overweight (n=10) mice at 17 weeks of age; 11 weeks on specific diet. Overweight mice weighed significantly more than lean mice (p<0.001)

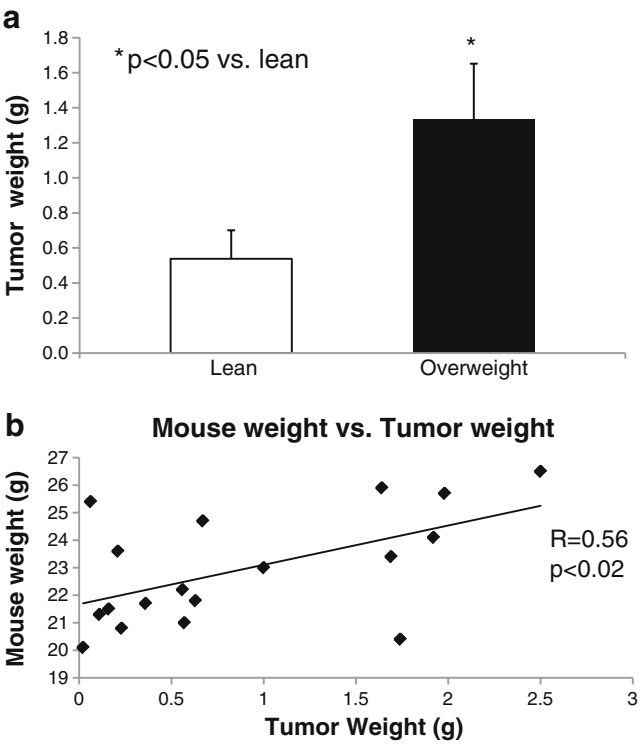

Fig. 2 **a** Weight of tumors in lean (n=10) and overweight (n=8) animals 6 weeks after tumor inoculation. **b** Significant positive correlation between mouse weight and tumor weight was observed (R=0.56, p<0.02)

Table 1 Serum biochemistry in lean and overweight mice

	Adiponectin (μg/ml)	Leptin (ng/ml)	Glucose (mg/dl)	Insulin (ng/ml)	HOMA-IR
Lean	4.2±0.5	1.4±0.2	175.0±8.0	0.18±0.02	1.8±0.3
Overweight	4.9±0.3	3.1±0.7	201.0±15.0	0.48±0.2	5.6±2.2
p	0.33	0.05	0.11	0.02	0.04

Tumor Proliferation

Tumor cell proliferation was measured by number of BrDU-labeled cells per HPF. Similar proliferation indices were observed in lean (45±10 BrDU cells/HPF) and overweight (21±7 BrDU cells/HPF, $p=0.07$) groups.

Tumor Apoptosis

Apoptosis was measured by Apoptag labeling. No significant difference in apoptosis was observed in tumors from lean mice (9±3) compared to tumors growing in overweight animals (3±1; $p=0.06$).

Tumor Adipocyte Histology

Adipocytes were observed in the microenvironment of tumors growing in both lean and overweight mice. Tumor fat content was similar in lean and overweight mice (5.6±1.1% vs. 4.2±0.5%, $p=0.32$). Interestingly, a significant positive correlation between tumor fat and tumor proliferation (BrDU) was observed in all tumors ($R=0.59$; $p=0.01$; Fig. 3).

Tumor-Infiltrating Lymphocytes

Immunohistochemistry demonstrated the presence of both T and B lymphocytes infiltrating the pancreatic tumor microenvironment (Fig. 4). A relatively greater number of T compared to B cells were seen in both lean and overweight tumors. No significant difference was observed in the score of tumor-infiltrating T (2.0±0.2 vs. 2.2±0.2, $p=0.5$) or B (0.7±0.1 vs. 0.7±0.1, $p=0.6$) cells in tumors growing in either lean or overweight mice.

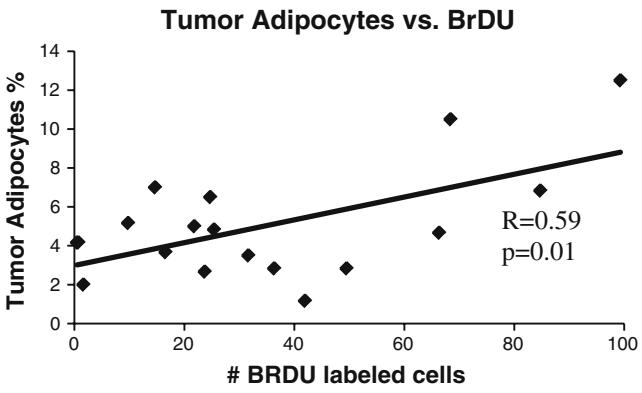

Fig. 3 Correlation of tumor adipoctyes and tumor proliferation (BrDU). A significant positive correlation was observed ($R=0.59$, $p=0.01$)

Discussion

The major finding of the current experiment was that weight gain (i.e., "overweight") from 11 weeks on a diet-induced obesity high-fat diet led to a significant increase in

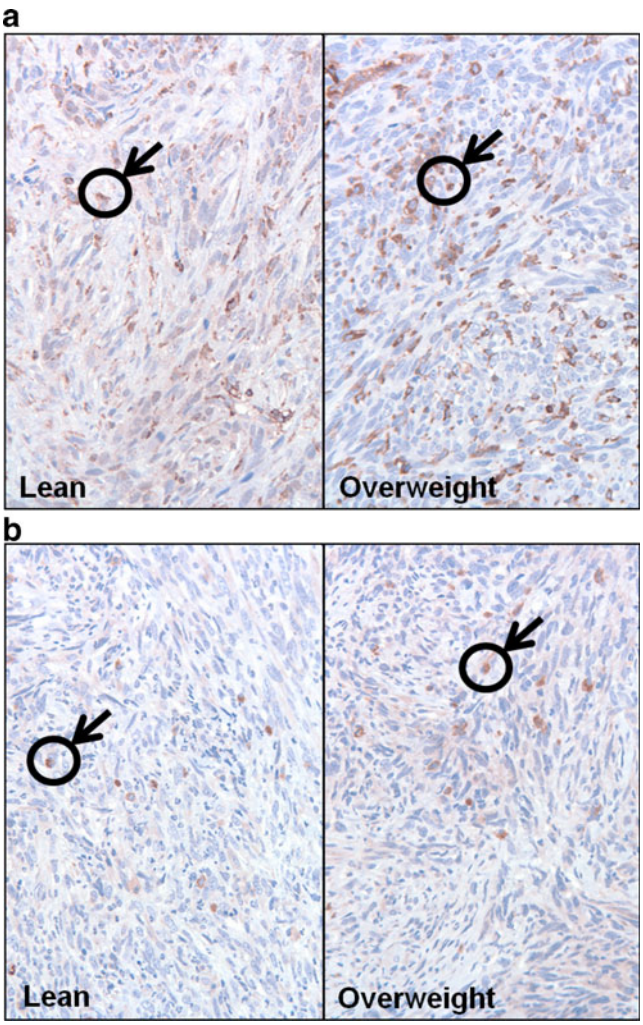

Fig. 4 **a** Immunohistochemical labeling of tumor-infiltrating T cells in lean and overweight mice with CD3 antibody. *Arrows* indicate labeled cells. **b** Immunohistochemical labeling of tumor-infiltrating B cells in lean and overweight mice with CD45/B220 antibody. *Arrows* indicate labeled cells

pancreatic cancer size. Tumor size showed a strong positive correlation with animal weight. Circulating leptin and insulin were increased in overweight mice compared to lean mice, while no difference was seen in circulating adiponectin or glucose. Similar to our prior observations, adipocytes were seen in the microenvironment of all tumors. No differences in adipocyte numbers were observed between overweight and lean mice; however, a significant correlation was observed between the number of intratumoral adipocytes and tumor proliferation. Tumor-infiltrating lymphocytes—both T and B cells—were identified in all tumors.

We recently reported a novel murine model of pancreatic cancer in obesity.[5] Congenitally obese leptin-deficient (Lep^{Ob}) and leptin receptor defective (Lep^{Db}) mice developed larger tumors, more frequent metastases, and increased mortality relative to lean wild-type mice. In this model, tumor proliferation correlated negatively with circulating concentration of the adipokine adiponectin and positively with serum insulin. In the current study, no significant correlation was observed between adiponectin concentration and tumor size or proliferation. However, serum adiponectin concentration did not differ between lean and overweight mice, likely because of the relatively small weight differential between these two groups.

On the other hand, circulating insulin and insulin resistance (measured by the HOMA-IR index) were found to be significantly higher in the overweight mice. Insulin is a mitogenic molecule, and the relationship of insulin, insulin-like growth factors (IGF), and IGF-binding proteins to pancreatic cancer growth has been the focus of a great deal of current investigation.[10,11] In this study, we were unable to establish a direct correlation between circulating insulin concentration and either tumor size or proliferative index. The relatively low degree of hyperinsulinemia and insulin resistance in this diet-induced model compared to congenitally obese mice is the likely explanation. Nevertheless, increased serum insulin and HOMA-IR levels in the overweight mice with larger tumors may be considered indirect evidence for hyperinsulinemia as one mechanism by which obesity promotes pancreatic cancer development.

Leptin, the first identified adipokine, is widely considered to be a pro-inflammatory molecule and also has significant effects on the immune response.[12,13] In some tumor model systems such as breast and colon cancer, leptin promotes tumor growth.[14] Leptin's precise role in pancreatic cancer development and progression is less clear. Two clinical studies have shown pancreatic cancer patients to have reduced circulating leptin concentrations compared to patients with chronic pancreatitis or healthy control subjects.[15,16] In cell culture experiments, leptin promotes the growth of insulinoma cell lines but was shown to inhibit growth of a human pancreatic adenocarcinoma cell line in vitro.[17,18] In our previous study, murine pancreatic cancers grew larger in obese mice without leptin (Lep^{Ob}) as well as in those with hyperleptinemia (Lep^{Db}). In the current study, circulating leptin was significantly increased in overweight mice (with larger tumors) relative to lean animals, but no direct correlation between circulating leptin and tumor size or proliferation was observed. In vivo experiments specifically designed to up- and downregulate leptin will be necessary to more accurately define leptin's role in pancreatic cancer.

Similar to our prior murine study [5] and observations of human pancreatic cancer specimens [unpublished data], we again observed adipocytes within pancreatic tumors growing in both lean and overweight mice. Adipocytes comprised a relatively small proportion of tumor volume, and no difference was appreciated in adipocyte number between tumors growing in lean and overweight animals. The importance of the tumor microenvironment in pancreatic cancer growth, invasion, and metastasis is becoming clearer. To date, most investigation of pancreatic cancer microenvironment has focused on fibroblast–tumor cell interaction.[19,20] The fact that adipocytes are biologically active cells,[21] and that adipocytes in co-culture potentiate the growth of pancreatic cancer cells,[22] illustrates the potential paracrine effects of intratumoral adipocytes.

A growing body of evidence supports the concept that immune dysfunction influences pancreatic cancer growth.[6,7] As obesity itself perturbs the immune system, altered tumor immunology represents another potential mechanistic link between obesity and accelerated cancer growth. In the current experiments, we observed the presence of both T and B lymphocytes infiltrating tumors. Relatively fewer B lymphocytes were present, and no difference in the absolute number of tumor-infiltrating lymphocytes (either T cells or B cells) was observed between tumors growing in lean or overweight mice. Similar findings have been observed in our congenital obesity model of pancreatic cancer (unpublished data). The identification of tumor-infiltrating B cells, though, is novel; this intriguing observation surely warrants further investigation.

Several animal models have been used to study the effects of obesity on various metabolic parameters. These models include congenitally obese mice, in whom spontaneous mutations of either the ob (leptin) or db (leptin receptor) genes lead to hyperphagia and massive obesity, specific gene knockout (i.e., MCR 4),[23,24] or hypothalamic ablation.[25,26] Each of these models has individual limitations. For example, ob/ob mice have no leptin, massive obesity, and inherent immune dysfunction. In contrast, the diet-induced model of obesity is likely more representative of the true human obese situation. The diet-induced obesity model also may be applied to other tumor systems such as the kras/p57 gene mutant mice, which spontaneously

develop pancreatic cancers or nude mice with human tumor xenografts.[27]

In summary, our data show that even moderate weight gain (overweight) induced by dietary modification results in significantly accelerated growth of murine pancreatic cancers. Increased insulin and leptin, adipocytes in the tumor microenvironment, and immunologic perturbation all represent potential mechanisms by which obesity may influence the growth of pancreatic cancer. The diet-induced obesity model will be useful in further dissecting the specific mechanisms by which obesity influences the growth and dissemination of pancreatic cancer.

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Discussant

Dr. Frank Makowiec (Germany): Thank you very much for this interesting presentation. You presented new data from a very exciting in vivo model from your institution. You could demonstrate that obesity results in accelerated growth of pancreatic cancer in your nice model. You could also identify several mechanisms potentially promoting accelerated tumor growth.

I have two small questions and one comment to your data.

I did not see in your presentation and in the manuscript whether the diet was continued after tumor cell injection and whether the animals were still on low- or high-fat diet.

Do you think that obesity is more relevant in the early tumor development or in later tumor progression? Or is it relevant in both periods?

And here my comment regarding weight analysis: You correlated mouse weight with tumor weight. Since the tumor weight itself contributes to the mouse weight, I suggest that you repeat this analysis of weight correlation after subtraction of the tumor weight from the mouse weight to see if there is still a significant correlation.

Closing Discussant

Dr. Patrick B. White: To address your first point, the diet was continued after injection of the tumor cells. It was continued up until sacrifice at age 17 weeks.

In regards to your second question, in our prior model and with our current model, we have been looking at the diet as it extends from prior to tumor injection up until sacrifice. So we haven't proven whether the obesity or the high-fat diet is more important, in either the early or the late aspect of tumor growth, but we believe that it is important in both parts; both in the early tumor development and then continuing on as the tumor proliferates.

In our prior model with the congenitally obese mice, those mice developed metastases, whereas the lean mice did not. It is possible that, had we allowed this study to carry on longer, we might have seen metastases. We did not, in this study, see any metastases.

A repeat analysis, as you said, taking out the body weight as a factor, I think, would be an excellent idea. We did actually look at tumor weight as a proportion of body weight, and that remains statistically significant between the two groups, i.e. the overweight mice tumor weight divided by body weight was significantly larger than the lean mice tumor weight divided by body weight.

Discussant

Dr. B. Mark Evers (Lexington, KY): This is a very nice paper, but you've not really shown us mechanisms. Maybe in previous studies you have. As you know, obesity sets up an inflammatory response. Have you looked locally at what's happening in the pancreas? Have you, for example, determined whether NF-?B is activated or whether inflammatory cytokines are increased to see if this could be an explanation for your findings?

Closing Discussant

Dr. Patrick B. White: We believe there are both systemic and local effects of the adipocytes. We have been looking at this from a number of different avenues, both in humans and in the murine model. We have not specifically looked at NF-kappa b, but we think that the adipokines, coupled with the systemic inflammation and perhaps some local growth factors such as IGF and HGF, could be contributing to tumor growth. And we are exploring many of those routes with cell culture, through co-culture of adipocytes with pancreatic cancer cells and co-culture of pancreatic cancer cells with various growth factors.

Discussant

Dr. Michael G. Sarr (Rochester, MN): Is it the obesity, is it the diet, is it both of them? Have you thought about feeding the animals in a paired fashion, with number of calories, the two diets to see if it is the fat? There is a lot of literature on fat in the diet and malignancy.

Closing Discussant

Dr. Patrick B. White: Thank you, Dr. Sarr. In this model, the mice ate an equivalent amount of food in each of the two groups. However, the high-fat diet provided one third more calories than the low-fat diet.

We have not looked at the effect of different fats in a tumor model, but we have looked at it in a pancreatitis model with the administration of Omega 3 fatty acids. In the future, I think it would be quite interesting to look at tumor growth as a mechanism of diet. As you pointed out, some groups have done that with other cancers, but not with pancreatic cancer.

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2010 SSAT QUICK SHOT PRESENTATION

Transoral Incisionless Fundoplication 2.0 Procedure Using EsophyX™ for Gastroesophageal Reflux Disease

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Abstract
Background Transoral incisionless fundoplication (TIF) using the EsophyX™ system has been introduced as a possible alternative for the treatment of gastroesophageal reflux disease (GERD). The efficacy of this procedure in our centers was evaluated.
Methods Patients were selected for treatment if they had typical GERD symptoms, failed management with proton pump inhibitors (PPIs), a positive esophageal pH test with symptom correlation, and no hiatus hernia larger than 2 cm.
Results Nineteen patients (11 men, 8 women) underwent the TIF procedure between April 2008 and July 2009. Mean age was 48.2 years and body mass index was 24.6. The major complication rate was 3/19, including esophageal perforation, hemorrhage requiring transfusion, and permanent numbness of tongue. At mean 10.8 months follow-up, 5/19 had completely discontinued PPIs, and 3/19 had decreased their PPI dose. However, 10/19 had been converted to laparoscopic fundoplication for recurrent reflux symptoms and an endoscopically confirmed failed valve. Nine of 17 were dissatisfied with the outcome, and eight were satisfied. Thirteen of 19 (68%) were considered to have been unsuccessful.
Conclusion At short-term follow-up, the TIF procedure is associated with an excessive early symptomatic failure rate, and a high surgical re-intervention rate. This procedure should not be performed outside of a clinical trial.

Keywords Transoral incisionless fundoplication · Gastroesophageal reflux disease · EsophyX · Selected population

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Introduction

Gastroesophageal reflux disease (GERD) is the most common esophageal disease in the United States and other Western countries. Population-based studies have demonstrated that 11% of Americans experience daily symptoms of reflux and 33% experience symptoms during a 72-h period.[1] Pharmacologic suppression of gastric acid secretion using proton pump inhibitors (PPIs) is the most common approach for long-term management of GERD.[2,3] However, medical therapy requires lifelong commitment and is often not effective in patients with volume reflux. Laparoscopic Nissen fundoplication is the gold standard for the surgical treatment of GERD, and it results in complete symptom relief in more than 90% of patients.[4,5] Despite

these benefits, surgical therapy carries the risk of operative morbidity and postoperative side effects such as dysphagia, hyperflatulence, and bloating. Furthermore, reports of late failure coupled with the associated side effects have tainted public perception and negatively impacted referral for surgical intervention.[6] For this reason, attention has been focused on the development of less invasive, easy to perform, reproducible endolumenal treatments for GERD.[7–10] The most recent endolumenal technique, transoral incisionless fundoplication (TIF) has been introduced as a possible less invasive alternative for the treatment of GERD, yet still constructing a surgical type of fundoplication. The TIF procedure envelopes the distal esophagus within the proximal stomach, and uses transmurally placed polypropylene tissue fasteners to attach these structures. The end result is the creation of a nipple valve that is resistant to retrograde gastroesophageal flow in the face of elevated intra-abdominal pressure. Initially, the TIF procedure entailed the construction of an omega-shaped valve of >220° by gastro-gastric plication (TIF 1.0). Subsequently, the procedure was modified (TIF 2.0) to construct a nipple valve of >240°, enveloping a segment of distal esophagus within the gastric fundus (gastroesophageal plication). The efficacy and safety of the TIF 2.0 procedure was demonstrated within an animal model over short-term follow-up.[11] Several clinical studies have evaluated the safety and efficacy of transoral fundoplication in patients with chronic GERD.[12–17] There has been a wide range of results reported for the TIF procedure, with rates of PPI cessation ranging from 25% to 83% within various studies (Table 1). We evaluated the efficacy and safety of the TIF 2.0 procedure as a substitute for a laparoscopic fundoplication in our centers.

Materials and Methods

Study Design

From April 2008 to July 2009, consecutive patients who had undergone the TIF 2.0 procedure at three tertiary care medical centers in USA and Australia were evaluated using a protocol approved by the institutional review board of each institution (note—all Australian patients were followed prospectively by a research nurse). These patients were referred to our practices for the surgical treatment of GERD. All patients underwent preoperative upper endoscopy, pH monitoring, and esophageal manometry. Most also underwent a barium esophagram before surgery. Patients were selected based on the following criteria; PPI responsive typical GERD symptoms (heartburn and/or regurgitation), positive esophageal pH test with >50% symptom correlation, and absent or small (<2 cm) hiatus hernia. The esophageal pH test was considered positive when the total period of time pH <4.0 is greater than 5.3%.[18] Pre-procedure valve grading was performed using the Hill classification system.[19] If any of the following exclusion criteria were met, the TIF 2.0 procedure was not offered: presence of larger (≥2 cm) hiatus hernia, severe esophagitis (>LA classification grade C), Barrett's esophagus, and severe esophageal motility disorders such as an aperistaltic esophagus. Patients underwent the TIF 2.0 procedure after informed consent was obtained, and alternative surgical and medical options were fully discussed.

Transoral Incisionless Fundoplication (TIF2.0) with the EsophyX Device

In this study, we used the EsophyX™ device (EndoGastric Solutions, Redmond, WA). The procedures were performed using the same technique at each site. The EsophyX™ device was inserted transorally over a standard 9.8 mm forward-viewing endoscope (Olympus America, Inc., Allentown, PA). The patient was placed in left decubitus position under general anesthesia with transnasal endobronchial intubation. The operator operated the device and controlled the implantation of fasteners, while the assistant operated the endoscope and ensured continuous visualization throughout the procedure. The fastener deployment process was initiated on the far posterior and anterior sides of the esophagogastric valve adjacent to the lesser curvature. During anterior and posterior fastener deployment, the tissue mold was rotated axially to slide the stomach over the esophagus, resulting in circumferential tightening and a valve circumference of >240°. Additional fasteners were

Table 1 Summary of previous clinical trials

Authors	Year	Follow-up	TIF	No.	Complication	Off PPI (%)
Cadiere GB, et al.	2008	12 months	1.0	84	3.6% (n=3)	83
Bergman S, et al.	2008	60±44 days	2.0	8	none	25
Demyttenaere SA, et al.	2009	10 months	2.0	26	7.7% (n=2)	32
Cadiere GB, et al.	2009	2 years	1.0	14	–	71
Repici A, et al.	2010	6/12 months	1.0	20	10% (n=2)	46
Testoni PA, et al.	2010	6 months	2.0	20	none	55.6

placed 3 to 4 cm proximal to the squamocolumnar junction on the esophageal side, thereby enveloping a longer segment of distal esophagus within the gastric fundus.

At the end of the procedure, Hill classification and the appearance of the newly created valve were recorded. During the TIF 2.0 procedure, procedural findings, complications, and results were recorded. A satisfactory TIF procedure was confirmed intra-operatively based on the endoscopic finding of a well-defined nipple valve (Fig. 1a). Patients were scheduled to stay in hospital overnight and a barium esophagram was obtained on the morning following the procedure. Patients were instructed to follow a liquid diet for 1 week and a soft diet for 5 weeks, and to avoid heavy lifting of greater than 10 kg for 6–8 weeks. PPIs were discontinued immediately following the procedure. The TIF 2.0 procedure was performed by a surgeon, who had previous experience and training in "in vivo" animal models. All surgeons underwent initial training provided by the device manufacturer, EndoGastric Solutions. In Pittsburgh, the surgeon undertaking the procedures had prior human clinical experience, whereas in Australia, both surgeons were proctored by an experienced operator.

Follow-Up and Data Collection

Patients were seen in the clinic for clinical follow-up at 2 and 6 weeks. A history, physical examination and review of symptoms and medication use were performed. Follow-up endoscopy was performed if patients had recurrent symptoms. Follow-up phone call was performed at 6 and 12 months to reevaluate medication use and patients satisfaction. In Australia this was undertaken by a research nurse, and in Pittsburgh by a research coordinator.

We defined a "failed TIF procedure" as (1) recurrent symptoms requiring resumption of PPIs, followed by resolution or amelioration of symptoms and (2) valve failure confirmed endoscopically. Valve failure was defined as a recurrent patulous Hill classification grade III valve, and H-fasteners which were observed to have pulled through the esophagus or stomach wall (Fig. 1b). If patients had a "failed TIF procedure", PPI medication was a first-line treatment. If this was inadequate or the patient wished an anatomic reconstruction, a redo-TIF procedure or revision to a laparoscopic Nissen or partial fundoplication was considered.

Results

Nineteen patients (11 men and 8 women) underwent the TIF 2.0 procedure between April 2008 and July 2009. Eleven patients were treated at University of Pittsburgh (UP), four at Flinders Medical Centre (FMC), and four at the Alfred Hospital (AH). Patient demographics and procedural data are summarized in (Table 2). Mean age and body mass index were 48.2 (range 26–81) years and 24.6 (range 19.6–29.4), respectively. ASA classification included 1 (n=9), 2 (n=8), and 3 (n=2). Preoperatively, 13 patients had heartburn and 14 had regurgitation. Six had

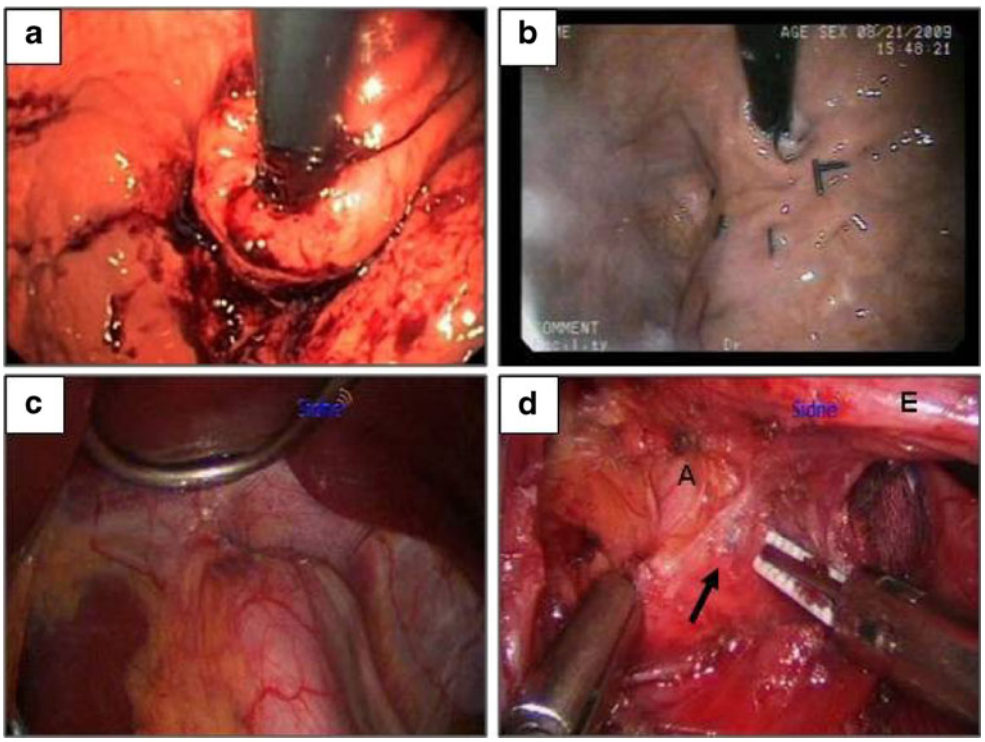

Fig. 1 Endoscopic and laparoscopic findings of TIF. **a** A well-defined nipple valve immediately after the TIF 2.0 procedure. **b** and **c** demonstrate valve failure confirmed by endoscopic and laparoscopic examination, respectively. **b** A recurrent patulous Hill classification grade III valve was observed endoscopically and H-fasteners had pulled through from esophagus. **c** In those who underwent laparoscopic revision, failure was determined to be when the stomach was pulled away from esophagus. **d** A pull-through H-fastener was found adjacent to aorta during the laparoscopic revision. *A* aorta, *E* esophagus, *arrowhead H*-fastener

Table 2 Patients demographics and procedure data

Patient demographics	
n	19 (UP 11, FMC 4, AH 4)
Female/male	8/11
Age (years)	48.2 (range, 26–81)
BMI ($kg\,m^{-2}$)	24.6 (range, 19.6–29.4)
ASA classification	1 (9), 2 (8), and 3 (2)
Preoperative symptoms	Heartburn (13)
	Regurgitation (14)
	Atypical + typical symptoms (6)
LES pressure	Hypotensive (11)
	Normotensive (8)
Esophageal motility	Normal motility (15)
	Ineffective esophageal motility (4)
pH monitoring test	Abnormal (10), normal (6)
Time pH <4.0 (%)	8.4 (range, 0.2–24.3)
Procedure data	
Procedure time (min)	98.3 (range, 50–193)
Hospital stay (day)	1 (range, 1–3)
Complicationss	15.8% (3/19) (UP 3, FMC/AH 0)
Redo-Esophyx	15.8% (3/19) (UP 3, FMC/AH 0)
Conversion to lap-fundoplication	52.6% (10/19) (UP 5, FMC 2, AH 3)

UP University of Pittsburgh, *FMC* Flinders Medical Centre, *AH* Alfred Hospital

typical GERD symptoms as well as atypical symptoms which included hoarseness, sore throat, cough, and shortness of breath.

Preoperative manometry demonstrated that eight patients had a normotensive lower esophageal sphincter (LES) and 11 had a hypotensive LES (normal range of LES pressure, 4.8–32.0 mmHg). Fifteen had normal esophageal motility and four had ineffective esophageal motility. Two of the four patients with ineffective esophageal motility had low amplitude esophageal peristalsis (21 and 27.5 mmHg mean wave amplitude, respectively), and the other two had failure of propagation of peristalsis in 40% and 60% of swallows, respectively. No hiatus hernia was present in 15 patients at preoperative endoscopy and esophagram. The other four patients had a 1 cm length hiatus hernia. Endoscopy showed a Hill classification II or III valve in the 15 patients who did not have a hiatus hernia. The preoperative pH monitoring test was performed on 17 patients. Two patients did not undergo pH testing because of the presence of a cardiac pacemaker. Eleven had an abnormal pH monitoring test based on the prolonged total period of time pH <4.0 (normal range, <5.3%). A mean of total period of time pH <4.0 was 8.4% (range, 0.2–24.3%). In six patients pH was less than 4.0 for less than 5.3% of the study duration, but with a 100% correlation between symptoms and acid reflux events. Additionally, all these six patients had PPI responsive typical GERD symptoms.

The mean procedure time was 98.3 min (range, 50–193 min) and the mean length of hospital stay was 1 day (range, 1–3 days). A satisfactory TIF 2.0 procedure was confirmed endoscopically in all patients at the end of procedure. All patients had postoperative upper abdominal or shoulder pain which required narcotic analgesia for a mean of 1 day (range, 1–5 days). Two patients required readmission because of nausea and hemorrhage. Three of 19 (15%) patients (UP) had major complications including esophageal perforation ($n=1$), hemorrhage requiring blood transfusion ($n=1$), and permanent numbness of tip of tongue ($n=1$). All of these complications were managed non-operatively. There were no major postoperative complications experienced at FMC and AH. All patients had initial good resolution of reflux symptoms, and successfully discontinued PPIs at the time of discharge.

At mean 10.8 months follow-up (range, 4–19 months), recurrent symptoms of heartburn were present in 10 patients, regurgitation in 10, dysphagia in 1, and atypical symptoms in 3. Five patients (26.3%) had completely discontinued PPI therapy, and three (15.8%) were able to decrease the dose of PPI from twice a day to once a day, or change to H_2 blockade. Three out of 19 (15.8%) patients (UP) underwent a redo-TIF procedure, and eventually 10 out of 19 (52.6%) patients (5 at UP, 2 at FMC, and 3 at AH) underwent conversion to a laparoscopic fundoplication (8 Nissen, 2 anterior partial) for a "failed TIF procedure" and recurrent PPI responsive GERD symptoms. Most patients (9/10) who underwent fundoplication had complete symptoms resolution at early follow-up (<1 year). Of the three patients who underwent a redo-TIF procedure, two ultimately failed again and went on to have laparoscopic Nissen fundoplication. At final examination, 13 out of 19 (68.4%) patients had a failure of the TIF procedure requiring re-intervention and/or the same dose of PPIs for recurrent GERD symptoms. At follow-up, 9 patients (53%) were dissatisfied with the outcome of the TIF 2.0 procedure, and only 8 (47%) were sufficiently satisfied with the outcome to "recommend the TIF procedure to a friend".

Discussion

GERD is caused by a deficient or absent gastroesophageal valve mechanism. The principal of surgical treatment for

GERD is to restore a functional gastroesophageal flap valve, with laparoscopic Nissen fundoplication being the gold standard surgical treatment. In this procedure, a valve is re-created by wrapping the end of esophagus with the gastric fundus. Over the past 15 years, a range of endolumenal approaches for the treatment of reflux have been developed and studied. Such therapies include plication techniques using such devices as the Endocinch (Endocinch; C.R. Bard, Inc., Murray Hill, NJ, USA),[7] the NDO Plicator (NDO Surgical, Mansfield, MA, USA), and radiofrequency energy delivered to the LES (Stretta; Curon Medical Inc, Fremont, CA, USA)[8] and injectable prosthetics such as Gatekeeper (Endonetics, San Diego, CA, USA)[9] and Enteryx (Boston Scientific, Boston, MA, USA).[10] Unfortunately, most of these devices aimed to narrow the gastroesophageal junction, and consequently clinical effectiveness was not demonstrated, with most of the companies no longer financially viable.

The EsophyX device was introduced more recently, and it is the first commercially available endolumenal device to attempt to mimic antireflux surgery by constructing an actual fundoplication. The initial efficacy of the device was demonstrated in a company sponsored European multicenter trial of 84 patients.[12] This study showed that 68% of the patients were not using any PPI medication at the 12-months follow-up. A clinically significant improvement in GERD-HRQL was achieved for 73% of the patients, but 20% were dissatisfied with their health condition. Acid exposure was reduced for 61% of the patients, but normalized for only 37%. Recently, they reported 2-years follow-up of these patients.[15] Even after 2 years, the TIF procedure achieved effective control of heartburn in 93% of patients and resulted in complete elimination of the need for antisecretory medication in 71% of patients. However, there has been a wide range of effectiveness reported among other published clinical trials, suggesting that the outcome of TIF procedure may not be stable or the technique may not easily reproducible. For the TIF procedure to be acceptable for routine clinical use, it needs to produce predictable and reliable results. Arguably, the outcome should be similar to that of conventional antireflux surgery in appropriately selected patients.

In our study, patients were selected based on the presence of PPI responsive typical GERD symptoms such as heartburn and/or regurgitation, a positive esophageal pH test, absent or small hiatus hernia (<2 cm), as well as absence of complicated reflux disease, Barrett's esophagus or a severe esophageal motility disorder. It is expected that patients meeting these selection criteria will have a good result from surgical fundoplication, with the likelihood of success at 12 months or longer follow-up exceeding 90%. Unfortunately, the success rate for TIF was much less than this, with more than 50% requiring surgery for recurrent reflux symptoms within the first 12 months follow-up, and only 26% able to cease all antisecretory medication following their TIF procedure.

At the completion of each procedure in our series, a well-defined nipple valve was visible, and all patients had good resolution of symptoms and completely discontinued PPI at the time of discharge. Our data suggests that in the majority of patients, the TIF procedure only controls GERD symptoms for a short period of time, and the rate of failure following this procedure was unacceptably high. The overall rate of patient satisfaction was poor with only 47% satisfied with the outcome. This compares poorly with the outcome for laparoscopic fundoplication at similar follow-up.

It is possible that there is a substantial learning curve for the TIF procedure, and this may influence our outcomes. However, all surgeons who performed the procedures in this study underwent initial training in an "in vivo" animal model provided by the device manufacturer, and had either prior human clinical experience, or were proctored on site by the device manufacturer's staff. Additionally, one of surgeons was among the developers of the technique (TIF 2.0). Finally, all participating surgeons are very experienced in performing laparoscopic antireflux surgery as well as flexible endoscopy. For these reasons, it seems unlikely that our outcomes were adversely impacted by a learning curve bias. Further, in all patients, immediate post-procedure endoscopy confirmed the construction of a satisfactory repair, and the initial outcomes suggested clinical success.

Why might the failure rate be high? In the TIF procedure, the nipple valve was created by invaginating the distal esophagus within the proximal stomach. Unfortunately, mobilization of stomach cannot be achieved to reduce the tension on gastric fundus, and this could apply continuous downward forcing tension onto the fundoplication and cause the H-fasteners to pull through from esophagus, leading to valve failure. This "suture loss" has been a persistent problem with every endolumenal procedure reported to date. Previous animal experiments suggested that endoscopic mucosal suturing performed with the EndoCinch™ device was unable to hold the repair in place permanently.[20,21] With the TIF 2.0 procedure, it was hoped that the placement of full-thickness fasteners at several locations around the valve circumference would overcome this problem by "un-weighting" the tension placed on any one fastener. Our experience suggests that this benchmark has not been realized, and that the natural process of the body to "heal" back to its original shape has worked against the formation of a permanent and symptom relieving endoscopic fundoplication.

Furthermore, based on our experience, a prior TIF procedure can make possible late laparoscopic fundoplication technically more challenging. This is because of

adhesions which develop between the esophagus and proximal stomach at the level of the esophagogastric junction and pull-through of fasteners, which were sometimes discovered within the crural pillars and adjacent to the aorta (Fig. 1d). What was consistent with the failed TIF procedures was that at revision surgery the repair had loosened and unraveled based on both endoscopic and laparoscopic examination, compared to the wrap constructed at the original procedure.

Another objective of our study was to evaluate the safety of the TIF procedure. Previous clinical trials have demonstrated that the rate of major complications ranged from 3.6% to 10%. In our study, although all major complications were treated non-operatively, the major complication rate was 15.8% (3/19), consistent with the higher end of the complication rates published previously. In the case complicated by esophageal perforation, there was difficulty deploying full-thickness fasteners due to device failure. This might lead to an incorrect angle of deployment of fasteners, thereby leading to perforation. Including this case, we experienced a device failure in three cases. Additional refinement in the design of the device might help reduce the risk of major complications.

There were several limitations to our study. One is the relatively small number of patients collated in this study. However, it is now very difficult for any of us to convince any patient presenting to us for antireflux surgery to undergo the TIF procedure, and this means that further patient recruitment is unlikely to happen. Another problem is the lack of routine postoperative objective tests such as esophageal pH testing to assess the effectiveness of this procedure. However, we defined a "failed TIF procedure" based on clinical recurrent symptoms with requirement to resume PPI therapy after good resolution of symptoms as well as endoscopically confirmed valve failure. Clinically, all patients had a good symptomatic response to the initial TIF 2.0 procedure and then developed recurrent symptoms requiring PPIs. However, all patients except one who underwent revision to a laparoscopic fundoplication had complete resolution of recurrent symptoms after their fundoplication. The clinical presentation of these patients supported the assessment that the TIF procedure had failed. A further limitation was that we did not apply a pre- and postoperative quality of life score such as the GERD health-related quality of life score. Nevertheless, the questions asked did address overall patient satisfaction with the outcome of their procedure.

In conclusion, in our hands the TIF 2.0 procedure was associated with a significant complication rate, and an unacceptably high symptomatic failure rate which required surgical re-intervention at short-term follow-up. At this point in time, the TIF 2.0 procedure should not be performed outside of a well-designed clinical trial.

Conflict of Interest Statement In August 2008 Andrew Smith and David Watson received support from Endogastric Solutions (Australian distributor for the EsophyX™ device) for travel from Australia to Seattle for training in the TIF procedure. The training was provided by Endotherapeutics. Blair Jobe underwent procedure training in Seattle at the Endogastric Solutions facility. Along with Stefan Kraemer, the device inventor, Dr. Jobe developed the TIF 2.0 procedure and this approach was validated within a preclinical study funded by Endogastric Solutions.

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ORIGINAL ARTICLE

Transcervical Heller Myotomy Using Flexible Endoscopy

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Abstract
Introduction Esophageal achalasia is most commonly treated by laparoscopic myotomy. Transesophageal approaches using flexible endoscopy have recently been described. We hypothesized that using techniques and flexible instruments from our NOTES experience through a small cervical incision would be a safer and less traumatic route for esophageal myotomy. The purpose of this study was to evaluate the feasibility, safety, and success rate of using flexible endoscopes to perform anterior or posterior Heller myotomy via a transcervical approach.
Methods This animal (porcine) and human cadaver study was conducted at the Legacy Research and Technology Center. Mediastinal operations on ten live, anesthetized pigs and two human cadavers were performed using standard flexible endoscopes through a small incision at the supra-sternal notch. The esophagus was dissected to the phreno-esophageal junction using balloon dilatation in the peri-esophageal space followed by either anterior or posterior distal esophageal myotomy. Success rate was recorded of esophageal dissection to the diaphragm and proximal stomach, anterior and posterior myotomy, perforation, and complication rates.
Results Dissection of the esophagus to the diaphragm and performing esophageal myotomy was achieved in 100% of attempts. Posterior Heller myotomy was always extendable onto the gastric wall, while anterior gastric extension of the myotomy was found to be more difficult (4/4 and 2/8, respectively; $P=0.061$).
Conclusion Heller myotomy through a small cervical incision using flexible endoscopes is feasible. A complete Heller myotomy was performed with a higher success rate posteriorly possibly due to less anatomic interference.

Keywords NOTES · Flexible endoscopy · Achalasia · Heller myotomy · Mediastinoscopy

Introduction

The last several years has seen a rapidly increasing interest in the use of flexible endoscopy outside of the confines of the GI tract. While the initial focus of the "NOTES" (Natural Orifice Translumenal Endoscopic Surgery) approach was the replication of laparoscopic operations, more recently, investigators have been exploring other areas such as the thorax, retroperitoneum, and mediastinum.[1–6] Mediastinoscopy using variations of rigid endoscopes has existed for over 60 years.[7] Access to the esophagus and distal mediastinum was, however, difficult if not impossible with rigid scopes. Several researchers have recently experimented with translumenal, flexible endoscopic approaches to mediastinal surgery.[5,8,9] In particular, there has been an interest in the possibility of performing esophageal myotomy (Heller myotomy) for achalasia. Transesophageal myotomy, first described by Pasricha et al., has in fact, already found its way into the clinical setting.[6,10] There remains great concern however regarding possible catastrophic complications from the esophagotomy needed for transesophageal approaches.

As it is well established that the cervical approach for mediastinoscopy is safe and well tolerated[11] and based on

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our own experience with flexible endoscopic surgery (endoluminal, translumenal, and via single port access), we considered that accessing the distal esophagus for a Heller myotomy would be feasible by using a combination of endoluminal endoscopy and flexible endoscopes inserted through a single small, cosmetically advantaged incision in the low neck.[12] While such an approach to a myotomy would be slightly more (visibly) invasive than the transesophageal approach, it is still less invasive than the typical five-incision laparoscopic approach and avoids the potential risks associated with perforating the esophagus. It also presents the opportunity to preserve the suspensory structures of the lower esophageal sphincter, which are necessarily disrupted with the laparoscopic approach, and thereby may reduce the need for an anti-reflux surgery.[10] Experience achieved with flexible endoscopic surgery in the mediastinum using this safe approach may eventually be adapted to a translumenal, "incisionless" protocol, when esophageal closure methods have improved.

We hypothesized that a transcervical flexible approach to the inferior visceral mediastinum to perform Heller myotomy would be feasible and that either an anterior or posterior Heller myotomy could be safely performed.

Methods

This study was conducted under a protocol approved by Legacy Institutional Animal Care and Use Committee (IACUC). Ten pigs (35–60 kg) were included in the study as well as two male human cadavers. Standard dual and single channel endoscopes (GIF 2T160 and GIF 140, respectively; Olympus, Tokyo, Japan) were used through a small cervical incision to perform mediastinal operations on the animals and the human cadavers. The endoscopes were connected to two CV-180 video processors and CLV-180 Xenon light sources (both Olympus) and displayed on two monitors (PVM-20M2MDU, Sony, Tokyo, Japan).

The animals were set on liquid diet for 24 h prior to the procedure. General anesthesia was induced with Telazole (6–8 mg/kg) and Atropine (0.06 mg/kg). The animals were then placed in supine position on the operating table, on a warm water circulating blanket, and endotracheal intubation was performed. An isoflurane (1.5%–3%) inhalation anesthesia was maintained throughout surgery; cardiac monitoring, pulse oximetry, end tidal CO_2, and blood pressure monitoring ensured a normal physiologic response to the anesthetic agent and CO_2 insufflation. If there were hemodynamic or respiratory problems, the mediastinum was deinsufflated, and if breath sounds were diminished, a needle was introduced into the pleural space to check for a pneumothorax. If there was one, chest tubes were placed. After the procedure, the animal was euthanized with sodium pentobarbital (80 mg/kg).

Surgical Technique

A small, transverse skin incision was made two-finger breadths above the supra-sternal notch in the human

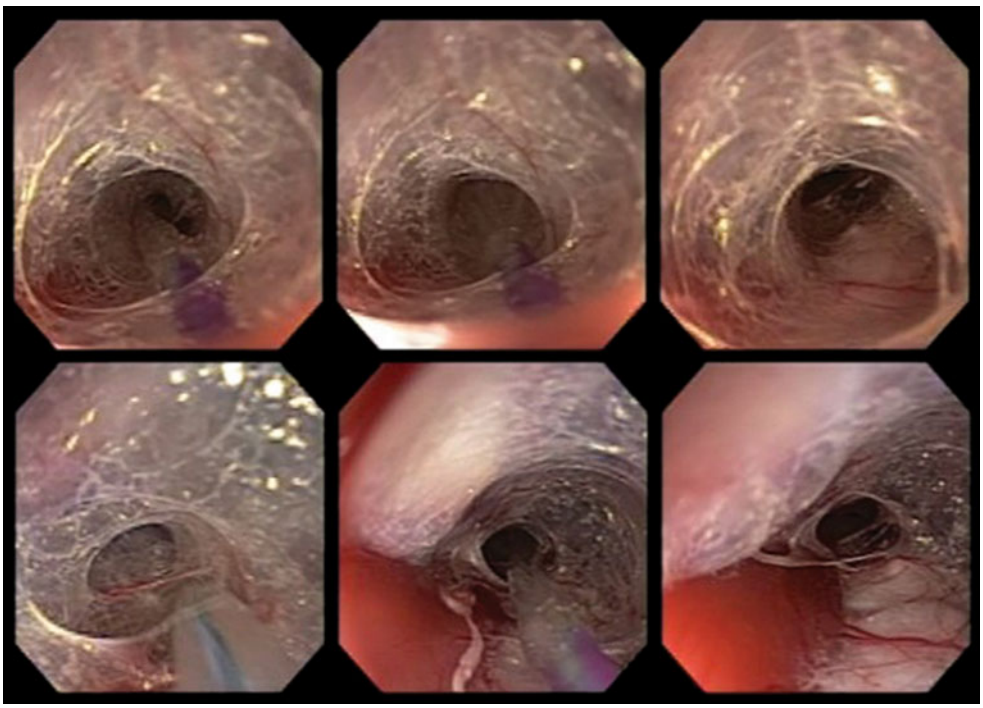

Fig. 1 A standard endoscopic dilatation balloon is used to create a connective tissue tunnel in which the endoscope can follow the esophagus (visible between 6 and 8 o'clock) safely

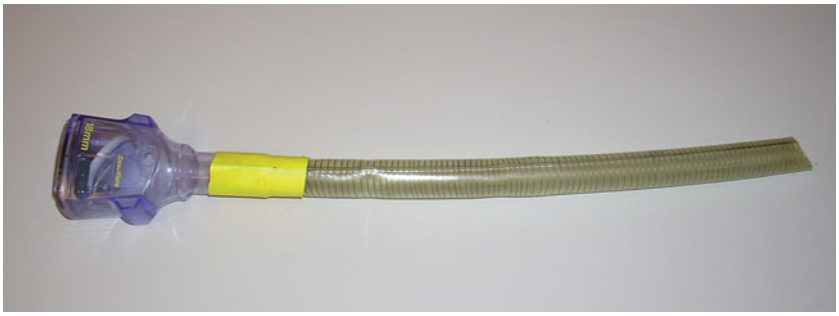

Fig. 2 The modified overtube is used to protect the cervical anatomy and facilitates endoscope insertion and removal. The endoscopic port was used with open insufflation valve to avoid mediastinal over-pressure. CO_2 insufflation was provided over the scope (minimal flow)

cadavers. When operating on pigs, we performed a longitudinal incision. Platysma and superficial cervical fascia were dissected using electrocautery, and the pretracheal muscles were separated vertically to expose the trachea. Dissection was performed on the left side of trachea and esophagus, and the left recurrent laryngeal nerve was routinely visualized. The pre- or post-esophageal plain was entered using both blunt and sharp dissection, and the esophagus was followed distally for 2 cm. The light of a second endoscope in the esophagus was useful to easily identify the esophagus from the outside through the small cervical incision.

The sternocleidomastoid muscle and carotid sheath were retracted laterally, the trachea to the opposite side, and the thyroid gland cranially. The endoscope was then inserted in the pre- or post-esophageal plane and blunt dissection with a grasper, or by sequentially advancing an endoscopic balloon (CRE 5842 and 5843, 12–15 and 15–18 mm, Boston Scientific, Natic, MA, USA), inflating it, and then advancing the scope along the resulting tract; it was used to follow the esophagus in a distal direction (Fig. 1). A modified flexible 18-mm overtube (NOTES toolbox, Ethicon Endo-Surgery, Cincinnati, OH, USA; Fig. 2) was used to protect the cervical anatomy, allowing atraumatic changes of the endoscope during the surgery and evacuation of insufflated gas.

CO_2 insufflation was provided through the overtube using laparoscopic insufflators with a maximal pressure of 8 mmHg for the first three animals; for the following seven animals, CO_2 insufflation was achieved using the endoscope but with a special insufflation flow reducer to avoid over-insufflating the mediastinum (Water bottle, MAJ-902, Olympus; pressure reduction valve, M1-940-12FM Western Medica, Wastlake, OH, USA).

The esophagus was followed to the diaphragm, and a Heller myotomy was performed in a manner similar to laparoscopic myotomies, starting proximally and extending well onto the gastric wall (Fig. 3). The full thickness of the muscle layers was divided and spread using a variety of flexible endoscopic instruments, both currently available and new prototype ones designed for NOTES (Table 1), such as articulating hook (Fig. 4) or needle knife, articulating graspers, and flexible Maryland Graspers (all NOTES toolbox, Ethicon Endo-Surgery); standard endoscopic instrumentation like snares and hook knifes (SD-221L-25 and KD-620LR, respectively; both Olympus), transparent caps (Fig. 3; cap of Speedband SuperView Super 7 Multiple Band Ligators; Boston Scientific Microvasive; or D-402-13212; Olympus), and balloon dilator (10–12 mm, CRE 5841; Boston Scientific Microvasive). We incidentally found that it was easier to perform the myotomy posteriorly. There seemed to be less dense connective tissues in the plane of dissection, and there was less risk of entering the peritoneal cavity with subsequent pneumoperitoneum.

A second endoscope in the esophagus facilitated orientation and was used to check for perforations and completeness of the myotomy.

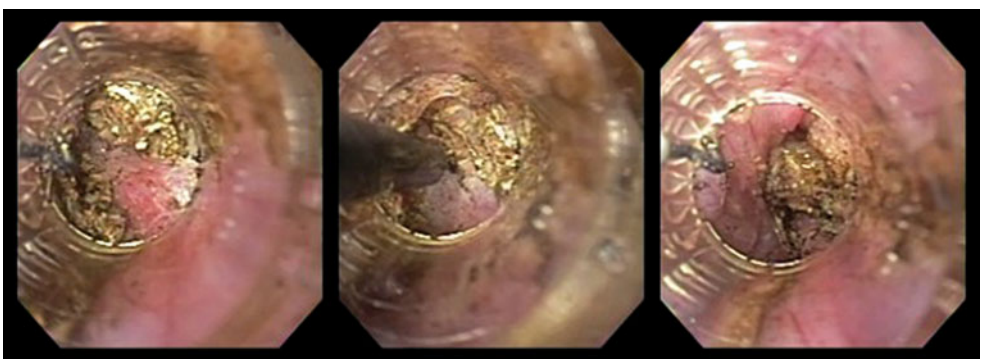

Fig. 3 Heller myotomy was performed using mostly standard endoscopic instruments like hook knife and transparent cap. The submucosal layer is visible between 3 and 6 o'clock (esophago-gastric junction). The prominent muscularis propria (already divided) of the stomach is visible in the upper quadrant of the cap between 10 and 3 o'clock

Table 1 Endoscopic instrumentation used with the standard endoscopes

Endoscopic instrument	Currently available	NOTES prototype	Manufacturer
Dissecting cap	+		Boston Scientific, Olympus
Balloon dilator (10–18 mm)	+		Boston Scientific
Polypectomy snare	+	+	Olympus, Boston Scientific, Ethicon
Hook knife	+	+	Olympus, Ethicon
Articulating hook knife		+	Ethicon
Articulating needle knife		+	Ethicon
Flexible Maryland dissector		+	Ethicon

Commercially available instrumentation and NOTES prototypes used for the endoscopic dissection and myotomy

Analysis

Necropsy was performed after the procedures in animals and human cadavers to assess the quality of the dissection. Operation time for the different steps of the procedure was recorded. Quality control called for a minimum length of 4 cm for the myotomy and 2 cm extension of the myotomy onto the gastric wall (Fig. 5). Failure to extend the myotomy onto the gastric muscularis propria was noted. Critical errors (death of the animal, injury of blood vessels, intraoperative laceration of the pleura, intraoperative laceration of the main bronchus, esophageal injury, injury of other vital organs, thoracic duct leak, injury of recurrent or vagal nerve, and blood loss >200 ml in animal studies) were documented. Comparisons were made between anterior and posterior myotomy performed on animals and cadavers on the critical errors, operative complications, operative times, and length. Categorical variables are compared using Fisher's exact test, and continuous variables have been compared with the unpaired Student *t* test (two sided, two tailed). *P* value <0.05 was considered statistically significant.

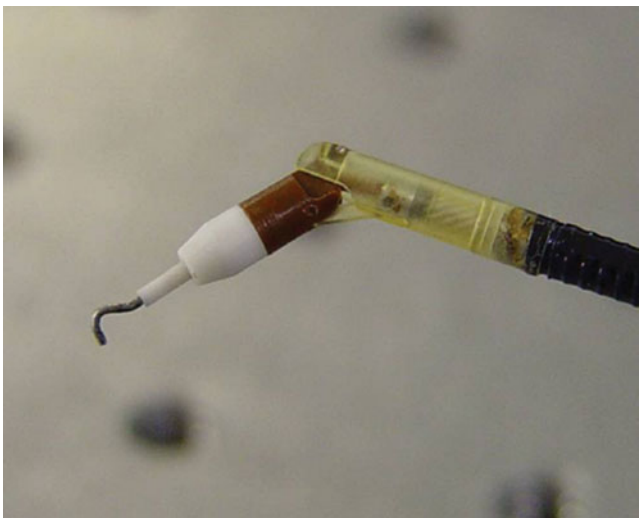

Fig. 4 A flexible articulating hook knife (prototype from a NOTES toolbox) has been used to create the first opening in the muscularis safely

Results

Dissection of the esophagus to the diaphragm and performing an esophageal myotomy was achieved in 100% of attempts. The esophagus was easily followed to the gastro-esophageal junction. The blood supply to the esophagus from the inferior thyroid arteries, the branches from the bronchial arteries, and aortic perforators could be partially visualized and avoided by creating connective tissue tunnels using blunt dissection. The small confines of the connective tissue tunnels provided excellent stability for the endoscope and allowed safe advancement and manipulation. Dissection through the phreno-esophageal ligament was more difficult. Table 2 provides a summary of procedure times and details about the performed myotomies.

Myotomy of the esophagus was successful 100% (12/12) of the time. Extension of the myotomy 2 cm onto the gastric wall was successful in 50% (6/12) of attempts (Fig. 5). Anterior myotomy was performed in seven pigs and one human cadaver, and posterior myotomy was performed in three pigs and a human cadaver. Posterior Heller myotomy was more often extendable onto the gastric wall for 2 cm than anterior myotomy. A 25% success rate (2/8) was recorded when the myotomy was performed anteriorly, and a 100% success rate (4/4) when performed posteriorly. However, due to the small numbers used in our feasibility study, the difference was not found to be statistically significant ($P=0.061$). Differences between anterior and posterior myotomy regarding esophageal dissection time, time for myotomy, length of myotomy, number of perforations, and blood loss were not found significant (Table 3).

One 20-mm-long esophageal perforation occurred in a human cadaver in the mid-portion of the esophagus during

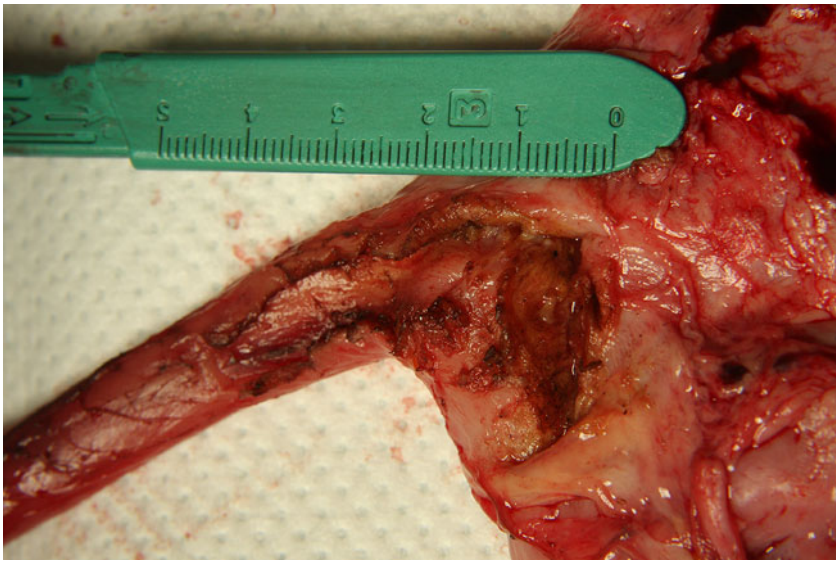

Fig. 5 Result of a successful posterior myotomy with extension onto the gastric wall

blind advancement of an overtube over the inserted endoscope. Unfortunately, the patient had had previous thoracic radiation and chemotherapy with an angled fixation of the esophagus to the right side, which facilitated the perforation to a high degree. The esophageal perforation could be closed endolumenally with T-anchors (Tissue Apposition System, NOTES toolbox, Ethicon Endo-Surgery). Three small (2 mm) perforations occurred during myotomy; all were closed by endoscopic clipping (Fig. 6; Resolution Clips, Boston Scientific Microvasive) and were well sealed by air leak testing. Minor bleeding (<10 ml) occurred in four myotomies, which were easily treated with electrocautery. Chest tubes were not used in the pig model during the myotomies. No death or severe complication occurred during the myotomies or related dissection in the pig model.

Discussion

Mediastinal surgery through a transcervical incision in the form of scalene lymph node biopsy originated over 60 years

Table 2 Procedural detail of the myotomies

	Heller myotomy	Cervical diss. (min)	Esoph. diss. (min)	Heller (min)	Myotomy length (cm)	2-cm gastric extension of myotomy	Perf.	Perf. diameter (mm)	Perf. management	Blood loss (ml)
Pig 1	Anterior	32	24	35	6	No	No			5
Pig 2	Anterior	11	6	8	4	No	No			0
Pig 3	Anterior	10	8	25	5	No	No			0
Pig 4	Anterior	9	8	20	5	No	No			0
Pig 5	Anterior	22	16	60	4	Yes	No			8
Pig 6	Posterior	31	11	55	6	Yes	No			0
Pig 7	Anterior	39	36	40	6	Yes	Yes	2	Endoscopic (clips)	5
Pig 8	Anterior	16	15	35	5	No	No			0
Pig 9	Posterior	28	23	51	5	Yes	Yes	2	Endoscopic (clips)	0
Pig10	Posterior	19	11	30	6	Yes	No			5
Cad.1	Anterior	35	30[a]	33	4	No	Yes	20[a]	T-anchors	n.a.
Cad.2	Posterior	15	26	55	5	Yes	Yes	2	Endoscopic (clips)	n.a.

Procedural details of Heller myotomies performed transcervically

Cad. human cadaver, *diss.* dissection, *Esoph.* esophagus, *Perf.* perforation

[a] Perforation of mid-portion of esophagus from outside (post radiation); time for esophageal closure (t-anchors) not calculated

Table 3 Detailed comparisons between anterior and posterior cardiomyotomy

Heller myotomy	Type of myotomy		Significance
	Anterior	Posterior	
Esophageal dissection (min)	17.9±11.1	17.8±7.9	n.s.
Heller myotomy (min)	32.0±15.3	47.8±12.0	n.s.
Myotomy length (cm)	4.9±0.8	5.5±0.6	n.s.
2-cm gastric extension of myotomy	25%	100%	n.s.
Perforation	25%	50%	n.s.
Blood loss (ml)	2.6±3.4	1.7±2.9	n.s.

Procedural details (average ± standard deviation) of the myotomies and significance level

n.s. not significant

ago.[7,13] Currently, mediastinoscopy with short rigid tools is an established, safe, and minimally invasive surgical procedure for diagnosis of anterior mediastinal lymph nodes or masses.[11] Since the early 1990s, the concept of expanding the use of mediastinoscopy to perform more advanced procedures through a cervical approach has been explored by different researchers using larger rigid platforms with the ability to perform simple bimanual tasks.[11,14–18] While generally adequate for superior mediastinal surgery, access beyond the tracheal bifurcation requires significant and difficult dissection to achieve sufficient working space for triangulation at the tip of the instruments. The other limitation with this type of rigid platform is the awkwardness of the extremely long rigid tools and the difficulty manipulating targets that are farther away.

We demonstrate that the use of flexible endoscopes allows advanced mediastinal dissection with little trauma because these instruments can operate in the small confines of connective tissue tunnels, which can be created by simple, atraumatic dilatation (Fig. 1). All blood vessels and nerves can be avoided, and these tissue tunnels collapse immediately after surgery with expected minimal scaring in uncomplicated procedures.

Technically simple procedures like lymph node harvest or esophageal myotomy can be achieved using this technique with standard endoscopic instrumentation like snares, hook or needle knives, and transparent dissecting caps. The biggest challenge we encountered was crossing the phreno-esophageal ligament anteriorly using only linear moving instruments without adequate counter-traction to maneuver and due to the dense vascular tissues of this structure. We found this anterior dissection to be difficult enough that we could only complete it two times out of eight attempts. Newer flexible endoscopic multitasking platforms with superior bimanual coordination abilities may make this more feasible in the future, but currently, they are still in the prototype stage.[19,20] Conversely, a complete posterior gastric myotomy was able to be performed 100% of the time due to the less dense and more fixed posterior attachments of the gastro-esophageal junction. This may be a viable clinical approach as well. In the original 1913 publication of myotomy for achalasia, Ernst Heller described both an anterior myotomy (as originally suggested by Gottstein in 1901) and a posterior myotomy as his treatment of achalasia.[21] The open and later the laparoscopic approaches favored the anterior myotomy because of easier exposure, and a second cardiomyotomy was found to be redundant, but one could presume that the same could be true for a posterior myotomy alone as well.

The preservation of the suspensory structures of the lower esophageal sphincter may be beneficial in different ways. We expect a reduced need for an anti-reflux procedure and would propose performing an endoscopic anti-reflux procedure only for patients with documented reflux.[10] Inoue et al. transformed the formerly experimental

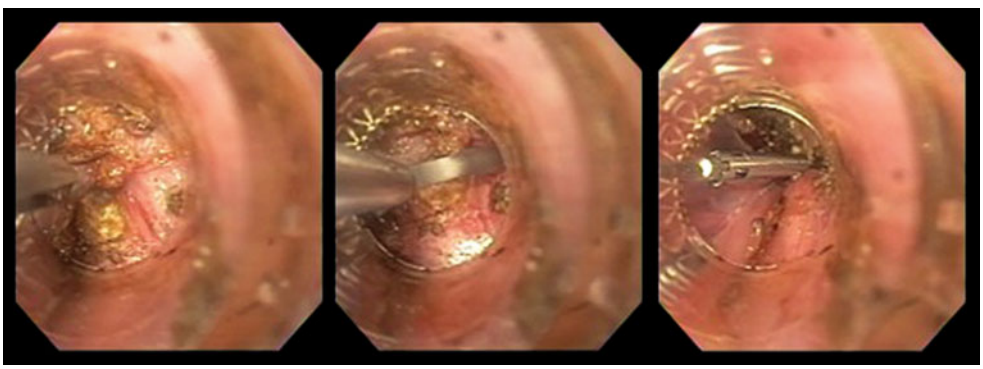

Fig. 6 A small perforation of the submucosal layer is closed using standard endoscopic clips

concept of transesophageal surgery into a clinical reality and performed the first endoscopic submucosal esophageal myotomy in 17 patients with achalasia.[6,10] Only one out of these 17 patients developed reflux esophagitis.

The transesophageal concept is very promising, but secure esophageal closure is still a matter of serious concern.[3,6,8,9,22,23] Experience in flexible endoscopic surgery achieved with a safe transcervical single port access may be helpful in establishing clinical translumenal mediastinal surgery in the future.

Maneuvering flexible endoscopes within the mediastinum relies upon anatomical landmarks for orientation. Following the esophagus anteriorly or posteriorly was found easy and safe using commercially available endoscopic instrumentation. The trachea and the main-stem bronchi, esophagus, heart, aorta, vagal branches, vertebrae, and diaphragm all provide reliable landmarks. The orientation in the animate model is easier than in the human cadaver because of the pulsations of heart and vascular system. The smaller amount of fatty tissue in the posterior mediastinum of the juvenile porcine model may also facilitate orientation compared to human anatomy. However, it was feasible to reproduce the dissection performed in the animals in the human cadaver as well. Virtual three-dimensional navigation systems would further enhance the applications of this approach.[24,25]

Conclusion

Heller myotomy through a cervical incision using flexible endoscopes is feasible and safe in an animal and human cadaver model. Posterior Heller myotomy was performed with a higher success rate than anterior myotomy and may be the preferred approach. With advancement in technology of flexible endoscopic multitasking platforms, the approach can be used for a multitude of mediastinal surgeries and interventions.

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ORIGINAL ARTICLE

Laparoscopic Repair of Large Hiatal Hernia Without Prosthetic Reinforcement: Late Results and Relevance of Anterior Gastropexy

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Abstract
Background Laparoscopic treatment of large hiatal hernias seems to be associated with a high recurrence rate that some authors suggest to bring down by performing prosthetic closure of the hiatus. However, prosthetic repair remains controversial owing to severe and still underestimated complications. The aims of this study were to assess the long-term functional and objective results of laparoscopic treatment without prosthetic patch, and to identify the risk factors of recurrence.
Methods From November 1992 to March 2009, 89 patients underwent laparoscopic treatment of a large hiatal hernia without prosthetic patch, involving excision of the hernial sac, cruroplasty, fundoplication, and often anterior gastropexy. The postoperative assessment consisted of a barium esophagram on day 2, an office visit at 2 months with a 24-h pH study, an esophageal manometry, and then a long-term prospective yearly follow-up with a barium esophagram at 2 years.
Results Out of the 89 laparoscopic procedures, four required a conversion (4.4%). Seventy-seven patients underwent a Boerema's anterior gastropexy (86.5%). The morbidity rate was 7.8%, and the mortality rate was nil. Eleven patients (12.3%) were lost to follow-up. We had 91.5% of very good early functional results and 75.3% of good results after a mean follow-up of 57.5 months. Fourteen recurrences of hiatal hernias (15.7%) were identified, four of which (28.6%) occurred early after surgery. Three factors seemed significantly associated with recurrence: the absence of anterior gastropexy (p=0.0028), the group of younger patients (p=0.03), and a history of abdominal surgery (p=0.01).
Conclusion Large hiatal hernias can be treated by laparoscopy without prosthetic patch with a satisfying long-term result. Performing anterior gastropexy seems to significantly reduce the recurrences.

Keywords Large hiatal hernia · Laparoscopic antireflux surgery · Cruroplasty · Anterior gastropexy · Recurrence

Introduction

Type III large hiatal hernias (paraesophageal hernias)[1,2] remains a rare pathology since it accounts for less than 10% of all hiatal hernias.[3,4] Although their symptomatology is variable and sometimes poor, the high frequency and severity of complications results in recommending surgery.[4–9]

Several studies have demonstrated the feasibility and advantage of fast-track laparoscopic surgery[3,10,11]; however, several authors have criticized this approach for being a risk factor of recurrence.[12] To reduce this high recurrence rate that can reach 42% in the literature,[13–15] several technical points have been suggested but remain controversial. Prosthetic closure of the esophageal hiatus remains one of the most debated issues given the risks of dysphagia and severe complications already reported in the literature

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(prosthetic migration, esophageal perforation, dysphagia, etc.).[14,16–18]

Starting from a monocentric series of 89 large hiatal hernias treated by laparoscopic surgery, the aim of our study was to assess the objective results of a cruroplasty with Nissen fundoplication and an anterior gastropexy without prosthetic patch. We tried to identify the risk factors of recurrence thanks to a long-term prospective follow-up going up to 161 months.

Patients and Methods

Population

From November 1992 to March 2009, 811 patients had undergone laparoscopic repair of hiatal hernia in our unit. Eighty-nine of them (12.3%) had a large (type III) hiatal hernia defined as more than two thirds of the stomach herniated into the thorax. Patients with a recurrence of hiatal hernia were excluded from the study.

There were 28 males and 61 females (sex ratio =2.2 women for one man), with a mean age of 65.8 years and a median of 67 years (range, 14–87). The mean body mass index was 27.3 kg/m^2 (range, 20–36). Thirty-two patients (38.5%) had a history of abdominal surgery, but none of them had undergone gastric or hiatus surgery; 16.7% of the patients had an American Society of Anesthesiology (ASA) score of 1, 47.6% had an ASA score of 2, 33.3% had an ASA score of 3, and 2.4% had an ASA score of 4.

All the patients were symptomatic: 67 patients (75.3%) had digestive troubles with epigastric pain and heartburn. Among them, 36 (40.5%) suffered from digestive hemorrhage sometimes revealed by isolated iron deficiency anemia (n=6), ten patients (11.2%) had dysphagia, and three had incoercible vomiting that was suggestive of gastric volvulus. Twenty-two patients (24.7%) had cardio-pulmonary symptoms often associated with reflux affecting the ears, nose, and throat sphere (details are summarized in Table 1). The symptoms had lasted on average for 100.3 months (range, 2–480) with a median of 48 months, and 58 patients (65.2%) were treated by proton pump inhibitors (PPI) with partial efficiency.

Table 1 Patients' preoperative symptoms

Symptoms	Patients (%)
Digestive troubles	67 (75.3)
Epigastric pain + heartburn	18 (20.3)
Epigastric pain + Dysphagia	10 (11.2)
Epigastric pain + hemorrhage	36 (40.5)
Epigastric pain + vomiting	3 (3.3)
Cardio-pulmonary symptoms	
Thoracic pain + dyspnea	22 (24.7)

Preoperative Assessment

All the patients underwent a preoperative barium esophagram showing 89 type 3 hiatal hernias: Large paraesophageal hernia was defined as the radiographic presence of one third or more of the stomach into the mediastinum. Eighty-five patients (95.5%) had a gastro-esophageal endoscopy to detect esophagitis, Barrett's esophagus with potential dysplasia, esophageal ulcer or gastric ulcer, and signs of gastric volvulus. Twenty-seven patients (30.3%) had a preoperative esophageal manometry. Ten patients (11.2%) underwent a preoperative 24-h pH study.

Surgical Technique

The patient was placed in supine position, with the surgeon standing between his legs. A naso-gastric tube was placed to flatten the stomach. Five trocars were used with a 30° angled camera. The procedure began with the reduction of the herniated stomach from the intrathoracic hernia sac and was systematically associated with a total excision of the hernia sac, allowing in most cases for the stomach to keep its intraabdominal place (except in case of brachyesophagus). The right and left crura were fully dissected as well as the inferior esophagus into the mediastinum. The crura were closed using interrupted nonabsorbable sutures (Mersuture® 2/0), and anterior or lateral crural stitches were added in case of a large hiatus. A fundoplicature was systematically performed, either a total Nissen–Rossetti procedure, or a 270° fundoplication in case of major risks of dysphagia, associated with a cruropexy. No prosthetic patch was ever used. A Boerema anterior gastropexy was performed initially in cases of very shortened esophagus or very large hiatus and then was done routinely at the end of our experience as it seemed efficient: The pneumoperitoneum was reduced to 8 mmHg so as to be able to suture the anterior stomach wall at the junction of the fundus and the antrum to the left abdominal wall at about 4 cm under the costal margin. We used two intraperitoneal stitches using 2/0 non-resorbable silk sutures. Drainage was rare.

Postoperative Assessment and Follow-up

On the second postoperative day, all the patients had a gastrograffin esophagram to assess the efficiency of the surgical procedure and to detect a digestive leak, an early recurrence of hiatal hernia, a slipped Nissen, an intrathoracic wrap migration, and a too tight fundoplication or an esophageal stasis. Postoperative complications, the length

of stay, and the need for early reoperation were analyzed. Postoperative follow-up was performed with office visits at 2 or 3 months to assess functional and objective results with an esophageal manometry and a 24-h pH study.

Then, they had a yearly visit for 5 years or more. A barium esophagram was routinely planned at the 2-year visit. Patients who did not come to the systematic visits were assessed by a standardized symptom questionnaire or phone interviews. "Good results" were defined as disappearance of preoperative symptoms. If patients complained of slight dysphagia or post-fundoplication syndrome, the results were qualified as "middling." Recurrence of hiatal hernia was defined as the esogastric junction moving back up into the mediastinum, whatever its size is. Additional examinations (gastrograffin esophagram, gastro-esophageal endoscopy, pH study, or esophageal manometry) were performed in case of signs of recurrence or new symptoms (heartburn, dyspnea, cough, and dysphagia) and to detect potential complications.

Statistical Analysis

All tests were performed using StatView ® (SAS Institute Inc. 1992–1998, Version 5.0).

Non-parametric tests were used for continuous data (Mann & Whitney test for independent groups and Wilcoxon test for paired groups) and Fisher exact test for categorical data.

A p value less than 0.05 was considered as statistically significant.

Results

Preoperative Data

Among the 85 patients who underwent a preoperative gastro-esophageal endoscopy, 28 had esophagitis, 11 of which were ulcerated, and one was stenosed. Seven patients had Barrett's esophagus without dysplasia, 26 showed signs of strangulation or gastric volvulus, seven had an esophageal ulcer, and six had a gastric ulcer. Among the 27 patients who had an esophageal manometry, 11 showed signs of dyskinesia that led to a 270° fundoplication for two of them in order to avoid a postoperative dysphagia. Out of the 10 preoperative pH studies, only one was pathological and showed a 315 Demeester score ($N<14.5$) in a patient whose gastro-esophageal endoscopy revealed an ulcerated esophagitis with Barrett's mucosa.

Perioperative Data

All the patients benefited from a laparoscopic approach. Conversions to an open procedure were necessary in four cases (4.4%): three due to dissection failure and one due to problematic exposition. Among the conversions, two patients had a history of abdominal surgery but the conversion rate was not significantly increased in cases of surgical history ($p=0.63$). Among the four conversions, two had a BMI>30 kg/m^2.

Eighty-three patients underwent a Nissen–Rossetti fundoplication, three had a 270° fundoplication owing to a severe peptic esophagitis, and three had a Nissen procedure with section of the short gastric vessels. The closure of the large hiatus was always possible by simple suture of the crura and without prosthetic patch. Seventy-seven patients (86.5%) underwent a Boerema anterior gastropexy.

Six intraoperative complications were recorded and were pleural breaches: All of them were sutured intraoperatively, and only two postoperative pneumothorax requiring drainage were observed. The mean duration of surgery was 154.4 min with a 150-min median.

Concerning the *early postoperative period*, the mortality rate was nil. The morbidity rate was 7.8%, including the two pneumothorax, one pneumonia, one acute pancreatitis, one dysphagia requiring an early endoscopic dilatation (day 28), one bilateral phlebitis, and one strangulation with gastric necrosis on day 1 resulting from an early recurrence of hiatal hernia. The last complication led to the only early reoperation that required a total gastrectomy in emergency. All the patients had a gastrograffin esophagram an postoperative day 2 with 82 good immediate results (92.1%). Among the seven abnormal esophagrams were:

- Three intrathoracic wrap migrations, one of which concerned the patient who had required the total gastrectomy. This was at the beginning of our experience and did not happen again as our skills improved.
- One small recurrence (a 2-cm hernia into the mediastinum) operated on again after 4 years because of dysphagia and dyspnea.
- Three relative stenosis of the cardia, only one of which required a dilatation on day 28.

The average length of stay was 6.2 days with a median of 5 days (range, 4–30).

Postoperative Assessment

Eighty-two patients (92.1%) were assessed subjectively by office visits at 2 or 3 months after surgery. Seventy-five patients (91.5%) had good functional results, three experienced slight dysphagia, only one of which required two consecutive endoscopic dilatations (on days 28 and 60), and another one had an esophageal ulcer on Barrett's mucosa. Two patients reported a post-fundoplication syndrome with diarrhea and bloating, one patient complained of reflux besides suffering from an early recurrence of hiatal hernia.

Objective follow-up criteria were obtained for 58 patients (65.2%) who underwent a 24-h pH study, and all of them had a normal De Meester score. Sixty-seven patients (75.3%) had a postoperative esophageal manometry, and two revealed dyskinesia without dysphagia. Fifty-eight patients (65%) had a systematic barium esophagram 2 years after surgery to detect a non-symptomatic recurrence.

Long-Term Results and Follow-up

Four patients died a long time after the surgery and from an unrelated cause. Among them, one patient suffered from an adenocarcinoma of the inferior third part of the esophagus 23 months after surgery and died 3 years after an esophagectomy. This patient had a Barrett's esophagus diagnosed on the preoperative endoscopy.

Since the first operation was carried out 16.5 years ago, 11 patients were lost to follow-up (12.3%). The mean duration of follow-up was 57.5 months (range, 2–161) with a median of 40 months.

The latest information from patients indicates that 75.3% of the patients had good clinical results; 8.9% had middling results with a majority of post-fundoplication syndromes (71.4%). Fourteen hiatal hernia recurrences (15.7%) were identified and confirmed by a gastrograffin esophagram, and all of them were symptomatic: 12 patients complained of reflux, one had dysphagia, and one had a gastric volvulus requiring a gastrectomy on day 2. Among the 14 recurrences, four (28.6%) occurred very early (right after surgery). Six recurrences out of 14 (42.8%) did not require reoperation: The six patients had good control of reflux with PPI. The remaining eight recurrences were treated by surgery: seven by open surgery and one by laparoscopic approach. The procedure involved doing again a fundoplication, a cruroplasty by simple suture without prosthetic patch associated with a systematic Boerema anterior gastropexy.

If early recurrences are not taken into account, other recurrences occurred on average 50.2 months after surgery (range, 4–112).

We tried to identify risk factors of recurrence of hiatal hernia. Three factors seemed significantly associated with recurrence: the absence of anterior gastropexy since we observed 50% of recurrences in the group without anterior gastropexy versus 10.8% in the group with anterior gastropexy (p=0.0028). This factor is all the more significant as the length of follow-up was comparable in the two groups (the mean duration of follow-up was 52.7 months in the group with gastropexy versus 73.2 months in the group without, p=0.17). There was no significant difference between the median delay of recurrence in the group with gastropexy (median, 21.5 months; range, 0–82) and the group without gastropexy (median, 25.5 months; range, 0–112 and p=0.56). The second factor was the age of the patients: The patients with a recurrence were significantly younger than those without a recurrence (60 versus 69 years old, p=0.03). However, the number of anterior gastropexies was significantly higher in the group of older patients (p= 0.01). Finally, there were fewer recurrences in the group with surgical history than in the group without (18% versus 35% and p=0.01).

A weight gain superior to 5 kg, a high ASA score, a Barrett's esophagus, and a gastric volvulus were not significantly associated with recurrence.

No patient had a recurrence among those who required a conversion.

Discussion

Our series of 89 large hiatal hernias (type III) treated laparoscopically without prosthetic patch shows 91.5% of very good early functional results and 75.3% of good results after a mean follow-up of 57.5 months. A 7.8% morbidity rate has been observed, and the mortality rate was nil. These data corroborate those of many studies which have shown that a laparoscopic approach is feasible in most cases with a low conversion rate (4.5% in our series versus an average of 4.2% in a review of literature by Draaisma et al.[4]). The results in terms of morbidity seem to be significantly better than those of open surgery in which the average morbidity rates are 16.2%.[4] If it is still debatable to operate on large asymptomatic hiatal hernias by laparotomy in patients often elderly and fragile, the advent of laparoscopy has reinforced the choice for surgical management, the mortality rate having become much lower in planned surgery than in emergency when an unexceptional complication occurs (gastric volvulus, digestive perforations, hemorrhage, etc.).[9,19–21] What is more, a laparoscopic approach makes it easier to expose the hiatus area, affording a better vision all the way up into the mediastinum and thus facilitates the successive surgical stages, namely the reduction of the hernial sac which often contains a strangled stomach, the excision of the sac, and the cruroplasty. Thus, laparoscopy provides good results in terms of recurrence with a rate of 15.7% in our series when recurrence rates reaching 42% in laparoscopy and 44% in laparotomy have been reported in the literature.[4,12,13,15]

The high recurrence rate in laparoscopic treatment of large hiatal hernias remains a highly debated problem. Several technical points have been suggested but remain controversial, mainly the use of a prosthetic patch to close the hiatus. Admittedly, many studies of laparoscopic treatment of large hiatal hernias with prosthetic reinforcement have been published with interesting results in terms of recurrence (Table 2).[3,22–28] However, these results appeared disparate. Three prospective randomized trials

Table 2 Recurrences after laparoscopic repair of large hiatal hernias using either prosthetic patch or not: main series results

Authors	Date	Population	Mean follow-up (month)	Type of study	Recurrence without prosthetic patch (%)	Recurrence with prosthetic patch (%)	Type of prosthetic patch used
Morino[20]	2006	65	58	Retrospective	35	35	PTFE and mixed (polypropylene+PTFE)
Ponsky[1]	2003	28	21	Prospective	0		
Andujar[23]	2004	166	15	Retrospective	28		
Diaz[22]	2003	116	30	Retrospective	21	33	Synthetic and biological
Champion[21]	2003	52	25	Retrospective		1.9	Polypropylene
Frantzides[25]	2002	72	30	Prospective randomized	22	0	PTFE
Oelschlager[28]	2006	108	6	Prospective randomized	24	9	Biological porcine small intestinal submucosa
Ganderath[24]	2005	100	<12	Prospective randomized	26	8	Polyester
Personal series	2009	89	55.5	Retrospective	15.7		

have compared laparoscopic repair with prosthetic patch and cruroplasty with simple suture[27,29] showing lower recurrence rates in the group with prosthetic patch: 24% of recurrence rate in the group with simple sutures versus 9% in the group with biologic prosthetic patch in Oelschlager's study,[28] 22% of recurrence in the group with simple suture versus 0% in the group with prosthetic patch in Frantzides's series,[27] and 26% of recurrence in the simple suture group versus 8% in the prosthetic patch group in Ganderath's series.[29] However, the follow-up was short (6 months in Oelschlager's study, median of 2.5 years in Frantzides's study, and less than 1 year in Ganderath's), and these early results did not show yet any later potential complications of these foreign bodies in closed contact with digestive tract. Ganderath already reported a significantly higher postoperative dysphagia rate in the prosthetic group. A recent study published by Stadlhuber et al.[14] has reported 28 cases of complications after prosthetic closure of the hiatus, whatever the prosthetic patch used (polypropylene, PTFE, biological mesh, and dual mesh). These complications occurred on average after 17.3 months with 14% of them occurring after more than 2 years. Among the 28 complications, there were 17 digestive erosions, six esophageal stenosis, and five dense fibrosis of the hiatus. Twenty-three patients required reoperation that led to an esophagectomy for six of them, a partial gastrectomy for two of them, and a total gastrectomy for one of them. The authors concluded that the incidence of complications related to prosthetic repair of the hiatus is higher than previously reported in the literature, regardless of the type of prosthetic patch used.

Many authors had already warmed against the high risk of esophageal erosion after prosthetic repair of the hiatus even though the publications were mainly case reports.[16–18,30–32]

Other complications related to the prosthetic patch have been reported (weight loss, sepsis, and abscess) with rates ranging from 1.3% (Trus et al.[9]) to 20% (Griffith et al.[18] and Edelman[32]), depending on the studies, and a mean occurrence rate of 23.4 months. In our experience, over the period studied (November 1992 to March 2009), 119 patients were reoperated on after failure of a first laparoscopic repair of a large hiatal hernia: 77 had a large recurrence treated laparoscopically without prosthetic patch, 42 had dysphagia resulting, for three of them, from prosthetic repair and were treated by prosthetic excision, cruroplasty by simple suture, fundoplication, and anterior gastropexy. Indeed, closure of the hiatus was systematically performed by cruroplasty and has always been possible whatever the diameter of the hiatus is, whether in the first or second operation. Therefore, the large size of the hiatus does not strike us as decisive in the choice to use a prosthetic patch, which we do not believe to be indispensable.

Other factors come into play and also seem important to reduce the recurrence rate after laparoscopic repair of large hiatal hernias. Performing the excision of the hernial sac rather than leaving it in place seems essential, with several studies showing a significant fall in the number of recurrences after its excision.[33,34] It permits to increase local adhesion and to perform a better cruroplasty on quality tissue with a clear vision of the crura.

Performing a fundoplication, which is total most of the time, also seems indispensable to us not only to reduce the recurrence rate in placing the large gastric tuberosity between the cruroplasty and the gastro-esophageal junction but also to reduce often asymptomatic reflux. In the literature, 5–50% of secondary reflux has been reported when a fundoplication is not associated with the reduction of the hiatal hernia and a cruroplasty.[35–37] In our series, 86 patients underwent a 360° fundoplication and three had a 270° fundoplication because of preexisting dysphagia due to peptic stenosis, knowing that postoperative dysphagia is more often linked to too tight a cruroplasty than to the type of wrap performed.

Few authors performed a Collis gastroplasty (eight out of the 32 studies reviewed by Draaisma et al.[4]), arguing that esophageal lengthening should decrease the recurrence rate. However, its indications remain unclear in the literature and are not based on uniform preoperative assessment protocols. This procedure also resulted in additional morbidity and longer surgical procedure. Thus, Collis gastroplasty remains controversial, and yet, no conclusions could be drawn with regard to the effect on recurrence. In our experience, the stomach is usually well reintegrated in the abdominal cavity after total excision of the hernia sac and is also maintained by the anterior gastropexy, the cruroplasty, and the cruropexy. Section of the short gastric vessels can help to perform the fundoplication in case of shortened esophagus.

Finally, our study has emphasized three factors significantly associated with the recurrence of hiatal hernia and above all the absence of Boerema's anterior gastropexy: We observed a 50% recurrence rate in the group without gastropexy versus 10.8% in the group with gastropexy ($p=0.0028$). Performing an anterior gastropexy could therefore significantly reduce recurrences as it had already been noted by other authors on smaller and non-comparative series.[3,24,32,38,39] The hypothesis is that anchoring the stomach anteriorly to the abdominal wall will prevent its reherniation into the mediastinum. Moreover, this pexy of the stomach would enable it to maintain its anatomic position and avoid organoaxial rotation with the risk of gastric volvulus or strangulation. This procedure is all the more interesting as it is technically easy to perform laparoscopically, not very invasive, and reproducible.

The second factor of recurrence emphasized in our series was the age of the patients: The recurrence rate seemed significantly higher in the younger patients; however, this result was biased as the younger patients had undergone fewer anterior gastropexies, which confused the two factors.

The third factor emphasized by our study also seemed less revealing: Patients with a history of abdominal surgery had a significantly lower recurrence rate compared with patients without a history. Postoperative abdominal adhesion could be a possible explanation.

Conclusion

At the end of this study, it appeared that large hiatal hernia can be treated laparoscopically without prosthetic reinforcement with a satisfying long-term result whether from a functional point of view or in terms of recurrence. Performing a Boerema's anterior gastropexy appears to significantly reduce the risk of recurrence the more so as it is associated with an excision of the hernial sac, a cruroplasty, and a fundoplication.

Although recent studies about prosthetic repair show encouraging results, the lack of follow-up and a non-negligible number of severe complications do not speak in favor of its systematic use. Furthermore, the disparity in the assessment criteria of the results makes it tricky to compare most of the published series.

Performing randomized trials with long-term follow-up and standardized assessment criteria could optimize the management of large hiatal hernias.

Conflicts of interest Drs. Poncet G., Robert M., Roman S. and Boulez J. have no conflicts of interest or financial ties to disclose.

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ORIGINAL ARTICLE

The Long-Term Results of Distal Gastrectomy by Mini-laparotomy in Early Gastric Cancer Patients

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Abstract
Introduction Radical distal gastrectomy by mini-laparotomy is an alternative surgical treatment modality with technical feasibility in early gastric cancer (EGC) patients. The aim of this study is to assess the oncologic feasibility of distal gastrectomy by mini-laparotomy in EGC patients through a long-term survival analysis based on the prospectively collected data.
Patients and Methods From January 2003 to November 2003, a total of 53 EGC patients who received distal gastrectomy by laparotomy were enrolled in this study. These patients were divided into two groups, that is, the mini-laparotomy group (ML, $n=22$) and the conventional laparotomy group (CL, $n=31$). A comparative long-term survival analysis was performed.
Results The hospital stay was significantly shorter in mini-laparotomy group ($P=0.002$). However, there were no significant differences in the pathologic results such as the resection margin and the number of harvested lymph nodes. In long-term survival results, there were no significant differences in disease-free and overall survival rate of the patients according to the method of laparotomy.
Conclusions Radical distal gastrectomy by mini-laparotomy in EGC patients would be also one of the minimally invasive surgical modality in oncologic aspect.

Keywords Mini-laparotomy · Early gastric cancer

Abbreviations

EGC	early gastric cancer
ERAS	early recovery after surgery
QOL	quality of life
KNSO	Korea National Statistical Office
DFS	disease-free survival
OS	overall survival

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Introduction

The conventional distal gastrectomy in gastric cancer patients has been usually performed through a long midline incision because adequate lymph node dissection should be needed for oncologic safety. However, it was reported that radical lymph node dissection should be limited in patients with early gastric cancer (EGC) because extended lymph node dissection in EGC patients had little survival benefits.[1–3] So, new treatment modalities with minimally invasive techniques such as endoscopic resection, laparoscopic gastrectomy, and robotics surgery in EGC patients have recently been reported and performed by many surgeons. These minimally invasive techniques are focused on enhanced recovery after surgery (ERAS) programs and improving quality of life (QOL) because EGC patients have shown long survival periods.[4–7]

Laparoscopic surgery for treating gastrointestinal cancer may result in a more rapid return of bowel function, less postoperative pain, and early discharge as compared with

conventional surgery.[4,6,8] However, laparoscopic surgery shows oncologic unreliability, and there are several technical problems with need of learning curve in beginner. In aspect of patients, it is still expensive.[8,9] To overcome these disadvantages, a few surgical techniques by minimal laparotomy have been performed for treating benign and malignant disease.[10–14] Moreover, it was reported that an early return of function and discharge were dependent on the use of a small incision, whether by mini-laparotomy or laparoscopy.[15]

The aims of this study were to assess the oncologic feasibility of radical distal gastrectomy in EGC patients by mini-laparotomy through a survival analysis with a long-term follow-up period and to compare the various pathologic outcomes with those obtained by conventional laparotomy.

Patients and Methods

Patients

This study was designed as a retrospective analysis based on prospectively collected data within a certain period of time. This study was approved by institutional review board of ethical committee of the college of medicine (KC10RISI0231). From January 2003 to November 2003, a total of 53 EGC patients who received distal gastrectomy by laparotomy were enrolled. All the enrolled patients signed a written informed consent form before their operations. The EGC patient was defined as a case with cancer confined only to the mucosa or submucosa regardless of the presence or absence of enlarged lymph node at the perigastric space on the preoperative esophagogastroduodenoscopy and computed tomography scan.

Methods

The enrolled patients were divided into two groups. One was the mini-laparotomy group (ML group, n=22) that underwent curatively distal gastrectomy with an incision less than 7.4 cm as a mean value (range, 6.5–8.2 cm), and the other was the conventional laparotomy group (CL group, n=31) that underwent curatively distal gastrectomy with a long midline incision. ML group was performed gastrectomy by a single specialized surgeon, and CL group underwent gastrectomy by another expert. All of the procedures were supervised by a single surgeon. Perioperative care progressed under the same standard protocol, and clinical factors were measured equally by the same protocol.

Surgical Procedures

All steps of the mini-laparotomy were performed using conventional surgical techniques and instruments by a small abdominal incision. All procedures were performed in the rules of oncologic principles.

An upper midline mini-laparotomy was performed from xyphoid processor toward umbilicus. The abdominal self-retractor (Kim's retractor), which could be freely controlled surgical field by regulating length of retractor and position of fixation, was positioned at both side. The surgical window was moved horizontally and/or vertically to make ideal surgical field (Fig. 1). Firstly, by moving surgical window fully to left side of patient, dissection of gastrocolic ligament, left side ometectomy, and lymphadenectomy around left gastroepiploic vessel were performed. Next, by moving surgical window fully to right side of patient, resection of duodenum, right side ometectomy, and lymphadenectomy around right gastroepiploic vessel and right gastric artery were performed. Lastly, surgical window was fixed in the center for resection of proximal gastric margin, lymphadenectomy around celiac trunk, hepatic artery, splenic artery, and lesser curvature side. The level of lymph node dissection was classified as D1, D2, or D2 + α according to the Japanese classification.[16] D2 or D2 + α lymphadenectomy were performed by the gross finding of enlarged lymph node during operation. The gastroduodenostomy in Billroth-I reconstruction was performed by using EEA (28 mm), and gastrojejunostomy in Billroth-II reconstruction was performed by hand-sewing technique through mini-laparotomy window (Fig. 2). The detailed operative technique and the technical feasibility have previously been reported.[17]

This technique facilitates radical gastrectomy with oncologic principles and is also feasible to perform an

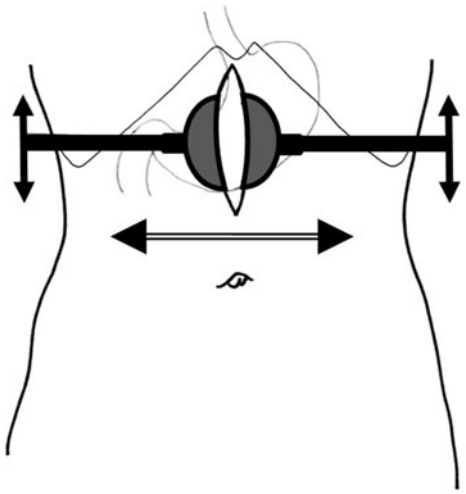

Fig. 1 Schematic drawing of mini-laparotomy and retractor installation.

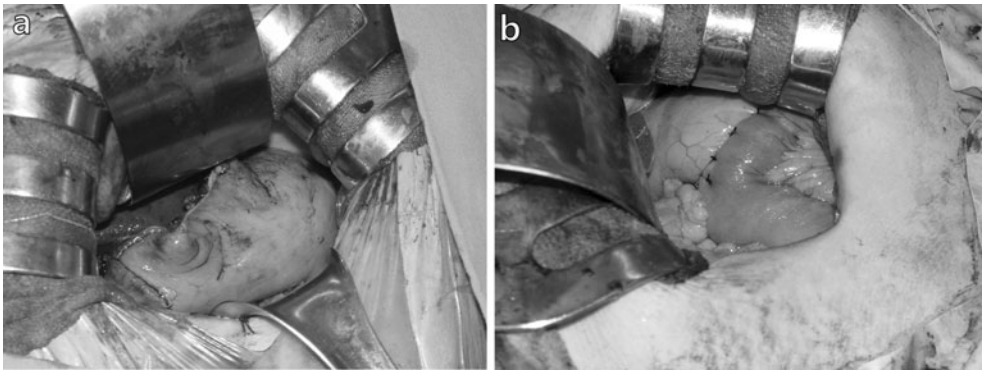

Fig. 2 Distal gastrectomy and reconstruction by mini-laparotomy (range, 6.5–8.2 cm). **a** gastroduodenostomy in Billroth-I reconstruction using EEA (28 mm), **b** gastrojejunostomy in Billroth-II reconstruction by hand-sewing technique.

extended lymphadenectomy along with reconstruction by accessible moving of surgical field. And, there was no necessity of using complex fixation devices and retractors which could disturb surgical procedures.

Follow-up

The follow-up data was obtained through a review of the medical records. The data collection followed the guidelines of the ethical committee. The median follow-up period was 61 months. The stages of gastric cancer were classified by the sixth AJCC/UICC TNM classification.[18] The pathologic features were confirmed by one pathologist who specialized in gastric cancer, and the survival results were repeatedly identified by using the registration data of the Korea National Statistical Office and the medical records.

Statistics

This study was designed to confirm the equivalence between the ML and CL groups. The results from the analysis of the continuous variables are expressed as means ± standard deviation. Univariate statistical analysis was performed using Chi-square or Fisher's exact test for the categorical variables, and independent *T*-test for continuous variables. The cumulative survival results were generated using the Kaplan–Meier method, and they were compared using the log-rank test. Statistical analyses were performed using SPSS software (ver. 13.0), and a *P* value<0.05 was considered to indicate a statistically significant difference with a 95% confidence interval (95% CI).

Results

Basic Characteristics of the Enrolled Patients

The summary of the basic characteristics of the enrolled patients is shown in Table 1. There were 43 men and 20 women. The median age was 55 years old (ranged from 26 to 77 years old). Distal gastrectomy with Billroth-I reconstruction was more frequently performed in the ML group as compared with that of the CL group with significance (P=0.002). The hospital stay was significantly shorter in ML group (P=0.002)

Pathologic Feature According to the Laparotomy Method

The pathologic results are shown in Table 2. There were no significant differences in pathologic results such as resection margin, the number of harvested lymph nodes, or tumor invasion status.

Long-Term Survival of the Patients According to the Method of Laparotomy

There were no significant differences of disease-free survival (DFS) and overall survival (OS) rates of the patients according to the laparotomy method (Fig. 3).

Table 1 Characteristics of the Enrolled Patients

Factors		Mini-laparotomy (n=22)	Conventional (n=31)	P value
Age		52.9±13.4	58.7±11.6	0.085
Sex (%)	Male	17 (77.3)	20 (64.5)	0.376
	Female	5 (22.7)	11 (35.5)	
Body mass index (Kg/m^2)		22.2±2.7	23.1±3.9	0.356
OP name (%)	B-I STG	12 (52.2)	4 (10.0)	0.002
	B-II STG	10 (43.5)	27 (67.5)	
Operation time (min)		188.6±29.0	200.5±41.6	0.216
Hospital stay (days)		8.09±0.9	11.8±1.4	0.002

B-I STG subtotal gastrectomy with gastroduodenostomy, *B-II STG* subtotal gastrectomy with gastrojejunostomy

Table 2 Comparison of Pathologic Features by Univariate Analysis

Factors		Mini-laparotomy (n=22)	Conventional (n=31)	P value
Tumor size (maximum value, cm)		1.92±1.23	1.95±1.19	1.000
Resection margin	Proximal	4.01±1.94	4.83±1.69	0.114
	Distal	4.39±2.66	3.93±2.19	0.515
Differentiation[a]	Differentiated	13 (59.1)	21 (67.7)	0.570
	Undifferentiated	9 (40.9)	10 (32.3)	
Lauren's classification	Intestinal	14 (63.6)	21 (67.7)	0.777
	Diffuse	8 (36.4)	10 (32.3)	
pT stage	T1a	14 (63.6)	12 (38.7)	0.098
	T1b	8 (36.4)	19 (61.3)	
pN stage	N0	20 (90.9)	29 (93.5)	1.000
	N1	2 (9.1)	2 (6.5)	
Harvesting LN		29.6±8.7	32.1±7.8	0.259
Lymphatic invasion	Negative	21 (95.5)	26 (83.9)	0.382
	Positive	1 (4.5)	5 (16.1)	
Vascular invasion	Negative	22	31	–
	Positive	–	–	
Neural invasion	Negative	22	30 (96.8)	1.000
	Positive	–	1 (3.2)	
Sixth UICC stage	IA	20 (90.9)	26 (93.5)	1.000
	IB	2 (9.1)	2 (6.5)	

Values in parenthesis indicate percentage (%) for each group

[a] Differentiated includes well and moderately differentiated types, undifferentiated includes poor and signet-ring cell type

During observation periods, DFS rates of the ML and CL groups were 100.0% and 89.5% (P=0.236), and OS rates of those groups were 100.0% and 85.6%, respectively (P=0.369).

Discussion

The technical and oncologic feasibility of open distal gastrectomy in gastric cancer patients has been clearly established. The incidence of early gastric cancer has recently increased because of advances in diagnostic techniques have made it possible to detect small lesions at an early stage, and the survival of EGC patient has improved evidently.[19,20] At present, ERAS programs and QOL have been emphasized for EGC patients, and surgeons must carefully consider whether innovative technical modifications of surgery can guarantee the quality of outcomes for improving patient's satisfaction after surgery.

Laparoscopic gastrectomy is now accepted as a common minimally invasive procedure and as an alternative modality

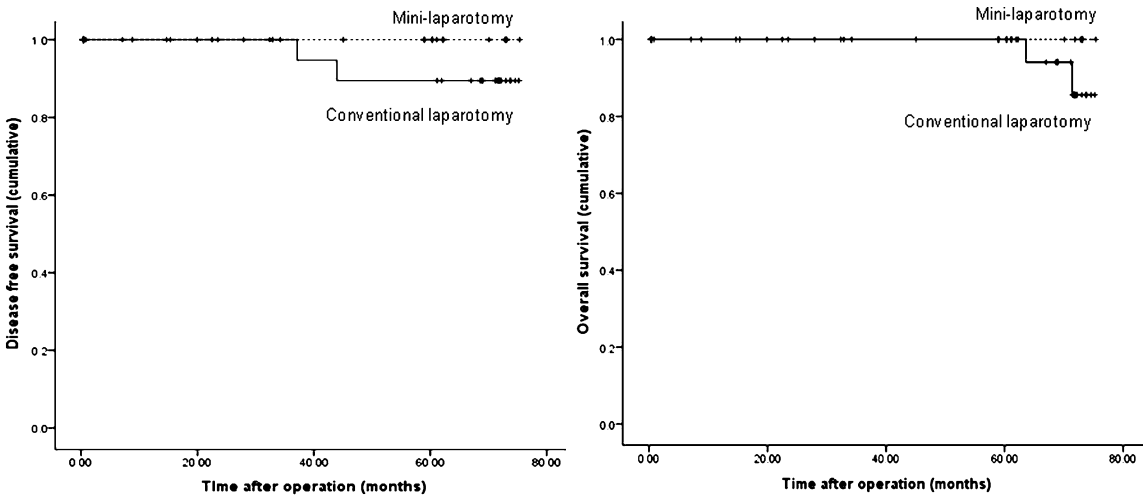

Fig. 3 The disease-free survival (DFS) for both groups (P=0.814), and the 5-year survival for both groups (P=0.369), stratified by the incision method. *Dotted line* mini-laparotomy group (n=22), *solid line* conventional laparotomy group (n=31).

to open gastrectomy for gastric cancer surgery. However, laparoscopic surgery still has several limitations such as oncologic unreliability, technical problems for surgeons, and cost-effectiveness.[8,9] Moreover, a single small laparotomy (roughly 4–7 cm) is required for extracorporeal anastomosis and removal of the specimen in laparoscopy-assisted gastrectomies.

Gastrectomy by mini-laparotomy is also an alternative modality for gastric cancer. The mean length of laparotomy for distal gastrectomy was less than 8 cm in this study. There has been no optimal incision length of laparotomy for distal gastrectomy. The optimal incision length should be determined according to several factors such as age, sex, body mass index, fat amount of subcutaneous layer, etc. From experience, 6.5 cm was the lower limit for mini-laparotomy because this represented the minimum size that allowed insertion of the surgeon's hand into the peritoneal cavity for traction or vessel ligation. However, incision length would be shortened in the future if a new sealing device may be developed. A length of mini-laparotomy may be roughly equivalent to the total incision length of laparoscopy-assisted distal gastrectomy (LADG). Some authors have reported that the grade of pain is related to the length of the incision.[12,15] Therefore, a randomized comparison study between gastrectomy by mini-laparotomy and LADG should be done prospectively after confirming the evidence for oncologic safety.

The technical feasibility of gastrectomy by mini-laparotomy has been described by a few authors.[21] Authors previously reported that performing distal gastrectomy by mini-laparotomy in EGC patients was feasible, resulted in a shorter hospital stay, required less use of analgesics, and showed no differences in bleeding volume or the number of harvested lymph nodes as compared with that of conventional laparotomy. But, in that paper, only the very short-term results for recurrence were reported.[17] This study demonstrates the feasibility and safety of the radical distal gastrectomy by mini-laparotomy approach in EGC patients according to the surgical and oncologic aspects through long-term survival results.

In this study, the numbers of retrieved lymph nodes were not significantly different between the two groups. Furthermore, there was no significant difference in DFS rate or OS rate between the two groups. However, the reason for the high values of the survival rates may be the relatively small number of enrolled patients in this study. There were only two deaths in the conventional laparotomy group during observation period. Two patients died at 63 and 71 months due to metastasis into bone and lung by hematogenous spreading. There were no deaths related to local recurrence of the regional lymph nodes or carcinomatosis peritonei. These results verify that radical lymphadenectomy by mini-laparotomy is also feasible in rules of oncologic aspect, as compared with conventional laparotomy.

This study suffers from some drawbacks. One is that this study had retrospective results from prospectively collected data. And, the other is that convincing long-term survival results were not adequately demonstrated because of the small volume. In addition, comparison of cost-effectiveness according to surgical modalities (open vs laparoscopic) should be needed.

Conclusion

Radical distal gastrectomy by mini-laparotomy in EGC patients is a minimally invasive surgical modality that is safe and technically feasible in the oncological aspect. Furthermore, a future large-scale study should be conducted to determine the proper indications for this procedure, which should be followed by randomized clinical trials comparing distal gastrectomy by mini-laparotomy with laparoscopic distal gastrectomy.

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Conflict of Interest Statement No actual or potential conflicts of interest on behalf of the authors of this paper do exist.

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ORIGINAL ARTICLE

Tumors Arising at Previous Anastomotic Site may have Poor Prognosis in Patients with Gastric Stump Cancer Following Gastrectomy

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Abstract
Introduction We analyzed the clinicopathological characteristics and outcomes of patients with gastric stump cancer (GSC) to identify important prognostic factors.
Patients and Methods We retrospectively reviewed clinical reports of 34 patients with GSC treated at Kochi Medical School from 1982 to 2008 to analyze the clinical and pathological factors that influenced patient survival.
Results The median interval between initial and second operation was 15.8 years; this interval was significantly longer in patients diagnosed originally with benign disease than in those with previous malignant disease. Histologically, the incidence of diffuse-type cancer was significantly prominent in patients with previous benign gastric disease than in those with previous malignant gastric disease. The overall 5-year survival rate was 53.3%, with presence of lymph node metastasis and pathological serosal invasion of the tumor associated with poor survival. The final analysis revealed tumor located at anastomosis, tumor size greater than 5 cm, serosal invasion, the presence of lymph node metastasis, and stage III or higher to be significantly associated with poor survival.
Conclusions Follow-up programs after gastrectomy should account for long latency periods of disease. Early detection, attentive observation of anastomotic site, and sufficient surgical resection were important influences on outcome for patients with GSC after Billroth I or Billroth II reconstruction.

Keywords Gastric stump cancer · Gastrectomy · Survival · Anastomotic site · Lymph node metastasis

Introduction

Gastric stump cancer (GSC) was originally defined as a gastric cancer that arises in the remnant stomach more than 5 years after primary surgery for a benign disease such as peptic ulcer,[1,2] and was first reported as an entity by Balfour in 1922.[2] However, it has been used since to define all cancers occurring in the remnant stomach after gastrectomy, regardless of whether the primary disease was benign or malignant.[3,4] Recent advances have enabled earlier detection of gastric cancer in many cases, resulting in more favorable surgical outcomes and increased long-term survival for these patients.[5,6] Consequently, GSC following distal gastrectomy for gastric cancer is becoming more common. Despite some studies of long-term prognosis for patients with GSC, few prognostic outcomes have been reported from large cohorts.[7,8] This study evaluated the clinicopathological features of patients with GSC to evaluate prognostic factors.

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Patients and Methods

A total of 1,320 patients who underwent surgery as a treatment for gastric cancer from 1982 to 2008 at Kochi Medical School

were reviewed. The standard operations for gastric cancer were distal, proximal, or total gastrectomy with D2 lymph node dissection in accordance with the rules of the Japanese Gastric Cancer Association.[9] Of 34 enrolled GSC patients, ten had undergone a previous distal gastrectomy for gastric or duodenal ulcer and 24 were previous gastric cancer patients. Among 24 previous gastric cancer patients, the initial gastrectomy was reported to be curative in all patients, and definite recurrence cases were not included. The main locations of GSC were classified as including an anastomotic site or as a nonanastomotic site. All histopathological data were analyzed and determined according to the International Union Against Cancer (UICC) TNM classification (7th edition)[10] and TNM supplement (3rd edition).[11] The histology was categorized as intestinal type (well-differentiated, moderately differentiated, and papillary adenocarcinoma) or diffuse type (poorly differentiated, mucinous adenocarcinoma, and signet ring cell carcinoma) according to Lauren's classification.[12]

We also analyzed the GSC following distal gastrectomy in terms of clinicopathological characteristics. Finally, we identified prognostic factors for long-term cumulative survival rate. The outcome of all patients was examined through a follow-up study, and only patients who died of gastric cancer were regarded as tumor-related deaths.

Statistical Analysis

The Mann–Whitney *U* test was used to assess correlations among the continuous variables for each group. The Pearson chi-square test was applied to qualitative variables. Cumulative survival rates were generated using the Kaplan–Meier method and were compared using the log-rank test to evaluate statistically significant differences.[13] P values<0.05 were considered significant. Statistical analysis was performed with SPSS for Windows version 13.0 (SPSS, Chicago, IL).

Results

Characteristics of GSC

Patients with GSC accounted for 34 (2.7%) of all gastric cancer patients treated by surgical resection. Of these, 28 patients were men and six were women, ranging in age from 34 to 85 years (median, 67.5). The median time interval between the initial gastrectomy and the treatment of GSC was 15.8 years (range 1–48), and the median tumor size was 5.1 cm (range 1.2–15) in diameter.

At the initial surgery, ten patients had benign disease, and 24 patients had malignant lesions. After the distal gastrectomy, 18 patients underwent a gastric reconstruction by the Billroth I method and 16 patients had reconstructions by the Billroth II method. There were 15 patients with tumors located around an anastomotic site, whereas the remaining 19 patients had tumors located at nonanastomotic sites.

Histological analysis revealed 17 intestinal-type and 17 diffuse-type carcinomas. The median number of dissected lymph nodes was 11 (range 4–34), and lymph node metastasis was evident in 12 of 34 patients, of whom two patients had infiltrated lymph nodes in the jejunal mesentery with tumors located at an anastomotic site. Stage I GSC disease was found in 16 patients, stage II in four, stage III in six, and stage IV disease in eight patients. We performed mainly completion gastrectomy as the second operation, and the overall resection rate of GSC was 91.2%.

Characteristics According to Previous Disease

Table 1 details the clinicopathological characteristics of 34 patients with GSC according to the nature of the previous disease. Initial surgery was performed for benign disease in ten patients and for malignant disease in 24 patients. The incidence of GSC in patients who had previously undergone a Billroth II reconstruction was significantly higher in patients with previous benign gastric disease than in those with previous malignant gastric disease (80.0% vs. 33.3%; $P=0.013$). The incidence of histologically diffuse-type cancer was significantly prominent in patients with previous benign gastric disease than in those with previous malignant gastric disease (80.0% vs. 37.5%; $P=0.024$). The interval between the previous operation and the second operation for the patients with previous benign disease was significantly longer than for those with previous malignant disease (24.5 years vs. 10.0 years; $P=0.046$). The median interval time for the anastomotic tumors and the nonanastomotic tumors in the previous malignant disease group were 19 and 7 years, respectively. There were no significant differences in age, gender, tumor size, tumor location, depth of invasion, incidence of lymph node metastasis, number of dissected lymph nodes and lymph node metastasis, or tumor stage between benign and malignant groups.

Resection rate of the GSC was 88.9% in patients with previous benign gastric disease and 91.3% in those with previous malignant gastric disease.

Characteristics According to Previous Reconstruction Method

Table 2 shows clinicopathological factors of 34 patients with GSC according to reconstruction method. The interval between the previous operation and the second operation for the patients who had previously undergone Billroth II reconstruction was significantly longer than those who had

Table 1 Clinicopathological characteristics of patients with gastric stump cancer according to previous disease

	Benign n=10	Malignant n=24	P value
Median (range) age (years)	71 (34–81)	66 (41–85)	0.998
Gender (%)			0.816
Male	8 (80.0)	20 (83.3)	
Female	2 (20.0)	4 (16.7)	
Median (range) interval (years)	24.5 (8–40)	10.0 (1–48)	0.046
Reconstruction with primary operation (%)			0.013
Billroth I	2 (20.0)	16 (66.7)	
Billroth II	8 (80.0)	8 (33.3)	
Median (range) tumor size (cm)	4.2 (1.5–8.0)	6.0 (1.2–15.0)	0.355
Tumor location (%)			0.229
Anastomotic	6 (60.0)	9 (37.5)	
Nonanastomotic	4 (40.0)	15 (62.5)	
Depth of invasion (%)			0.283
T1	2 (20.0)	9 (37.5)	
T2	3 (30.0)	4 (16.7)	
T3	3 (30.0)	5 (20.8)	
T4	2 (20.0)	6 (25.0)	
Lymph node metastasis (%)			0.677
Positive	3 (30.0)	9 (37.5)	
Negative	7 (70.0)	15 (62.5)	
Median (range) number of dissected lymph nodes	11.0 (7–21)	11.5 (4–34)	0.844
Median (range) number of lymph node metastasis	0 (0–6)	0 (0–11)	0.377
Histology (%)			0.024
Intestinal	2 (20.0)	15 (62.5)	
Diffuse	8 (80.0)	9 (37.5)	
Disease stage (%)			0.308
I	5 (50.0)	11 (45.8)	
II	2 (20.0)	2 (8.3)	
III	2 (20.0)	4 (16.7)	
IV	1 (10.0)	7 (29.2)	

previously undergone Billroth I reconstruction (24 vs. 10 years; P=0.050). The incidence of previous benign disease was significantly higher in the Billroth II group than in the Billroth I group (50.0% vs. 11.1%; P=0.013). The incidence of tumor located in the anastomotic site was significantly higher in the Billroth II group than in the Billroth I group (62.5% vs. 7.8%; P=0.042). There were no significant differences in age, gender, tumor size, depth of invasion, incidence of lymph node metastasis, number of dissected lymph node or lymph node metastasis, histological type, and disease stage between the Billroth I and the Billroth II group.

Survival Analysis

The overall 1-, 3-, and 5-year survival rates of patients with GSC was 64.7%, 53.3%, and 53.3%, respectively (Fig. 1). Although 5-year survival rate of patients with previous benign disease was higher than those with previous malignant disease (75.0% vs. 51.4%), the difference was not statistically significant.

Comparing the survival rate among the subgroups identified by each predictive factor by univariate analysis of prognostic factors identified the following factors as significantly associated with a poor outcome: (1) tumor located at anastomosis, (2) tumor size >5 cm, (3) T3 or more, (4) presence of lymph node metastasis, and (5) stage III disease or higher (Table 3, Fig. 2). No independent prognostic factors were identified by multivariate analysis, probably due to the small patient number. There were no significant influences on survival rate by age, gender, reconstruction procedure, or histological type.

Discussion

This study of prognosis in patients with GSC demonstrated an association between poor outcome and each of the

Table 2 Clinicopathological characteristics of patients with gastric stump cancer according to previous reconstruction method

	Billroth I n=18	Billroth II n=16	P value
Median (range) age (years)	67 (45–81)	72.5 (34–85)	0.569
Gender (%)			0.874
Male	15 (83.3)	13 (81.3)	
Female	3 (16.7)	3 (18.7)	
Median (range) interval (years)	10 (2.4–29)	24 (2–48)	0.050
Previous disease (%)			0.013
Benign	2 (11.1)	8 (50.0)	
Malignant	16 (88.9)	8 (50.0)	
Median (range) tumor size (cm)	4.1 (0.8–15)	5.5 (3–9)	0.945
Tumor location (%)			0.042
Anastomotic	5 (27.8)	10 (62.5)	
Nonanastomotic	13 (72.2)	6 (37.5)	
Depth of invasion (%)			0.186
T1	8 (44.4)	3 (18.8)	
T2	3 (16.7)	4 (25.0)	
T3	2 (11.1)	6 (37.5)	
T4	5 (27.8)	3 (18.8)	
Lymph node metastasis (%)			0.331
Positive	5 (27.8)	7 (43.8)	
Negative	13 (72.2)	9 (56.2)	
Median (range) number of dissected lymph nodes	11 (0–34)	12 (2–27)	0.443
Median (range) number of lymph node metastasis	0 (0–11)	0 (0–8)	0.977
Histology (%)			1.000
Intestinal	9 (50.0)	8 (50.0)	
Diffuse	9 (50.0)	8 (50.0)	
Disease stage (%)			0.709
I	10	6	
II	2	2	
III	3	3	
IV	3	5	

following factors: (1) tumor located at anastomosis, (2) tumor size >5 cm, (3) T3 or more, (4) the presence of lymph node metastasis, and (5) stage III disease or higher. Previous investigations identified initial disease, tumor size, and jejunal infiltration as prognostic factors in GSC patients in addition to the TNM categories[8,14,15] (Table 4). The particularly noteworthy finding in the present study was therefore that cases of GSC with tumor located at anastomosis showed a poor prognosis compared to those tumors located at a nonanastomotic site.

Anatomical disruption of lymphatic flow due to the first operation could be a key factor underlying this finding since lymphatic flow after distal gastrectomy with lymph node dissection frequently penetrates between adherence sites and adjacent structures toward the para-aortic, jejunal or colonic mesentery lymph nodes.[16] Therefore, the lymphatic flow from a gastrojejunal anastomosis to the jejunal mesentery could facilitate lymph node metastases in these regions. In the present study, two patients with GSC

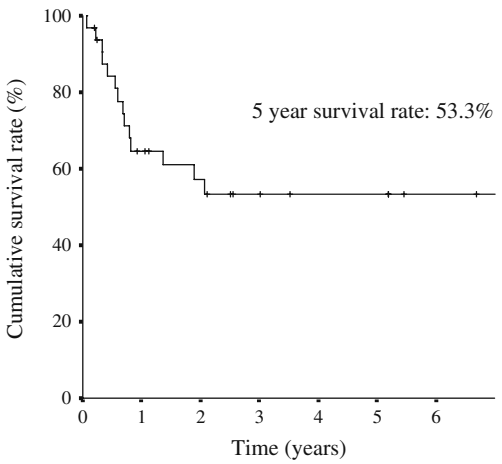

Fig. 1 Survival curves for 34 patients with gastric stump cancer

Table 3 Prognostic factors of the gastric stump cancer

Characteristics	Number of patients (%)	Survival rate (%)			*P* value
		1 year	3 year	5 year	
Tumor location					0.016
Nonanastomotic	19 (55.9)	76.5	76.5	76.5	
Anastomotic	15 (44.1)	58.7	23.5	23.5	
Tumor size (cm)					0.001
<5	18 (52.9)	100	92.9	92.9	
>5	16 (47.1)	53.6	38.5	30.8	
Tumor depth					<0.001
T1, T2	18 (52.9)	100	100	100	
T3, T4	16 (47.1)	31	23.2	12.6	
LN metastasis					<0.001
Negative	22 (64.7)	89.5	89.5	83.1	
Positive	12 (35.3)	30.6	10.2	0	
Stage					<0.001
I, II	20 (58.8)	100	100	100	
III, IV	14 (41.2)	31	7.7	0	

located at an anastomotic site showed infiltrated lymph nodes in the jejunal mesentery, and both individuals showed a poor prognosis. Thus, lymphatic flow through an anastomotic site should be considered with respect to GSC prognosis. In addition, metastatic infiltration of the jejunum at the anastomosis worsens the prognosis of patients with GSC.[14,17] Accordingly, resection of the anastomosis together with the adjacent mesentery of the jejunum and sufficient lymphadenectomy around the anastomotic site is recommended.

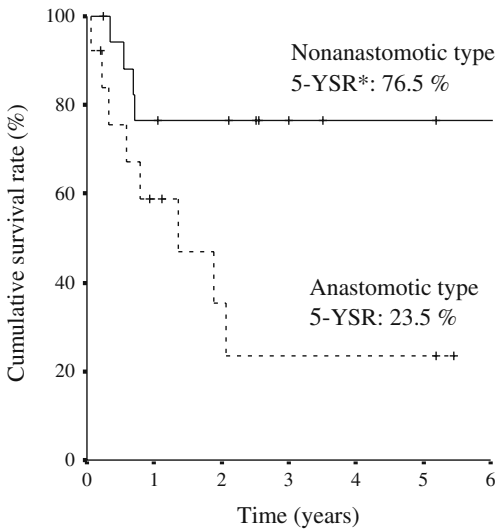

Fig. 2 Survival curves for 19 patients with gastric stump cancer located at a nonanastomotic site (*solid line*) and 15 patients with gastric stump cancer located at an anastomotic site (*dotted line*). There was significant difference in survival between the two groups (P= 0.016). Data were analyzed using a log-rank test. **5-YSR* 5-year survival rate

In the present study, patients with GSC classified as T1 or T2 showed a 100% 5-year survival rate, whereas those with a T3 or T4 GSC showed a 5-year survival rate of only 12.6%. If newly developed cancer is diagnosed at an early stage, the outcome of treatment can therefore be as satisfactory as that reported for early gastric cancer, even in patients with GSC. However, the likelihood of an unfavorable outcome for patients with T3 GSC or higher, lymph node involvement, or at least stage III disease is extremely high.

Tumor diameter in gastric cancer currently is not included in the staging system recommended by the UICC classification.[10,11] However, a previous study indicated that tumor size in gastric cancer is a reliable prognostic factor that might be suitable for use in the staging system in addition to conventional factors such as the presence of lymph node metastasis and depth of invasion.[18] Specifically, these authors demonstrated that patients with gastric cancer >10 cm in diameter had far poorer prognosis than patients with smaller tumors. The present study accorded with this previous work in that tumor size >5 cm in diameter was related to poor prognosis in GSC patients.

The most reasonable approach for treating GSC is radical resection,[17] although several previous studies have demonstrated low resectability rates and poor prognosis in GSCs compared with primary gastric cancer.[1,19] However, GSCs are now being detected at a relatively early stage due to improvements in endoscopic diagnosis,[20] and recent investigations showed no significant difference in outcome between GSC and upper one-third gastric cancer cases.[14,17,21,22] Although the 5-year survival rates for patients with previous benign disease in the present study were slightly higher than those with previous malignant

Table 4 Prognostic factors of gastric stump cancer besides TNM categories in the literature

Author	Factor		Number of patients	5-year survival rate (%)	*P* value
Ahn HS et al.[8]	Tumor size				<0.001
		<6 cm	31	86.3	
		>6 cm	27	34.1	
Schaefer N et al.[12]	Infiltration of jejunum				0.002
		Negative	6	80	
		Positive	8	0	
Hu X et al.[13]	Initial disease				<0.05
		Benign	42	38.1	
		Malignant	47	10.4	

disease, there was no significant difference between the two groups. Contrary to this result, Hu et al.[15] reported a mean 5-year survival rate of 38.1% for patients with previous benign disease and 10.4% for those with previous malignant disease, with significant difference.[15] The authors speculated that the biological behavior of previous malignant GSC might not mirror that of previous benign GSC because of the initial malignancy.

We found GSC in 2.7% of all gastric cancers surgically resected in our hospital, which agrees with previous studies showing that GSCs constitute 0.7–6.3% of all gastric cancers.[1,4,7,14,17,21,23] The exact mechanism for the development of GSC remains unclear, although many causative factors have been reported. It is widely accepted that the predominant factor underlying the development of GSC is duodenogastric reflux including bile and pancreatic juice.[24] On the other hand, genetic factors such as p53 signaling might also contribute to the metachronous multiple carcinogenesis,[24] while Kaminishi et al. reported that denervation of the stomach during gastric surgery plays an important role in weakening the defense mechanisms of the gastric mucosa and promoting the development of GSC.[25]

Reflux of bile and pancreatic juice is reportedly carcinogenic and related with GSC.[25] In the present study, anastomotic sites of all patients are exposed to the bile and pancreatic juice because reconstruction method is limited to Billroth I or Billroth II, and did not include Roux-en-Y reconstruction. This is a limitation of the present study. Although there are few reports on GSC including Roux-en-Y reconstruction, the number of cases was too small to compare clinicopathological factors.[7,8] Because Roux-en-Y reconstruction has some advantages over Billroth I or Billroth II reconstruction in preventing duodenogastric reflux and remnant gastritis,[26] it may be inapplicable in patients after Roux-en-Y reconstruction that GSC located at anastomosis has poor outcome shown in the present study.

Previous studies have emphasized a close association between *Helicobacter pylori* infection in the stomach and gastric cancer.[27] Although *H. pylori* infection may also be a causative factor in GSC, the rate of *H. pylori* infection in patients with GSC is lower than those with primary gastric cancer.[28] The gastric stump may be unsuitable environment for *H. pylori* colonization because of increased bile reflux associated with gastrectomy. However, the rate of *H. pylori* infection was demonstrated to be lower in patients with Roux-en-Y reconstruction than in those with Billroth I or Billroth II reconstruction.[29] Other factors besides bile reflux may inhibit *H. pylori* colonization. Thus, the role of *H. pylori* infection in the development of GSC is still uncertain.

Interestingly, the present study also revealed that cases of GSC with benign previous disease showed a significantly higher incidence of diffuse-type histology than those with previous malignant disease. These data conflicted with several studies showing no such significant difference between the groups.[8,20,21] Patients with gastric cancer undergo a wide range of disrupted nerve distribution to the stomach due to lymph node dissections, and denervation of the gastric stump has been associated with the development of intestinal-type cancer.[30] Accordingly, denervation in the initial surgery could be a crucial factor underlying the histological type difference between patients with previous benign disease and those originally with malignant disease.

The present work also demonstrated that patients with previous benign disease did not develop GSC until approximately 14 years later than patients with previous malignant disease, and that this was a significant difference. This finding agrees with other studies that reported a time interval to the occurrence of GSC in patients with previous benign disease and in patients with previous malignant disease of 23.8–32.4 years and 6.8–18.8 years, respectively.[20,21,25,31] The interval between the initial gastrectomy and the subsequent stump cancer was longer in benign gastrectomy cases. This is quite natural because the patients' age at the initial gastrectomy is different, namely ulcer disease requires surgery in much younger patients than cancer. The increased time interval to GSC

developing might indicate that the cause of the first gastric cancer does not affect the subsequent stump cancer.

Because the primary disease was significantly related to the reconstruction with primary operation, patients who had undergone Billroth II reconstruction at the initial surgery also did not develop GSC until approximately 14 years later than those who had undergone Billroth I reconstruction. Interestingly, patients with previous Billroth II reconstruction had tumors more frequently in anastomotic site than those with previous Billroth I reconstruction, which issue agrees with a recent report of the large survey regarding GSC.[31] The high level of duodenogastric reflux in Billroth II reconstruction may be associated with mucosal inflammation and regeneration, resulting in high incidence of GSC in anastomotic site.[32,33] To improve surgical management of GSC, a periodic endoscopic follow-up examination, especially around anastomotic site, is thought to be important. This surveillance program commencing 1 year after the gastrectomy for at least 10 years is in line with the other reports.[7,34]

Conclusion

Earlier detection and the simultaneous, careful observation of anastomotic site are important considerations for improving long-term prognosis of GSC. Thorough follow-up programs should be conducted, continuing up to 10 years after initial gastrectomy and taking account of the potentially different latency periods for GSC development between patients with previous benign disease and those with malignant disease. Appropriate extensive lymph node dissection including the jejunal mesentery in addition to sufficient surgical resection is also crucial for the curative resection of GSC after Billroth I or Billroth II reconstruction.

Conflict of interest statement We certify that there is no actual or potential conflict of interest and no grants or financial support in relation to this article.

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ORIGINAL ARTICLE

Intestinal Lengthening in Adult Patients with Short Bowel Syndrome

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Abstract
Introduction Limited information regarding the usefulness of bowel lengthening in adult patients with short bowel syndrome is available.
Methods Retrospective review of a single center series of intestinal lengthening over 15-year period in patients ≥18 years old.
Results Twenty adult patients underwent Bianchi (n=6) or serial transverse enteroplasty (STEP) (n=15). Median age was 38 (18–66) years and 11 were female. Indications were (a) to increase the enteral caloric intake thereby reduce or wean parenteral nutrition (PN) (n=14) or (b) for bacterial overgrowth (n=6). Twelve patients required additional procedures to relieve the anatomical blockade. Median remnant bowel length prior to surgery, length gained and final bowel length was 60, 20, and 80 cm, respectively. Survival was 90% with mean follow-up of 4.1 years (range=1–7.9 years). Two patients died during follow-up. Intestinal transplant salvage was required in one patient 4.8 years after STEP. Overall, of 17 patients, ten (59%) patients achieved enteral autonomy and were off PN. Of seven patients who are on PN, three patients showed significant improvement in enteral caloric intake. All except one showed significant improvement in symptoms of bacterial overgrowth.
Conclusions Bowel lengthening is technically feasible and effectively leads to weaning from PN in more than half of the adult patients. Lengthening procedures may be an underutilized treatment for adults with short bowel syndrome.

Keywords Bowel lengthening in adults · Short bowel syndrome · TPN dependence

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Introduction

With institution of multidisciplinary intestinal failure centers[1] and with advances in intestinal transplantation (IT), survival of patients with short bowel syndrome (SBS) improved considerably during the past two decades.[2] Survival after IT now approaches that of other solid organ allograft recipients and is similar to survival on long-term parenteral nutrition (PN). Despite these advances, IT is associated with a high risk for infection, rejection, and other complications related to immunosuppression.[2] For this reason, when other medical and surgical alternatives are available for SBS, these should be maximized. Several medical and surgical management strategies have been described for SBS with variable results.[3–6] The goals of surgical treatment are to improve function of the intestinal remnant, expand intestinal surface area and treat intestinal complications. Bowel lengthening procedures (Bianchi

and recently the serial transverse enteroplasty (STEP)) are two of the surgical alternatives for SBS. Although bowel lengthening procedures have been used extensively in pediatric patients with excellent results,[7] there is paucity of information in adults with SBS.[7–10] This is the first study specifically describing surgical lengthening in adults. Patient characteristics are described and risk factors for survival and ability to wean from PN are examined.

Patients and Methods

We retrospectively reviewed the medical history including clinical and laboratory data, and operative records for all patients over 18 years of age who underwent intestinal lengthening procedures for short bowel syndrome between January 1993 and March 2008 at the University of Nebraska Medical Center. This study was approved by the Institutional Review Board.

All patients in the study were referred to our institution for evaluation for intestinal rehabilitation program or intestinal transplantation. All of them are on various degrees of PN for their total caloric requirement. Most of them had experienced various complications of SBS, which include bacterial overgrowth, diarrhea, weight loss, and recurrent septicemia. Patients were divided into two groups depending upon the predominant reason for surgical lengthening (a) to increase the enteral caloric intake (decrease/wean PN requirement) in patients with poor enteral progression/adaptation and had dilated small bowel loops on endoscopy or imaging studies (preferably ≥4 cm in diameter). (b) Intractable symptoms of bacterial overgrowth in the setting of SBS not controlled with antibiotics and had dilated small bowel loops. Patients who had anatomical causes of bowel obstruction were corrected at the time of bowel lengthening. Careful evaluation was performed to exclude patients with end-stage liver disease and/or complications of cirrhosis, who were likely better candidates for liver/small bowel transplantation.

During the operation, an intraoperative measurement of the remnant small bowel from the ligament of Treitz to the ileocolonic junction/ostomy along the antimesenteric border was performed. In most cases, repeat measurement was performed after lengthening. The technical details of Bianchi-type bowel lengthening[11] and STEP procedure[12] have been previously described.

The endpoints of the analysis were resolution of primary symptoms in the patients as discussed above along with patient survival, weaning from PN, or need for intestinal transplantation.

Results

We performed 21 lengthening procedures (6 Bianchi and 15 STEP procedures) in 20 patients between January 1993 and March 2008. One patient underwent STEP and Bianchi procedures at the same time. There were nine males and 11 females. Median age of the patient population was 38 years (range, 18–66 years). The primary diagnosis responsible for SBS was listed in Table 1. The indications for lengthening procedure include inability to wean TPN ($n=14$) and bacterial overgrowth ($n=6$). Twelve patients required additional surgery to correct anatomical bowel pathology. There were two patients in this series who underwent STEP procedure after prior Bianchi, and two additional patients had a prior reversed intestinal segment procedure. Intestinal anatomy includes: initial length of remnant bowel, bowel length gained after the procedure, final length of bowel, percentage of small bowel length gained along with colon anatomy is shown in Table 2. Mean/median (range) remnant bowel length prior to surgery, length gained, and final bowel length was 71/60 (25–150), 29/20 (10–92), and 101/80 (38–172) cm, respectively.

Outcomes of Surgical Lengthening

Bacterial Overgrowth (n=6) One patient in this group required additional stricturoplasty. All except one showed significant improvement in symptoms. One patient had initial improvement with recurrence of symptoms and on further investigations found to have a stricture and this patient is being considered for re-STEP. In addition, three out of six patients were weaned of PN.

For Enteral Autonomy (n=14) Although every patient in our series was on some degree of PN dependence, 14 patients required surgery primarily to increase the enteral intake thereby reduce/wean PN. In these patients we were unable to advance enteral intake prior to surgery. In this group, two patients died during follow-up and one patient underwent transplantation and was off PN. Seven out of

Table 1 Etiology of SBS

Causes of SBS	No.
Recurrent SBO requiring multiple resections	5
Midgut volvulus	4
Traumatic small bowel injury	4
Mesenteric thrombosis	3
Crohn's disease	2
Radiation enteritis	1
Intestinal atresia	1
Congenital SBS	1

Table 2 Summary of patient characteristics

Patient no.	Procedure	Bowel anatomy					TPN		Complications	
		Length of SB remnant	Additional SB length gained	Final SB length	% of SB length gained	Colon anatomy	Off (m)[e]	Last FU	Early	Late
To increase enteral caloric intake										
1	Bianchi and STEP	80	60	140	75	TC and LC	6	Off	–	–
2[c]	STEP	55	12	67	21	LC	–	Off after TX	–	Recurrent line infection—liver failure-transplant
3	STEP	58	92	150	158	LC	7	Off	–	–
4	STEP	62	110	172	177	All	2	Off	–	–
5[b]	Bianchi	48	36	84	75	All	18	Off	–	–
6[b]	Bianchi	150	10	160	6	Left	–	Died	–	–
7[b]	STEP	64	12	76	18	TC and LC	–	On	–	–
8[b]	STEP	52	13	65	25	All	9	Off	–	–
9[d]	STEP	25	13	38	52	Rectum	–	Died	–	–
10[b]	STEP	113	36	149	31	TC and LC	12	Off	–	–
11[b]	STEP	62	22	84	35	All	25	Off	–	–
12[b]	STEP	45	10	55	22	All	–	On	–	–
13[b]	STEP	50	15	65	30	Left	–	On	–	Enterocutaneous fistula
14[b]	STEP	33	33	66	100	Left	–	On	Surgical drainage for abdominal abscess	–
Bacterial overgrowth										
15	Bianchi	120	25	145	20	All	–	On	Pneumonia, SBO-laparotomy	SBO managed conservatively
16	Bianchi	45	25	70	55	TC and LC	–	On	SBO-adhesiolysis	SBO resection of ischemic stricture at prior Bianchi site
17	Bianchi	60	15	75	25	All	NA	Off	SBO-laparotomy	–
18	STEP	90	20	110	22	TC and LC	7	Off	–	–
19[a]	STEP	150	20	170	13	All	11	Off	–	–
20[b]	STEP	60	10	70	16	TC and LC	–	On	–	–

TC transverse colon, *LC* left colon, *NA* data not available

[a] Recurrence of bacterial overgrowth symptoms

[b] Required correction of anatomical bowel obstruction

[c] Enterocutaneous fistula

[d] Marked stoma output

[e] Time taken in months after surgery for enteral autonomy

remaining 11 patients, were weaned off PN. Nine patients required operation for various types of intestinal obstruction, one patient required surgery for high ostomy output with the plan to do reversal of intestinal segment to reduce the stoma output, and one additional patient needed repair of enterocutaneous fistula from prior Bianchi procedure. All these patients had no further bowel obstructions, but one has developed enterocutaneous fistula which is being managed conservatively at the time of last follow-up. In the patient who was scheduled for reversal of intestinal segment during operation small bowel was very short (25 cm long). Additionally, this length of bowel was moderately dilated and after careful consideration, it was determined that patient may benefit from a STEP enteroplasty with a modest gain in length and perhaps slowing of her ostomy output. In subsequent months patient developed rapid worsening of her liver disease and was referred for liver and small intestine transplantation, but died after the patient elected not to pursue transplantation.

Overall, of the 17 patients, 10 (59%) patients achieved enteral autonomy and were off PN at last follow-up. Additionally, three patients, who had previously weaned from PN reverted back to PN dependence, at the time of last follow-up. Of seven patients who are on PN, four patients did not show any improvement in enteral caloric intake during follow-up, three patients showed significant improvement (enteral calories as percentage of total calories before/after= 10% vs 50%, 10% vs 50% and 30% vs 50%, respectively).

1. Survival
   Patient survival 90% with mean follow-up of 4.13 years (median, 3.8 years; range, 1–7.9 years). One adult died with liver failure and sepsis after refusing intestinal transplantation and another patient due to line sepsis.
2. Intestinal Transplantation
   Intestinal transplantation was performed in one patient in this series after 4.8 years after STEP enteroplasty (20.4 years after Bianchi). The indications for transplantation were continued dependence on PN, recurrent line related septicemia and development of PN induced end-stage liver disease. This patient underwent combined liver small bowel transplantation and is doing well at 2 years 3 months follow-up.
3. Complications
   A summary of early and late major postoperative complications that occurred after intestinal lengthening is listed in Table 2. Early complications occurred within a month after surgery. In addition, most of the patients experienced at least one episode of central line infection after lengthening and many had repeated episodes until the central venous catheter was removed. Many of the patients required hospitalization on multiple occasions for management of fluid and electrolyte balance and intravenous antibiotics, but generally the infections were not life threatening and were not attributable to the surgical lengthening per se. The re-hospitalizations were attributed to the short bowel syndrome and due to the ongoing need for central venous access and PN.

Discussion

Most of patients were referred to our center for evaluation in our intestinal rehabilitation program or for small bowel transplantation. Initial strategy was to maximize the enteral tolerance through feeding and gut adaptation. All patients were evaluated for clinical or laboratory evidence of liver disease prior to recommending lengthening procedures. In patients with complications of cirrhosis, lengthening was not offered and these patients were referred for intestinal transplantation. Bowel lengthening was done when patients did not show any further progression with enteral tolerance with persistent need for PN or patients, who had evidence of dilated small bowel loops on imaging studies and symptoms of bacterial overgrowth unresolved with antibiotics.

There is no published data on bowel lengthening procedure exclusively in adults. Most reported series describe exclusively the pediatric population[8] or predominantly pediatric patients with some adults included in one series[7] and two additional single case reports.[9,10] In children, bowel dilatation may be due to natural adaptation and increased growth, but the mechanism is unclear. In several adults in this series, the major indication for the surgical intervention was bowel obstruction secondary to strictures. The obstruction, rather than adaptation may explain the relative rarity of lengthening procedures in adults when compared with children.

To aid the bowel dilatation to perform lengthening procedure later, Georgeson et al. constructed a nipple valve sufficiently obstructive to force proximal bowel dilatation but not enough to precipitate pathologic obstruction. After a period of time, he followed this up with a Bianchi procedure.[14] Construction of the Georgeson valve requires potential sacrifice of a segment of small bowel in the already short bowel and may be difficult to calibrate the degree of bowel obstruction. At present we do not know whether this procedure is applicable in adult patients with non-dilated bowel. In two patients in this series, the creation of a prior reversed intestinal loop may have acted as a functional obstruction, although the intention was not deliberate to achieve "sequential lengthening".

In the initial part of the study, we had patients with Bianchi procedure (historically because it was the only

option) and from 2002, we started performing STEP. As we gained more experience with STEP, we now preferentially perform the STEP as a primary procedure. This is due to following reasons. (a) Some of our primary STEP patients were not candidates for a Bianchi lengthening due to loss of vascularity in one leaf of the mesentery from prior surgery and/or a foreshortened mesentery. (b) The Bianchi procedure can only be performed once, as the mesentery cannot be further divided safely after the leaves have been separated. But STEP procedure can be performed either after prior Bianchi or other intestinal procedures or after STEP successfully.[13] In our study, two patients had prior Bianchi lengthening and two had prior reversed intestinal segment prior to STEP. (c) As noted previously, one advantage of STEP over Bianchi lengthening is the ability to increase the final bowel length by greater than 100% of the original length. In the present series we have three patients in the STEP series had bowel lengthened 1, 1.58, and 1.7 times from original length.

Overall, 59% of patients were completely weaned off PN in our series. Weaning from PN in our series is comparable with published results of Bianchi and STEP (comparable with overall 54% in Bianchi[4,14–21] and better than the 48% reported in the STEP registry[8]). When we analyzed factors affecting the PN dependence, we noticed that final length of the bowel (p=0.01) and length of the bowel added after lengthening procedure (p=0.04) were statistically different between patients who are enterally independent and PN dependent.

Of the six patients who underwent the bowel lengthening for bacterial overgrowth, five have experienced complete resolution of their symptoms. In addition, three of these patients had achieved enteral autonomy. Similar experience reported in pediatric patients who had STEP procedure.[9,10] In view of the discussion above, finding bowel lengthening has a role in SBS patients with intractable symptoms of bacterial overgrowth.

Patient survival in 132 patients who have undergone Bianchi lengthening reported in various publications in the English literature was 80% and 92% in 38 patients reported in the STEP registry,[8] which is comparable with 90% in our series. Because of the small sample group, we did not study factors affecting survival.

This is the largest single center series at this time with experience of bowel lengthening in adults; the study has some inherent drawbacks. (1) The number of patients is small and this hampered the ability to identify potential risk factors for survival, weaning from PN or need for intestinal transplantation. (2) It is difficult to separate the contribution of the medical management from the results of surgical intervention due to the multidisciplinary nature of this intestinal rehabilitation program. (3) Retrospective nature of study. (4) Short follow-up of the STEP patients in this series prevents assessment of the durability of the STEP procedure as has been demonstrated for the Bianchi procedure.

Conclusions

Intestinal lengthening is feasible and efficacious in the management of SBS in adult patients. Intestinal obstruction is a common cause of bowel dilatation in these patients. Bowel lengthening procedures may be an underutilized treatment for adults with short bowel syndrome.

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ORIGINAL ARTICLE

Chronic Idiopathic Intestinal Pseudo-obstruction Treated by Near Total Small Bowel Resection: A 20-Year Experience

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Abstract
Background Patients suffering from chronic idiopathic intestinal pseudo-obstruction (CIIPO) clearly benefit from home parenteral nutrition (HPN) to maintain adequate nutritional status and general health. But intestinal dismotility can seriously disturb their quality of life (QOL) to the point of making it intolerable.
Aim Report our clinical experience on the management of chronic severe occlusive symptoms in CIIPO by near total small bowel resection.
Methods A 20-year retrospective study of eight patients with end-stage CIIPO maintained on HPN and suffering of chronic occlusive symptoms refractory to medical treatment underwent extensive small bowel resection preserving less than 70 cm of total small bowel and less than 20 cm of ileum. The jejunum was anastomosed either to the ileum or to the colon.
Results Six patients were completely relieved from obstructive symptoms. Two patients needed a second operation to remove the residual ileum because of recurrent symptoms. Two were significantly improved. There was no post-operative death. All patients experienced a significant improvement in their QOL.
Conclusion Near total small bowel resection appears to be a safe and effective procedure in end-stage CIIPO patients, refractory to optimal medical treatment.

Keywords Chronic idiopathic intestinal pseudo-obstruction · Home parenteral nutrition · Near total small bowel resection

Abbreviations

CIIPO	Chronic idiopathic intestinal pseudo-obstruction
HPN	Home parenteral nutrition
IT	Intestinal transplantation
QOL	Quality of life

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Introduction

Patients suffering from chronic idiopathic intestinal pseudo-obstruction (CIIPO) are helped by home parenteral nutrition (HPN), which has improved markedly their treatment and survival.[1] However, while these patients now live longer, their gastro-intestinal symptoms may increase and become resistant to medical treatment. Symptoms of vomiting requiring naso-gastric drainage for long periods, at home or in hospital may result in prolonged time off work or school. Pain, diarrhea, massive abdominal distension, fatigue, inability to eat are frequent additional symptoms. Psychologically, these patients can be depressed due to their inability to work and participate in any social activity. Their body image is often impaired because of massive abdominal distension making them look “9 months pregnant”.

The place of surgery in the treatment of CIIPO is somewhat controversial. The generally accepted procedures are laparotomy for diagnosis[20], venting stomies for recurring obstruction, and diverse operations for specific surgical

problems such as malrotation or megaduodenum. Intestinal transplantation (IT) is increasingly used as a life saving procedure mostly in children with liver failure and HPN line complications.[2–4] Because of the improved survival with recent improvements in immunosuppressive therapy, IT has been done in lieu of HPN for end-stage CIIPO.[4–6] However, a recent editorial suggested that HPN is superior to transplantation in the long term.[7]

Venting ostomies as advocated by some authors,[8–10] have improved the treatment of CIIPO in many patients, mostly children. But others[2,11,12] experienced only temporary relief or no benefits at all; our personal experience with this procedure in seven adult patients was disappointing. Multiple other surgical interventions, such as antrectomy, duodenoplasty, duodeno-jejunostomy, Ladd's procedure, Duhamel pull-through, segmental colectomy and others, have been attempted with limited success and have often complicated the evolution of the disease.[2,12–14] Consequently, most recommendations are to limit surgery to bowel decompression. However, few authors have recommended more aggressive surgical interventions such as subtotal small bowel resection to relieve the symptoms in end-stage CIIPO.[15–18]

In the mid-eighties, on an emergency basis for an acute hemorrhage from a duodeno-jejunostomy, we operated on a 10-year-old boy suffering from CIIPO and on HPN for 8 years. The bowel was so dilated that we had to resect all but 165 cm of small bowel and most of the colon. After surgery, his CIIPO symptoms improved markedly for 2 years until he developed liver insufficiency. Since 1993, encouraged by that experience as well as the few cases reported in the literature, and feeling helpless in face of CIIPO patients refractory to medical treatment or dying from their disease, we have performed near total small bowel resections. In this paper, we report our experience and the results obtained and discuss the pertinence and the indications of such a radical treatment.

Patients and Methods

Among the 227 patients included in the HPN program at Hôtel-Dieu de Québec, Université Laval since 1976, 27 of these patients were suffering from CIIPO. Thirteen died from complications of their disease or HPN; 14 are alive and HPN-dependent for life. Ten of these 27 patients have undergone subtotal small bowel resection. One patient was excluded from this series because a partially obstructive adenocarcinoma of the colon was discovered at surgery. Another patient was excluded because 165 cm of small bowel were preserved during an emergency operation for bleeding, hence not meeting the criterion for near total resection as described below.

Indications for this Surgery

The indications to undergo this radical surgery included all following criteria: (1) diagnosis of CIIPO and nutritional failure requiring HPN, (2) symptoms of gastro-intestinal obstruction with severely compromised quality of life (QOL), (3) symptoms refractory to all medical treatment for a prolonged period of time, (4) good general condition allowing surgery, and (5) health condition with general good long-term prognosis.

Type of Surgery

In our series, we defined near total small bowel resection when there were less than 70 cm of residual small bowel. The goal of the surgery was to remove a large portion of the small bowel thought to be responsible for the patients' dysmotility symptoms. Location of proximal and distal sections was determined according to the quality of intestinal tissues documented peroperatively. Proximal anastomosis was planned to save as much proximal jejunum as possible, but in some cases the proximal jejunum or the distal duodenal walls were so thin and dilated (up to 13 cm in diameter) that they ruptured on very gentle manipulation. So, in two patients, an anastomosis had to be done on the second part of the duodenum. Distally, our goal was to do the anastomosis on the non-dilated part of the ileum, but, in some patients, the transverse colon had to be used for anastomosis to the proximal gut. Using these criteria, the maximal length of small bowel saved was 70 cm and there was 20 cm or less of non-dilated ileum suitable for a safe anastomosis. Two patients with jejuno-ileal anastomosis had to be converted to jejuno-colic anastomosis because of recurrence of severe obstructive symptoms.

Evolution Assessment

After surgery, patients were examined at least twice a year. Response to surgery was estimated on global clinical status and based on the clinical judgment of the author, comparing the status of the patient before and after the resection. But the patient's evaluation of his own status was a most important determinant.

Results

Clinical characteristics of the patients in this study are presented in Table 1. Three men and five women with a mean age of 32 years (range, 15–65) and on HPN for

Table 1 Patients included in this study

Pt	Sex	Age at resection	HPN (years) before resection	Previous surgery	Anastomosis		GI evolution post surgery	Overall outcome
					Proximal	Distal		
1	M	24	2		Duodenum 3rd portion	Ileum 20 cm	Improved Oral feeding	Recurrent acute pancreatitis Superior vena cava thrombosis. Death 9 years after resection Drug abuser's pneumonitis
2	F	28	7		Jejunum 50 cm	Ileum 10 cm	Partially improved, but obstructive recurrence	Medical treament reinstituted
					Jejunum 40 cm	Right colon	Vomiting and diarrhea much less frequent, but with the addition of octreotide	HPN and oral feeding. Obstructive symptoms for 1 to 2 days every 1–2 months, and narcotic addiction suspected. 10 years after resection.
3	F	15	2	Duodeno-jejunostomy	Jejunum 20 cm	Ileum 30 cm	Very well for 2 years	Well on oral feeding and HPN after last resection, but osteoporotic vertebral fracture and pathologic behavior
			4	Venting jejunostomy	Jejunum 10 cm	Transverse colon	Oral feeding for 6 months without HPN but obstructive recurrence.	8 years after resection.
				Gastrostomy			Markedly improved	
				colostomy			Vomiting once a month	
4	F	23	2	Gastrostomy Jejunostomy Ileostomy	Jejunum 15 cm	Ileum 10 cm	Very well for 9 years HPN and oral feeding Frequent vomiting for last 2 years	Multiple pulmonary emboli. Infectious complications Death 11 years after resection Drug abuser's pneumonitis
5	M	65	3.5		Duodenum 2nd portion gastrostomy	Ileum 10 cm	Well 2.5 years on HPN and gastrostomy for severe gastroparesis	Terminal liver failure Death 3 years after resection
6	M	28	9		Jejunum 30 cm	Transverse colon	Markedly improved on oral feeding and HPN	Very well on oral feeding and HPN 5 years 9 months after resection
7	F	38	10		Jejunum 30 cm	Ileum 8 cm	Very well but diarrhea	Very well on oral feeding and HPN 5 years 9 months after resection
8	F	35	20	Gastrostomy	Jejunum 30 cm	Ileum 20 cm	Occasional nausea and vomiting controled by octreotide	Very well on oral feeding, HPN and Octreotide 5 years after resection

6.9 years (range, 2–20) were followed up from 2 to 11 years (mean, 6.1 years) after surgery.

All eight (8) patients showed rapid improvements of their CIIPO symptoms after near total small bowel resection. Unable to eat before the operation, all patients but one (patient #6) resumed oral feeding although they all stayed HPN-dependent. Six patients had three to five stools per day depending on their oral food and liquid intake. Two patients (#3 and #8) presented more important diarrhea (10–20 stools per day) and one of them was partially improved by treatment with octreotide. Paradoxically, these two patients have had a jejuno-ileal anastomosis. All patients, without exception, enjoyed a markedly improved QOL, as shown by their return to work or to near normal social activities. All patients enjoyed an improved body image, from looking 9 months pregnant to having a flat abdomen. When asked to evaluate the results of the operation, all patients felt that the surgery saved their life and most wonder why the operation was not done earlier.

The immediate post-operative complications were mild, the most severe being a prolonged ileus which happened in one patient. Late complications were related to the disease or to the HPN. Three patients have died from late complications: one patient died of liver failure and two patients had fatal drug abuser's pneumonitis many years after surgery (patient 5 was asymptomatic for 9 years, then had severe thrombo-embolic disease and recurrent bowel obstruction, while patient 1 suffered from recurrent pancreatitis which led to recurrent drug abuse and death 9 years after surgery). Five patients are alive and in a stable good to excellent general condition. Two patients (patients 3 and 4 with ileal anastomosis) had recurrence of their symptoms and required resection of the residual ileum and jejuno-colic anastomosis. Patient 8 developed mild symptoms of recurring obstructions after being asymptomatic for 3 years; she became asymptomatic on octreotide treatment.

These patients represent a total of 117 years of HPN, 57.5 years of survival post-resection and 53 years of markedly improved QOL.

Discussion

Our experience suggests that in patients with severe CIIPO refractory to medical treatment, near total small bowel resection can be an effective treatment to relieve the symptoms and improve their health status and quality of life.

Small bowel resection in CIIPO has been recommended by very few authors in the literature. Single cases of successful segmental or subtotal small bowel resections were reported in 1961 by Paul,[15] in 1985 by Schuffler,[16] and in 2003 by Nayci et al.[14] These three case reports had 3 ft (90 cm) or more of non-dilated ileum that was anastomosed to a short segment of jejunum so that all these patients could be fed orally and did not need HPN. Schuffler concluded that "radical small bowel resection is not recommended for patients with CIIPO, except in carefully defined, extreme circumstances".[16] In 1988, Mughal and Irving reported on subtotal enterectomy as treatment of end stage of chronic intestinal pseudo-obstruction from different etiologies.[17] In these three patients, a short segment of jejunum was anastomosed to the transverse colon and the longest survival was 2 years. Recently, Joly et al. described five cases of subtotal small bowel resection with jejuno-colic anastomosis in CIIPO patients refractory to treatment and with a post-surgical follow-up of 2–12 years.[18]

In our series of eight patients, we have performed near total small bowel resections, leaving 70 cm or less of residual small bowel length including 20 cm or less of ileum. This was based on the finding of 20 cm or less of non-dilated ileum. Surgery was done to remove a non-functional organ, which was causing intractable bowel obstruction, refractory to all medical treatment. In our series, surgery was not always done as a life saving procedure like in some of the cases reported, but to palliate symptoms that were resisting to maximal medical treatment and that made life intolerable.

The timing of the resection has changed over the past 15 years. The first patient underwent extensive resection while operating for a localized small bowel volvulus. The second patient requested the intervention, threatening to commit suicide if something was not done to relieve his symptoms. The last patients were offered extensive resection when we noticed that the symptoms were refractory to optimal medical treatment for a few months while sustaining progressive worsening of the disease. In our series, this intractable situation presented itself as early as 2 years or as long as 20 years after initiation of HPN. The findings at laparotomy comforted us in our decision. Indeed, the bowel in our patients was aperistaltic, diffusely and extremely dilated (up to 13 cm) and its wall was so thin that mere touching or delicate traction caused complete transverse rupture of the intestine. It was not surprising that this atonic dilated bowel had become an insurmountable obstacle to rehabilitation.

In our series, contrary to the last two reports,[17,18] we have anastomosed the jejunum or the second part of the duodenum to a small segment of ileum (5–20 cm), in seven surgical interventions, hoping to diminish the diarrhea and preserve the entero-hepatic cycle. But our hopes were short-lived. Indeed, two patients with jejuno-ileal anastomosis still had severe diarrhea (more than ten (10) liquid stools per day) while three patients with a jejuno-colonic anastomosis did not complain of excessive diarrhea (less than five liquid stools per day). Another patient developed hepatic failure but this could be attributed to HPN. Many patients developed cholelithiasis, probably because of a disrupted entero-hepatic cycle. Furthermore, four patients with jejuno-ileal anastomosis had recurrence of their obstructive symptoms and two had to undergo a new jejuno-ileal resection and jejuno-colic anastomosis, with good results and one patient presenting with mild obstructive

symptoms was successfully treated with octreotide. The fourth patient, who could not be reoperated because of severe thrombo-embolic disease, died of drug abuse: the recurrence of obstructive symptoms after extensive resection has occurred as long as 8 years after its initial surgery.

Our experience therefore suggest to us that preserving some centimeters of terminal ileum did not offer any benefit or protection against diarrhea or malabsorption and seemed, in fact, responsible for the recurrence of obstructive symptoms in half of our patients. These results and the evolution of the disease suggest to us that only a short segment of the jejunum (10–20 cm) should be saved and anastomosed to the transverse colon as mostly reported in the literature. Lloyd's series of 188 patients on HPN shows that "with short bowel syndrome analysed separately, no statistically significant association was found between survival and either small bowel length or presence of colon in continuity and survival".[19] Furthermore, removing the terminal ileum and the right colon and most of the jejunum would avoid the need of a second resection in some patients.

Our series of eight cases of near total bowel resections performed over a 15-year period resulted in significant improvement which lasted up to 10 years of follow-up and seems to confirm the few reports from the literature which advocate this operation in end-stage CIIPO. We believe that there is enough evidence of its effectiveness to offer this therapeutic modality when the patient becomes refractory to optimal medical treatment after a progressive continuous worsening of the symptoms during many months. The reluctance to consider this operation comes from the fact that we create a definitive short bowel in these patients with its associated complications. This argument is questionable since these patients already present with the malabsorptive symptoms and complications of short bowel failure, but secondary to CIIPO. Furthermore, Lloyd et al.[19] report a 30% survival rate at 20 years for patients on HPN, and their study shows that "patients with short bowel syndrome had the most favorable outcome, while gastrointestinal dysfunction/dysmotility was associated with a three-fold increase in mortality". These findings add arguments in favor of near total small bowel resection leaving about 20 cm of jejunum anastomosed to the transverse colon. Finally, if these patients should develop HPN complications, they could be candidates for intestinal transplantation.

Conclusion

In conclusion therefore, patients with CIIPO resisting to optimal medical treatment can be successfully treated by near total small bowel resection and HPN. The indication of such an operation should be carefully weighed by a team of surgeons and gastro-enterologists experienced with the treatment of CIIPO patients and with HPN. We believe that, in most cases, the resection should include removal of practically all the small bowel, leaving only a short segment of the jejunum or duodenum anastomosed to the transverse colon. If it is elected to preserve some ileum, it should be non-dilated and long enough to expect weaning from HPN. Preserving non-dilated ileum of 20 cm or less appears, in our series, responsible for recurrent obstruction and of no benefit. Medical treatment of these recurrences with octreotide should be attempted before reoperation although it is not always efficacious. In our series, all eight patients had a non-dilated ileum of 20 cm or less. We recognize that these recommendations are based on our limited clinical experience with few patients, but this is related to the infrequent nature of this disease.

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Conflicts of interest None

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ORIGINAL ARTICLE

Evaluating Causes of Death in Familial Adenomatous Polyposis

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Abstract
Background Familial adenomatous polyposis is a genetic syndrome associated with an increased risk of colorectal cancer (CRC) and different extracolonic manifestations.
Goals The goal of this study is to evaluate the frequency of death causes.
Material and Methods Charts from 97 patients treated from 1977 to 2008 were reviewed. Retrieved data and family information allowed us to classify causes of death in those related to CCR to other malignancies or other causes.
Results There were analyzed data from 46 men (47.4%) and 51 women (52.6%) with an average age of 35.1 years (14 to 82). At diagnosis, 57 patients (58.7%) already had CRC-associated polyposis. There were performed 93 colectomies, one internal diversion, and one partial resection. Two patients were not operated on. Results from 19 deceased patients (19.5%) were analyzed. CRC, other tumors (desmoid tumors, lymphoma, and gastric cancer), and other causes (complication of duodenal cancer surgery, complication after ileorectal anastomosis (IRA), and coronary disease) were responsible for 12 (63.1%), four (21.1%), and three (15.8%) of all deaths, respectively. Death from CRC occurred in the context of either systemic, rectal, or pouch recurrence. Desmoid disease was the second cause of death (10.5% of all causes), leading to a fatal outcome 22% of all patients who developed DT during the study period. Upper digestive carcinomas were responsible for other two death cases.
Conclusions (1) CRC is still the most prevalent cause of death; (2) even after curative resections, CRC can cause death through rectal or pouch malignization; (3) long-term survival was also strongly related to the development of extracolonic neoplasia, especially desmoid tumors and gastroduodenal carcinoma; (4) our results raise the need for local improvement in familiar screening and help us to define follow-up strategies and patient-information standards.

Keywords Adenomatous polyposis coli · Colorectal neoplasms · Mortality · Desmoid tumor · Duodenal cancer

Campos FG, Perez RO, Imperiale AR, Seid VE, Nahas SC, and Cecconello I. Evaluating causes of death in Familial Adenomatous Polyposis.

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Introduction

Familial adenomatous polyposis (FAP) is an inherited autosomal dominant disease that usually begins during puberty, with the development of hundreds to thousands of colorectal adenomatous polyps usually by the teenage years, with an almost inevitable tendency of colorectal polyp degeneration into cancer in nontreated patients.[1]

Colorectal cancer (CRC) has been implicated as the main cause of death in FAP patients for many years.[2,3] However, since the pioneer efforts of Drs. Cuthbert Dukes and J.P. Lockhart-Mummery through the foundation of the first Polyposis Registry in St. Mark's Hospital in 1924,[4] many Polyposis Registries have been established in many countries, leading to a decrease in CRC prevalence and improved life expectancy.[5,6]

Since the classical papers from Gardner[7] and Crail[8] describing Gardner and Turcot syndromes, much knowledge has been accumulated regarding the importance of extracolonic manifestations (ECM) of the disease. Today, it is well recognized that FAP is a complex systemic disorder that may affect tissues from ectodermal, endodermal, and mesodermal germ layers. Thus, prophylactic colectomy will not prevent the development of benign or malignant lesions in other organs, since all the cells of the body carry the genetic information determined by the germinative mutation in APC gene.[9,10] For this reason, all the multidisciplinary team taking care of FAP patients should have familiarity with these ECM, once estimated lifetime risk of the syndrome-related complications presumably exceeds 30%.[11]

Our surgical group has already addressed the high incidence (40%) of ECM in FAP, raising their importance by affecting disease's outcome and patient's quality of life.[12] Desmoid tumor (DT) was the third most common ECM. The incidence and types of ECM has also been correlated to many aspects such as length of follow-up, frequency of work-out, polyposis phenotype, and genetic features.[12,13]

Management of FAP patients must focus special attention on the development of three ECM: duodenal polyposis, desmoid tumors, and ileal pouch adenomas. Within this context, patterns of surveillance recommendations in this population have suffered important modifications during the recent decades.[13] Thus, as they potentially may impact outcome, we decided to evaluate their role in causing death in order to raise diagnostic, therapeutic, and surveillance criteria within our medical practice.

Patients and Methods

The present work was approved by the Ethics Committee of the Gastroenterology Department in Hospital das Clínicas in São Paulo.

Between January 1977 and December 2008, prospective data were collected from FAP patients treated at the colorectal unit in our hospital. Diagnosis of FAP was established through medical history and after colonoscopy with histological analysis of polyps.

Preoperative workup included clinical, endoscopic, radiological, and histological examinations such as proctoscopy, colonoscopy, abdominal computed tomography, ophthalmological evaluation, jaw, skull, and long bone X-rays.

There were also retrieved data from surgical treatment (types and character of procedures), immediate or late morbidity, and long-term follow-up regarding cancer recurrence, development of polyps/cancer (in the rectal stump or ileal pouch), reoperations, and length of follow-up.

Causes of death were determined from review of registry charts and family information. These causes were generally classified in three categories: (a) those related to CCR; (b) related to other malignancies; and (c) nonspecific causes. The causes related to other malignancies included desmoid tumors, gastrointestinal tumors, hepatoblastomas, and others.

Results

There were retrieved data from 97 Individuals affected with FAP. Forty-six men (47.4%) and 51 women (52.6%) with an average age of 35.1 years (14 to 82) were treated. At diagnosis, 57 patients (58.7%) already had polyposis-associated CRC, with one (35; 61.4%), two (14; 24.6%), or three (8; 14.0%) primary lesions. Tumors were most commonly located in the rectum and sigmoid colon.

Among the 97 treated patients, two were not operated on due to diffuse hepatic metastasis and religious motives. Six operations were considered palliative (including one internal diversion and one partial resection). Thus, 93 patients underwent colectomies comprising 16 rectocolectomies with ileostomy, 33 restorative proctocolectomies (RPC), and 44 total colectomies with IRA.

A total of 19 patients (19/97; 19.5%) had a fatal outcome in this series (Table 1). Early and late morbidity occurred in 27/95 patients operated on (28.4%), with only one fatal complication on the 15th postoperative due to respiratory failure following an uneventful IRA. This patient represents one death (1.0%) related to postoperative complications.

Within the remaining group of 94 patients, follow-up information was lost in another nine. The remaining 85 patients were followed up for an average amount of 70.1 months (18 to 557 months). During this period, mortality causes were represented by CRC in 12/86 (13.9%) patients, including one that was not operated on due to hepatic dissemination at diagnosis. The other CRC-related causes include five palliative R2 resections and six potentially curative resections. Within this group, two patients died with cancer recurrence at the ileal pouch and rectal stump, respectively. The other four patients developed distant metastasis during follow-up.

DT caused death in two patients (2.3%). Operative complication after duodenopancreatectomy for the treatment of duodenal cancer was the cause of death of patient. One patient died due to hepatic metastasis from a gastric cancer treated before the polyposis. Non-polyposis-related causes were represented by a lung lymphoma and coronary disease in one patient each. Thus, CRC, other tumors (DT, lymphoma, and gastric cancer), and other causes (complication of duodenal cancer surgery, complication after IRA, and coronary disease) were responsible for 12 (63.1%), four (21.0%), and three (15.8%) of deaths, respectively.

Table 1 Causes of Death in Patients with Familial Adenomatous Polyposis

Cause	Number	Percentage (of all patients)	Percentage (of all deaths)
Colorectal cancer	12	13.9[a]	63.1
Desmoid tumor	2	2.3[b]	10.5
Postoperative complication (IRA)	1	1.0[c]	5.3
Complication after GDP	1	1.8[b]	5.3
Metastasis from gastric cancer	1	1.8[b]	5.3
Lung lymphoma	1	1.8[b]	5.3
Other cause	1	1.8[b]	5.3
Total	19	19.5	100

IRA ileorectal anastomosis; *GDP* duodenopancreatectomy

[a] Among 86 patients with follow-up

[b] Among 85 patients with follow-up

[c] Among 95 resection procedures

In the present series, there were detected 76 extracolonic manifestations (ECM) in 44.3% of the FAP patients at diagnosis or during follow-up (Table 2). Conventional upper endoscopy was performed in 65 patients, revealing fundus polyposis in 12 (18.5%), gastric adenoma in eight (12.3%), and duodenal adenomas in seven (10.7%).

Extracolonic tumors with malignant features were detected in 12 patients (12.3%). Age and management of the patients are described in Table 3.

Among this group, one patient developed a lung lymphoma and died, besides treatment with chemotherapy. The other patients died from a gastric cancer that had been resected before the diagnosis of polyposis. She was diagnosed with hepatic metastasis 12 months after the colectomy. The colorectal specimen did not display cancer.

The other patients with gastric cancer were diagnosed 12, 30, and 106 months after colectomy, respectively. One of them also presented a retroperitoneal DT. Duodenal carcinomas developed in three patients (3.4%) in different periods (1, 13, and 47 years) after colectomy. One patient died 30 days after GDP due to pulmonary embolism.

DT were found in nine patients (10.2%) at an average age of 35.8 years (19 to 55), being seven women and two men. The lesions were found in the abdominal cavity and wall (2), at the mesentery (2), abdominal wall (2), abdominal cavity, and retroperitoneum (2). Three patients were diagnosed before colectomy, and the others developed DT in a period of 20–61 months after one or two surgical procedures. Among the patients with follow-up, incidence of DT was 11.1% (4/36) after IRA and 7.6% (2/26) after RPC. DT led to major complications in four patients (three intestinal obstruction and one nephrosis), culminating with death in two cases (22.2%).

The two patients with thyroid cancer were followed up over 60 months without evidence of tumor recurrence. A breast cancer was detected 12 years after colectomy, being treated with radical mastectomy and no signs of recurrence.

Table 2 Frequency of Extracolonic Manifestations Diagnosed during Treatment or Follow-up

Extracolonic manifestation	Number	Percentage
Sebaceous cysts and lipomas	15	17.0
Retinal pigmentation (CHRPE)	6/41	14.6
Osteomas	8/46	17.4
Desmoid tumors	9	10.2
Gastric adenoma	8/65	12.3
duodenal adenoma	7/65	10.8
Gastric fund hyperplastic polyps	12/65	18.5
Gastric cancer	4/65	6.1
Duodenal cancer	3/65	4.6
Thyroid cancer	2	2.3
Dental abnormalities	1	1.1
Adrenal nodule	1	1.1
Total	76	

Fraction represents the number of findings on examinations

CHRPE congenital hypertrophy of the retinal pigment epithelium

Discussion

During lifetime of FAP patients, fatal outcome has been related to disseminated or recurrent CRC, extracolonic tumors, surgical, or ECM complications. Traditionally, CRC has been incriminated as the main cause of death in this population, but it turned to be progressively less common within families under surveillance, occurring almost exclusively in individuals exhibiting new mutations and no family history of the syndrome.[2,3]

The development of many Polyposis Registries around the world helped to spread the importance of screening, prophylactic colectomy, and surveillance strategy translating into better prognosis.[6] This fact is clearly reflected in the CRC incidence reported in countries with regular surveillance, where figures of 50–70% and 3–10% are, respectively, found among symptomatic probands and screened patients.[14,15] Furthermore, survival advantages have been registered, with death occurring in 10 of the 120 call-up patients (8.3%) and 58 of the 116 probands (50%).[16]

Table 3 Mean age and treatment of extracolonic malignant tumors

Local	Mean age (years)	Treatment
Stomach (4)	49.5	Total (3) and subtotal (1) gastrectomy
Duodenum (3)	55.6	Duodeno-pancreatectomy
Thyroid (2)	21.5	Total thyreoidectomy
Breast (1)	66.0	Mastectomy
Myeloid leukemia (1)	38.0	Systemic chemotherapy
Lung lymphoma (1)	68.0	Systemic chemotherapy

As most of the patients in the present series were diagnosed out of screening programs, CRC was implicated as the main cause of death in 13.9% of patients, either in the setting of primary association with FAP or after curative or palliative resections. This represented 63% of all deaths in the present series, and it is within the range of 59–85% (see Table 4) previously reported in important centers.[2,9,10,16,17]

Besides the reported positive effects of prophylactic colectomy on prognosis and survival, the cancer problem is not finished even after a curative surgery for FAP. This fear is clearly justified from the long-term risk of neoplasia in the rectal stump after IRA, not infrequently leading to secondary proctectomy.[16,18] A less frequent potential for malignization within the ileal pouch after RPC has also been reported.[19] Among our patients, 2/12 (16.6%) CRC related-causes (representing 10.5% causes of death) were due to cancer developing in the remaining rectum after IRA or at the ileal pouch after RPC.

In the Finnish Polyposis Registry experience, rectal stump cancer was the second cause of death. In a group of 236 FAP, primary CRC determined 43 deaths (18.2%) and rectal cancer after IRA was the cause in 11 (4.6%), comprising nearly one fifth of all FAP-related causes.[16] Similarly, Arvantis et al[2] have reported that rectal cancer caused 8.3% of all deaths after prophylactic colectomy.

This risk was addressed in long-term follow-up studies, suggesting that a more frequent indication of RPC instead of IRA may improve life expectancy by reducing rectal stump cancer rates.[16,18] Data from the St. Marks Hospital had previously shown a three-fold relative risk of death after IRA.[20] Regarding our patients, the decision to perform an IRA or RPC was established at an individual basis, taking into account a less severe colonic and rectal polyposis, although this endoscopic feature does not guarantee that a rectal cancer will not develop in the future, as we attested in two patients.

Besides these data, the detection of pouch adenomas and even pouch cancer definitively confirmed that RPC is not a "cancer free" alternative to IRA, although RPC was initially thought to abolish the risk of colorectal adenoma development in FAP. The incidence of adenomas developing within the ileal pouch several years after restorative proctocolectomy varies between 20% and 62%, and this occurrence is mostly dependent on duration of follow-up.[21] Consequently, recommendations for close lifelong surveillance either after IRA or RPC have been recently raised in the literature.[19,22] Our group reported a pouch cancer diagnosed 12 years after RPC with mucosectomy and hand-sewn anastomosis. According to the pathologist, a mucinous adenocarcinoma developed from

Table 4 Literature series showing causes of death in familial adenomatous polyposis

Authors	Number of patients and deaths		Colorectal cancer		Non-colorectal neoplasia		Operative morbidity		Other or unknown	
			N	%	*N*	%	*N*	%	*N*	%
Vasen 1990	230	45	29	64.4	4	8.8	6	13.3	6	13.3
Arvantis 1990	465	110	65	59.1	30	27.3	5	4.5	10	9.1
Iwama 1993	1050	414	335	80.9	43	10.4	0	0	36	8.7
Järvinen 1992	192	59	50	84.7	4	6.9	2	3.4	3	5.1
Bertario 1994	971	350	299	85.4	26	7.4	0	0	25	7.1
Belchetz 1996	461	140	103	73.6	27	19.3	2	1.4	8	5.7
Heiskanen 2000	236	68	54	79.4	4	5.9	2	2.9%	8	11.8
Bullow 2003	434	175	121	69.1	23	13.1	4	2.0	27	15.4
Present series	97	19	12	63.1	4	21.0	1	5.2	8	5.7

N number

a remnant rectal mucosa, invading the anal canal through the submucosa.[19]

Despite the frequency of CRC-related death, the long-term mortality pattern has progressively changed over the years. A realistic example of this new scenario was provided by information retrieved from 461 FAP patients followed by a Familial Cancer Registry in Toronto.[3] This extensive work allowed the stratification of 140 death causes by decade, revealing a rise in the ratio of ECM and CRC deaths over the past seven decades. The authors described that during the 1970s, the ratio ECM/CRC was 1:5. In the 1980s, CRC was still causing 2.4 more deaths than ECM, but after the 1990s, both CRC and ECM presented equal rates of death.

With these changes in mind, surveillance of FAP patients focused attention to ECM such as abdominal DT and periampullary cancer.[13,23] In the literature (Table 5), the relative incidence of death due DT or to duodenal carcinoma have presented some variation, with ranges of 0–12.5% and 1.7–8.2%, respectively.[2,3,10,14,15,24] These variations among reference centers and national registries are probably due to population differences concerning the frequency of specific genetic mutations, screening programs, and periods of evaluation. For example, in Japan, results from two consecutive series[10,25] showed a fall in death age due to a reduction in CRC causing problems, with subsequent elevation of death caused by DT from 0.7% to 10% in a period of 13 years. Data from the Canadian Registry indicate that periampullary tumors became more frequent after the 1970s, when prophylactic surgery became a routine.[3]

DTs are usually diagnosed during the third decade, with a lifetime incidence varying between 7% and 26%.[13] Surgical trauma, genotype, female sex, and family history are considered the main predisposing factors.[26] They generally develop inside the abdomen (80%) but may be found within the abdominal wall (10–15%) or extra-abdominal (5%).[27]

Since there is no effective way to prevent their occurrence, DT poses a stressing problem. Furthermore, they are notoriously difficult to treat and represent a great challenge due to its variable response to medical treatment and to the high surgical recurrence rates (50%).[28] Apart from its histological benign features and non-metastasizing behavior, DT may infiltrate surrounding structures, leading to intestinal obstruction, ureter involvement, fistula, and masses formation. Among our patients, DT led to four major complications (three intestinal obstruction and one hydronephrosis), culminating with death in two cases (28.7% of abdominal DT). As already reported in other series,[3,21] DT was the second leading cause of death, being responsible for 10.5% of all deaths.

Many patients may live long periods with intermittent symptoms.[27] Concerning their evolution, 5–10% may resolve spontaneously and 30% undergo cycles of progression and resolution. Although half of them may remain stable after diagnosis, 10% of the cases may present a rapid progression, growing and infiltrating the adjacent area.[11,29] In a proposed stratification of DT, Church et al.[30] suggested that disease severity (stage IV) may be associated with some features such as sex (women), low pregnancy rate, de novo APC mutations, and smaller incidence of familiar history. Since new preventive measures or effective treatment are not available, the early diagnosis may allow partial control either with drugs, chemotherapy, or surgery with limited perspectives.

Another important source of morbidity lies on the gastroduodenal mucosa of FAP patients. While gastric lesions such as fundic gland polyps may be found in half of patients, adenomas (10%) and carcinomas are less frequently detected.[31,32] We diagnosed eight (12.3%) gastric adenomatous polyps and four (6.1%) gastric cancers in 65 patients who performed upper endoscopy.

At diagnosis, the average age in gastric cancer patients was 49.5 years, and they underwent partial (1) and total (3)

Table 5 Non-colorectal neoplasia causes of death in familial adenomatous polyposis series

Authors	Number of deaths	Gastric cancer		Duodenal cancer		Desmoid tumor		Other tumors	
		N	%	*N*	%	*N*	%	*N*	%
Vasen 1990	45	0		1	2.2	3	6.7	0	
Arvantis 1990	110	0		9	8.2	12	10.9	9	8.2
Iwama 1993	414	12	2.9	11	2.6	8	1.9	12	2.9
Järvinen 1992	59	1	1.7	1	1.7	0		2	3.4
Bertario 1994	350	4	1.1	2	0.6	8	2.3	12	3.4
Belchetz 1996	140	1	0.7	7	5.0	12	8.6	7	5.0
Heiskanen 2000	68	2	2.9	2	2.9	0		0	
Bullow 2003	175	0		5	2.8	3	1.7	15	8.6
Present series	19	1	5.2	0		2	10.5%	1	5.2

gastrectomies. While three lesions were discovered during follow-up (12, 30, and 106 months after colectomy), one patient was diagnosed as having gastric cancer before the diagnosis of FAP. She died of hepatic metastasis some months after colectomy and represents 5.2% of our death causes.

The incidence of gastric adenocarcinoma varies between Western (0.5%) and Asian countries (4.5–13.6%).[10,32] Previous reports showed that gastric cancer was responsible for 0.7–2.9% of all deaths (Table 5).

Regarding the upper digestive tract, a more relevant problem is the development of small or microscopic duodenal adenomas that may be found in at least 50% of patients, with a lifetime risk approaching 90–100%.[33–36] These lesions are generally discovered 10–20 years after the colorectal polyps, and the risk of advanced duodenal adenomatosis increases with age.

The 10.8% incidence of duodenal adenomas in present series may be explained by the young age of most of the patients that underwent upper endoscopy. Moreover, most endoscopies were performed without lateral vision or multiple blind biopsies around the periampullary area. For this reason, we decided to develop a prospective study with NBI (*Narrow-band Imaging System*), after what we detected duodenal adenomas in 78% of consecutive subjects (unpublished data).

Duodenal cancer was diagnosed in 4.6% of the exams at a median age of 55.6 years, in different periods (47, 13, and 1 year) after colectomy. In the literature, progression to carcinoma may occur in 4–12% (average 5%) of cases, at a median age of 45–52 years.[36,37] As this transformation into carcinoma may take almost two decades, prophylactic examination of the gastroduodenal mucosa should start at 25 years of age, with reduced intervals according to the severity of adenomatosis. This recommendation is based on the rationale that identification of advanced duodenal disease or treatment of early adenomas may reduce duodenal cancer-related mortality.[36]

In this setting, patients who develop severe adenomatosis (Spigelman IV) may require yearly endoscopies and turn into candidates for a cancer prophylactic operation (pylorus sparing or pancreas sparing duodenectomy). Otherwise, a more radical treatment (pancreatico-duodenectomy—Whipple's operation) has only been advocated for patients with carcinomas due to its associated morbidity.[38]

Although none of our three patients died from the duodenal cancer so far, this malignancy may represent 1.7–8.2% of all deaths in FAP (Table 5). However, one of the patients operated on died 30 days after a duodenopancreatectomy due to pulmonary embolism.

The issue of operative complications has also been associated with fatal outcome after performing a colectomy for FAP treatment. In the reviewed series (Table 4), surgical morbidity was incriminated in about 0–13.3% of all cases of death. Among our patients, only one (5.2%) died as a consequence of a surgical intervention to treat the polyposis.

Thus, CRC, non-colorectal tumors (DT, lymphoma, and gastric cancer) and other causes (complication of duodenal cancer surgery, complication after IRA, and coronary disease) were responsible for 12 (63.1%), four (21.0%), and three (15.8%) of deaths, respectively. Table 3 shows the reported frequency of non-colorectal tumors leading to death in FAP patients. On this category, there were included DT, gastric cancer, duodenal carcinoma, and other malignancies not necessarily associated with FAP. As a group, all these non-colorectal tumors comprised 6–27% of all causes of death.

On the basis of a genetic mutation causing cell proliferation, it is not a surprise to find other malignancies occurring in FAP patients, although some ECM are not predictable based on germ line APC mutations.[3] It has already been addressed that this cumulative probability increases with age, and it is also greater than the general population.[39] Among our patients, there were diagnosed malignant tumors in stomach, duodenum, thyroid, breast, lung, and a myeloid leukemia.

Thus, the data discussed here show that the leading cause of death is CRC and that surveillance of FAP patients can reduce CRC and CRC-associated mortality. With improved longevity, long-term morbidity and mortality have been increasingly determined by the development of desmoid disease and gastroduodenal, rectal, and ileal-pouch neoplasia. There is also evidence that deaths resulting from ECM will continue to increase even when CRC deaths remain stable.[3,9]

As a consequence, late prognosis of FAP patients requires surveillance through computed tomographic scanning, gastroduodenoscopy, and pouchoscopy. Furthermore, future studies should focus on discovering new risk factors that could predict the malignization of duodenal, rectal, and pouch adenomas. Additionally, efforts should be driven towards the control of desmoid disease, addressing the potential of drug prophylactic treatment in patients at risk and as well as new effective therapeutic options to progressive growing desmoids.

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ORIGINAL ARTICLE

Single-Incision Laparoscopic Endorectal Pull-Through (SILEP) for Hirschsprung Disease

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Abstract
Background Over the last 15 years, the laparoscopic-assisted endorectal pull-through procedure first described by Georgeson has become the standard treatment for Hirschsprung disease in many centers around the world. We report the first six patients who were operated using a single-incision endosurgical approach.
Methods Six infants (one female) diagnosed with Hirschsprung disease underwent laparoscopic endorectal pull-through via a single 1 cm horizontal skin incision in the umbilicus. Firstly, laparoscopic seromuscular leveling biopsies of the rectum and sigmoid were obtained. The affected rectosigmoid colon and rectum was then mobilized distally beyond the peritoneal reflection, facilitating the subsequent perineal dissection, pull-through, and coloanal anastomosis. Operative variables were compared between single-incision and conventional laparoscopic endorectal pull-through.
Results The patients' average age and weight was 28 days and 3.8 kg, respectively. Operative time ranged from 90 to 220 min, with a mean estimated blood loss of 3.7 ml. There were no intraoperative complications. Postoperatively, all six patients recovered uneventfully and were discharged home on full feeds after a median of 7 days. On follow-up, the patients had virtually no appreciable scar, were feeding well, stooling, and gaining weight appropriately. The results were similar to those of conventional laparoscopic endorectal pull-through.
Conclusion Although technically challenging, laparoscopic-assisted endorectal pull-through in infants with Hirschsprung disease can be performed safely through a single umbilical incision with good postoperative results and excellent cosmesis.

Keywords Single-incision · Laparoscopy · Hirschsprung · Pull-through

Introduction

Only three decades ago, infants diagnosed with Hirschsprung disease were invariably committed to a multistage sequence of operations, including the creation of a colostomy, an open surgical pull-through procedure, followed by a colostomy takedown. In 1995, Georgeson first described the primary laparoscopic pull-through for Hirschsprung disease.[1] Since then, this concept has gained popularity in many centers around the world. It is usually accomplished through a total of 4 small incisions in the abdomen to accommodate the laparoscopic trocars.

Recently, single-incision laparoscopy has gained momentum and popularity in adults as a way to reduce the visible scars on the abdomen. It has also been described for basic endosurgical procedures such as appendectomy, cholecystectomy, splenectomy, and inguinal hernia repair in children.[2–5] In our center, we have performed over 200 single-incision pediatric endosurgical procedures, and pyloromyotomies are now routinely performed using single-incision pediatric endosurgery in infants.[6]

In the following, we report the first six infants with Hirschsprung disease who underwent a single-incision laparoscopic endorectal pull-through (SILEP) procedure.

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Materials and Methods

After approval of the institutional review board of our institution was obtained (Protocol number X090814001), data on the patients was collected prospectively.

Patients

The patients were transferred to our neonatal intensive care unit with clinical symptoms of neonatal constipation. Suction rectal biopsies showed the absence of ganglion cells and abnormal acetylcholinesterase staining. A barium contrast enema showed a transition zone at the rectosigmoid junction. After informed consent was obtained from the parents, the patients were scheduled for a laparoscopic endorectal pull-through procedure. Data on operative times, estimated blood loss, complications, postoperative length of stay, and outcome were acquired in a prospective fashion, and compared to those of the first author's last four conventional laparoscopic endorectal pull-throughs.

Technique

The technique is similar to the one described by Georgeson[1] but uses a single, 1-cm horizontal skin incision in the umbilicus for laparoscopic access.

The patient is placed supine, transversely across the end of the bed and the entire body caudal to the nipple line is prepared and draped in a sterile fashion. The monitor is positioned at the patient's feet. A 1-cm horizontal skin incision is made in the umbilicus, and two 4-mm trocars are placed into the abdomen through small fascial incisions on both sides laterally. The capnoperitoneum is established using a pressure of 8 mmHg and a flow of 2 l/min. Another stab incision is made centrally in the wound through which a 3-mm Maryland dissector is introduced. With the 4-mm 30° optic through the left port, and the 3-mm endosurgical Metzenbaum scissors through the right-sided port, two or three seromuscular leveling biopsies of the rectum and sigmoid colon are obtained and sent for rapid frozen section to pathology to determine the presence or absence of ganglion cells in the submucosal nerve plexus (Fig. 1). In the setting of a clear transition zone upon laparoscopic inspection, at least one biopsy was taken from the dilated proximal bowel. In the first patient, we closed the seromuscular biopsy sites with 6–0 polyglactin sutures using extracorporeal knot-tying and a knot pusher (Fig. 2). We abandoned this step in the following two patients since the biopsy sites would be incorporated in the resected specimen. In two patients (patients 2 and 6), a proprietary single-access device (TRIPORT Access System, Olympus, Center Valley, PA) was used instead of the conventional laparoscopic trocars.

According to the biopsy results, the affected portion of rectum and sigmoid was then mobilized 5 cm proximal to the most distal biopsy site showing ganglion cells by taking down the mesentery using the electrocautery hook. In one patient, a 5-mm expandable trocar was placed in the central incision to introduce a 5-mm high-frequency cutting and sealing device (EnSeal (TM), SurgRx Inc, Redwood City, CA) for this task (Fig. 3). The dissection was continued to the peritoneal reflection of the rectum (Fig. 4). The instruments were removed, the carbon dioxide was desufflated, and the legs were elevated to expose the perineum.

The anoderm was everted by radial simple 2–0 silk sutures. The mucosa was incised circumferentially approximately 1 cm proximal to the dentate line using the electrocautery and 4–0 Vicryl traction sutures were placed. Dissecting in the submucosal plane circumferentially, the muscular layer was stripped to create an everted muscular cuff. The muscular cuff was then circumferentially and dorsally incised and the affected segment of bowel was pulled through the anus until 5-cm proximal to the lowest biopsy site demonstrating ganglion cells. The colon was cut transversely at this level and a coloanal anastomosis was performed using interrupted 4–0 polyglactin sutures.

Appropriate position and laxity of the remaining colon was confirmed endoscopically and then the instruments and trocars were removed. The umbilical fascia was closed using 3–0 polydioxanone (PDS) suture and the skin was approximated using 5–0 Poliglecaprone (Monocryl (TM)).

All patients were offered oral formula on postoperative day 1. They were discharged once they reached full oral feeds, were off all analgesics, and were gaining weight. Follow-up was scheduled at 2 to 3 weeks postoperatively.

Results

The procedure was performed on a total of six patients (one girl). The average age was 28±32 (median 13.5) days, with

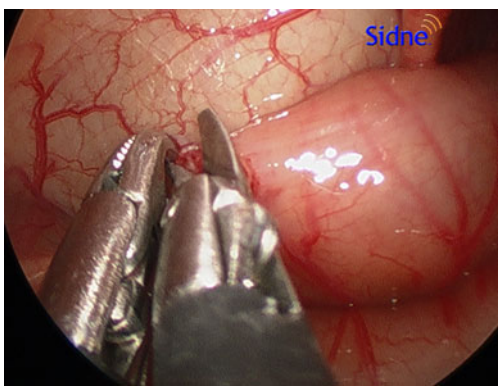

Fig. 1 Obtaining a seromuscular biopsy using the 3-mm Maryland grasper and Metzenbaum scissors

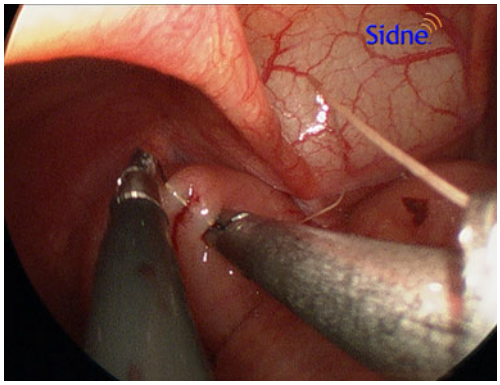

Fig. 2 In cases when biopsy sites are left in situ, they are closed using a 6–0 Vicryl suture, extracorporeal knot-tying, and a 3-mm knot pusher (instrument entering from lower right)

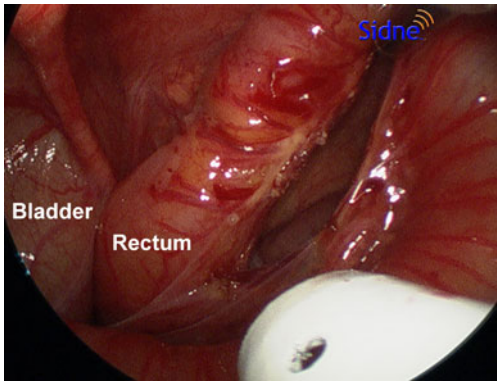

Fig. 4 View of the mobilized portion of rectum. In most cases, this dissection can be safely performed using hook electrocautery

a mean weight of 3.8±0.8 kg at the time of the operation. Operative time was 145±44 min (range, 90 to 220 min), and estimated blood loss 3.7±1.2 ml (Table 1). There were no unanticipated intraoperative events or complications. Postoperatively, all three patients recovered uneventfully and were discharged home on full feeds after a median of 7 days (range, 3 to 12 days). At the time of follow-up in the ambulatory clinic, the patients had virtually no appreciable scar (Fig. 5), were feeding well, stooling spontaneously multiple times a day, and had gained an average of 37 g per day. At that time, a dilation program was initiated, and the parents were instructed how to dilate at home.

The patients who had undergone conventional laparoscopic endorectal pull-through were similar in age, weight, operative times, blood loss, postoperative length of stay, and number of biopsies taken (last two rows of Table 1).

Discussion

Traditionally, transanal pull-through operations have been performed in an open surgical fashion via a transverse or low midline laparotomy, usually along with a protective colostomy, resulting in prominent abdominal scars. In 1995, Georgeson described the single-stage, primary laparoscopic-assisted endorectal pull-through,[1] which consists of laparoscopically obtaining seromuscular biopsies and mobilization of the affected rectosigmoid segment, followed by perineal pull-through and colorectal anastomosis.

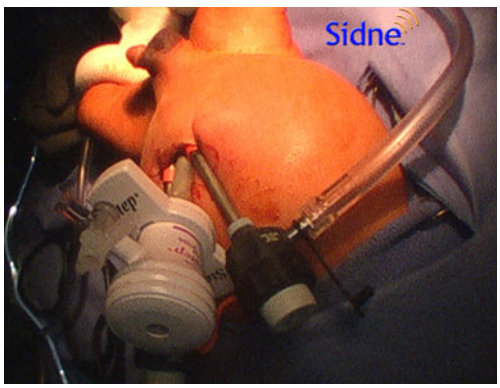

Fig. 3 Four-millimeter trocars are placed laterally in the skin incision. A third 5-mm trocar may be inserted centrally to accommodate a high-frequency sealing–cutting device

Three years later, De la Torre-Mondragón described the purely transanal endorectal pull-through,[7] in which the mucosectomy, colectomy, and pull-through are performed without the aid of laparotomy or laparoscopy. Drawbacks to this procedure are the lack of seromuscular guiding biopsies, which may result in removing an unnecessarily large or too small segment of bowel.[8] Furthermore, in our experience, mobilizing the rectum without prior dissection of the mesentery and peritoneal reflection makes this part of the operation more difficult and, more importantly, may result in a colonanal anastomosis on tension which thereby eliminates the natural anorectal angle.

Sauer et al. have proposed obtaining seromuscular biopsies through an open transumbilical incision[9] instead of laparoscopy. Although this allows histopathologic guidance of the extent of resection, some segments of the bowel, such as the rectum, may not be accessible by this technique. Furthermore, dissection of the mesentery for mobilization is not feasible.

In contrast, the SILEP allows the surgeon to take multiple seromuscular biopsies at all levels of the rectum and colon, and the affected portion of bowel can be mobilized completely down to below the peritoneal reflection. The 1-cm incision in the umbilicus necessary for the placement of the trocars is smaller than what is necessary for open biopsies.

The SILEP procedure can be performed without using any special equipment other than standard laparoscopic instruments and trocars. Therefore, the cost should be the same as for the standard multi-site laparoscopic endor-

Table 1 Characteristics and operative data

Patient number	Age (days), gender	Weight (kg)	Operative time (min)	EBL (ml)	Postoperative stay (days)	Bx sites, sutured?	Access technique, notes
1	10, male	3.4	220	5	5	2, yes	2 free 4 mm trocars, one 5 mm central trocar
2	17, male	3.4	126	3	12	2, no	TRIPORT
3	31, male	4.3	143	2	9	3, no	Additional bx, proximal bx inconclusive
4	91, male	5.2	164	5	3	2, no	2 free 4 mm trocars, Down syndrome
5	10, male	3.6	90	4	5	2, no	2 free 4 mm trocars
6	10, female	3.0	125	3	9	2, no	TRIPORT
SILEP Median (range)	13.5 (10–91)	3.5 (3–5.2)	134.5 (90–220)	3.5 (2–5)	7 (3–12)	2 (2–3)	
CLERPT Median (range)	18.5 (7–573)	3.85 (3.5–13)	158 (145–186)	5 (3–10)	4.5 (3–7)	2 (1–4)	5 mm umbilical trocar, 2×4 ;mm lateral trocars

bx biopsy, *EBL* estimated blood loss, *SILEP* single-incision laparoscopic endorectal pull-through, *CLERPT* conventional laparoscopic endorectal pull-through

ectal pull-through, while all other evaluated parameters were similar as well. For most infants, simple hook cautery is sufficient to take down the mesentery and coagulate the vessels. The 5-mm centrally placed trocar is only necessary if a high-frequency sealing–cutting instrument is used, as may be practical in older children. Using two 4 mm trocars on the sides of the wound rather than placing the instruments directly through the fascia provides flexibility in camera positioning, and also facilitates the removal of the biopsy specimens. In the cases where the proprietary single-access device was used, it was placed through a 1 cm full-thickness horizontal incision without using the introducer device (to save space and allow for a smaller incision). The perceived advantage of this special trocar was substantially less gas leak. The disadvantage is the considerable cost that it adds to the procedure.

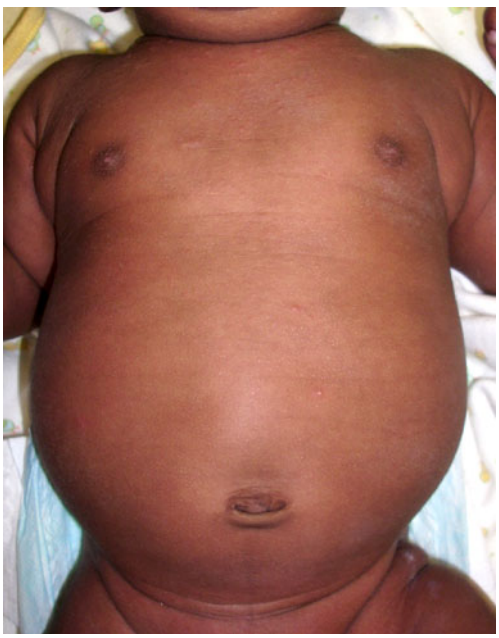

Fig. 5 Two weeks postoperatively, the child has no appreciable scars

If the most proximal biopsy is the only one containing ganglion cells, as in most cases, then all of the biopsy sites will eventually be part of the resected specimen and seromuscular closure is unnecessary. If one of the sites remains in situ, however, suturing the defect can readily be accomplished in single-incision technique using extracorporeal knot-tying along with a 3 mm knot pusher (Fig. 2). Suturing may also be necessary if a full-thickness biopsy is obtained accidentally to avoid contamination of the abdominal cavity.

Conclusion

The difference between SILEP and conventional laparoscopic pull-through may principally be cosmetic in nature. Whether the smaller scar also results in less pain or faster recovery is speculative and cannot be concluded from this small series. Obtaining the biopsies using a parallel, nonangulated instrument configuration in particular is technically demanding. However, we believe that the quality of the operation itself is in no way compromised by the single-incision approach. Thus far the parents have been extremely content with the results. With the SILEP procedure, an accurate, histopathologically guided pull-through procedure including full mobilization of the affected bowel can be performed in children with Hirschsprung disease, avoiding any visible abdominal scars.

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ORIGINAL ARTICLE

Laparoscopic Versus Open Appendectomy: An Analysis of Outcomes in 17,199 Patients Using ACS/NSQIP

Andrew J. Page · Jonathan D. Pollock · Sebastian Perez · S. Scott Davis · Edward Lin · John F. Sweeney

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Abstract
Background The current study was undertaken to evaluate the outcomes for open and laparoscopic appendectomy using the 2008 American College of Surgeons: National Surgical Quality Improvement Program (ACS/NSQIP) Participant Use File (PUF). We hypothesized that laparoscopic appendectomy would have fewer infectious complications, superior perioperative outcomes, and decreased morbidity and mortality when compared to open appendectomy.
Study Design Using the Current Procedural Technology (CPT) codes for open (44950) and laparoscopic (44970) appendectomy, 17, 199 patients were identified from the ACS/NSQIP PUF file that underwent appendectomy in 2008. Univariate analysis with chi-squared tests for categorical data and *t* tests or ANOVA tests for continuous data was used. Binary logistic regression models were used to evaluate outcomes for independent association by multivariable analysis.
Results Of the patients, 3,025 underwent open appendectomy and 14,174 underwent laparoscopic appendectomy. Patients undergoing laparoscopic appendectomy had significantly shorter operative times and hospital length of stay. They also had a significantly lower incidence of superficial and deep surgical site infections, wound disruptions, fewer complications, and lower perioperative mortality when compared to patients undergoing open appendectomy.
Conclusions Using the ACS/NSQIP PUF file, we demonstrate that laparoscopic appendectomy has better outcomes than open appendectomy for the treatment of appendicitis. While the operative treatment of appendicitis is surgeon specific, this study lends support to the laparoscopic approach for patients requiring appendectomy.

Keywords Laparoscopy · Appendectomy · Complications

Introduction

McBurney first described the surgical treatment of acute appendicitis using the classic right lower quadrant incision in 1894[1]. Subsequently, appendectomy has become one of the most frequently performed abdominal procedures, with about 8% of the population in industrialized countries requiring removal of the appendix over the course of their lifetime[2]. Since the initial reports of the first successful laparoscopic cholecystectomy for the treatment of symptomatic biliary tract disease, virtually every abdominal organ has been approached using minimally invasive surgical techniques[3]. The benefits of smaller incisions and less wound morbidity, less postoperative pain, shorter length of stay (LOS), and earlier return to work when compared to standard open operations to treat the same condition make the laparoscopic approach extremely advantageous. The first laparoscopic appendectomy was performed in 1988 by Semm[4]. However, the laparoscopic approach to appendectomy has not been championed by all surgeons like it has for cholecystectomy and other intra-abdominal organs. This is primarily because the

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benefits of the laparoscopic approach for appendectomy are not quite as obvious as they are for these other procedures. To date, over 50 studies have been undertaken comparing laparoscopic to open appendectomy for the treatment of acute appendicitis[5]. Many of these studies have been underpowered and therefore have failed to show significant differences in outcomes between the two approaches leading to controversy surrounding this particular topic.

The American College of Surgeons: National Surgical Quality Improvement Study (ACS/NSQIP) is a risk-adjusted outcomes program that was initially developed in the early 1990s by the Surgical Service in the Department of Veterans Affairs in response to a Congressional mandate to report risk adjusted surgical outcomes on an annual basis[6]. The results of the program in the Veterans Affairs sector were overwhelmingly positive, demonstrating significant reductions in both morbidity and mortality. This led to a trial in the private sector to determine if the risk adjustment models were applicable to a more heterogeneous population of patients[7]. Ultimately, the American College of Surgeons embraced the program, making it the cornerstone of the College's quality program.

The ACS/NSQIP collects data on 135 variables, including preoperative risk factors, intraoperative variables, and 30-day postoperative mortality and morbidity outcomes for patients undergoing major surgical procedures in both the inpatient and outpatient setting. Using these data, the ACS/NSQIP has been able to develop predictive models that apply to a broad range of surgical procedures. The current study was undertaken to evaluate the outcomes for open and laparoscopic appendectomy using this data set. We hypothesized that laparoscopic appendectomy would have fewer infectious complications, superior perioperative outcomes, and decreased morbidity and mortality when compared to open appendectomy

Materials and Methods

To address the question of laparoscopic versus open appendectomy, we utilized the ACS/NSQIP Participant Use File (PUF file) from 2008, which contains de-identified patient data for over 250,000 surgical cases performed at the 250+ hospitals that participate in ACS/NSQIP at the present time. Using the Current Procedural Technology (CPT) codes for open (44950) and laparoscopic (44970) appendectomy, we reviewed 17,199 patients that underwent appendectomy in 2008. ACS/NSQIP assesses a total of 43 demographic and preoperative risk factors, 13 preoperative laboratory values, 14 perioperative risk factors, and 28 postoperative complications for each patient. For the purposes of the current study, demographic variables including age, race, gender, American Society of Anesthesia (ASA) status, and body mass index (BMI) were compared between the two groups. The following preoperative risk factors were also assessed; presence or absence of hypertension, emergency, diabetes mellitus type II (DM), tobacco use, and pregnancy. Postoperative outcomes and complications evaluated include operative time, LOS, surgical site infections, pneumonia, renal insufficiency and acute renal failure, urinary tract infection, deep venous thrombosis (DVT), presence of sepsis or septic shock, and 30-day mortality.

All statistical calculations were performed using SPSS Version 14.0 (SPSS, Inc., Chicago, IL, USA). To identify clinical variables associated with the outcomes of superficial or deep incisional surgical site infection, wound disruptions, organ space infection, sepsis, septic shock, or 30-day mortality, univariate analysis with chi-squared tests for categorical data and *t* tests or ANOVA tests for continuous data were used. Binary logistic regression models were used to evaluate outcomes for independent association by multivariable analysis. Patients with missing data were excluded from multivariable analysis. Further, patients with an ASA classification of five or moribund were also excluded from multivariable analysis. A P value <0.05 in multivariable analysis was used to determine final significance in all analyses.

Results

Patient Demographics

Patient demographics are detailed in Table 1. A total of 17,199 patients were identified from the 2008 PUF file that met the criteria listed in the "Materials and Methods" section; 3,025 patients underwent open appendectomy and 14,174 underwent laparoscopic appendectomy. The mean age of patients undergoing open appendectomy was about 2.5 years greater than that of patients undergoing laparoscopic appendectomy. In addition, a significantly higher percentage of non-white patients underwent open appendectomy. Patients undergoing laparoscopic appendectomy were more commonly female; however, a significantly higher percentage of pregnant females underwent open appendectomy. Finally, patients in the laparoscopic group had a higher BMI.

Patients undergoing open appendectomy had a significantly higher incidence of hypertension but there was no difference in the incidence of DM between the two groups. Patients in the open appendectomy group trended toward a higher ASA classification and more commonly underwent their appendectomy in emergency circumstances. There was no difference in the incidence of tobacco use between the two groups. There was a higher incidence of contaminated wounds in the laparoscopic group and dirty wounds in the open group. The preoperative serum albumin and creatinine were statistically

Table 1 Patient demographics

Variable	Subset	Totals	Open appendectomy	Laparoscopic appendectomy	*P* value
Patients		17,199	3025	14174	
Mean age			40.5	37.9	<0.001
Gender (%)	Male	8,836 (51.4)	1,644 (54.3)	7,192 (50.7)	<0.001
	Female	8,363 (48.6)	1,381 (45.7)	6,982 (49.3)	
Race (%)	White	13,701 (79.7)	2,263 (74.8)	11,438 (80.7)	<0.001
	Other	3,498 (20.3)	762 (25.2)	2,736 (19.3)	
ASA class (%)	1	6,120 (35.6)	994 (32.9)	5,126 (36.2)	<0.001
	2	9,123 (53.0)	1,587 (52.5)	7,536 (53.2)	
	3	1,765 (10.3)	398 (13.2)	1,367 (9.6)	
	4	154 (0.9)	40 (1.3)	114 (0.8)	
	5	2 (0)	2 (0.1)	2 (0)	
	Unknown	29 (0.2)	4 (0.1)	29 (0.2)	
Wound classification (%)	Clean/contaminated	5,918 (34.4)	975 (32.2)	4,943 (34.9)	<0.001
	Contaminated	8,215 (47.8)	1,399 (46.2)	6,816 (48.1)	
	Dirty	3,066 (17.8)	651 (21.5)	2,415 (17.0)	
Mean BMI	26.5		26.2	26.6	0.02
Diabetes (%)	None		2,882 (95.3)	13,620 (96.1)	0.05
	Oral		87 (2.9)	305 (2.2)	
	Insulin		56 (1.9)	249 (1.8)	
Smoking (%)	No	13,487 (78.4)	2,378 (78.6)	11,109 (78.4)	0.78
	Yes	3,712 (21.6)	647 (21.4)	3,065 (21.6)	
HTN (%)	No	14,381 (83.6)	2,430 (80.3)	11,951 (84.3)	<0.001
	Yes	2,818 (16.4)	595 (19.7)	2,223 (15.7)	
Pregnant (%) (only females)	No	8,089 (96.7)	1,282 (92.8)	6,807 (97.5)	<0.001
	Yes	274 (3.3)	99 (7.2)	175 (2.5)	
Emergency (%)	No	4,520 (26.3)	737 (24.4)	3,783 (26.7)	0.01
	Yes	12,679 (73.7)	2,288 (75.6)	10,391 (73.3)	
Mean creatinine		0.90	0.89	0.93	<0.001
Mean albumin		4.2	4.2	4.1	<0.001
Mean WBC		13.0	13.0	12.9	0.30

BMI body mass index, *ASA* American Society of Anesthesiologists, *WBC* white blood cell count, *HTN* hypertension, *NIDDM* non-insulin dependent diabetes, *IDDM* insulin dependent diabetes mellitus

different between the two groups; however, the values were well within normal limits. Preoperative white blood cell count (WBC) was elevated in both groups, and not statistically different.

Perioperative Outcomes

Table 2 documents the perioperative outcomes for patients undergoing appendectomy. Mean operating time was significantly shorter in those patients that underwent a laparoscopic appendectomy. Patients undergoing laparoscopic appendectomy also had a significantly lower incidence of returning to the OR in the postoperative period and had a significantly shorter postoperative LOS. The impact of various demographic factors and operative approach on LOS and operative time was next evaluated using a multivariable model (Table 3). In this model, the laparoscopic approach was found to independently influence both operative time ($p<0.001$) and length of stay ($p<0.001$) in patients undergoing appendectomy. Operative time was also independently influenced by male gender, BMI, wound classification, emergency status, ASA classification, and preoperative serum albumin level. In addition, LOS was independently influenced by patient age, BMI, wound classification, ASA classification, preoperative serum albumin and preoperative WBC.

Postoperative Occurrences

Table 4 documents the postoperative occurrences for the study population. Patients undergoing open appendectomy had significantly higher rates of superficial and deep surgical site infections (SSI), and wound disruptions. Patients undergoing laparoscopic appendectomy had a

Table 2 Perioperative outcomes

	Open appendectomy	Laparoscopic appendectomy	*P* value
Patients	3025	14174	
Mean LOS	3.1 days	1.8 days	<0.001
Mean OP time	56.8 min	50.5 min	<0.001
Return to OR (%)	60 (2.0)	177 (1.2)	0.002

LOS length of stay, *OP* operative

higher rate of organ space infection, but this did not reach statistical significance (p=0.114). Patients undergoing open appendectomy were also significantly more likely to develop pneumonia, DVT, sepsis, septic shock, and death in the postoperative period when compared to patients who underwent laparoscopic appendectomy.

We next performed a multivariable analysis of various demographic factors and the operative approach to determine their impact on these wound occurrences (Table 5). The laparoscopic approach was found to be independently associated with a lower incidence of superficial SSIs (p< 0.001, OR 0.30), deep SSIs (p<0.001, OR 0.26), and wound disruptions (p=0.03, OR 0.26). Operative approach however was not found to be an independent predictor for organ space infections. Other factors found to independently predict the incidence of superficial SSIs included wound classification and diabetes status. In the case of deep SSIs, DM status and preoperative serum albumin were found to be independent predictors. Factors that were found to independently predict the incidence of organ space infections included wound classification and preoperative WBC level.

Table 6 demonstrates the results of a multivariable analysis that was undertaken to determine the impact of various demographic factors and operative approach on the occurrence of sepsis, septic shock, and mortality for patients undergoing appendectomy. The operative approach was not found to independently predict the occurrence of sepsis or septic shock, but it was found to be a weak independent predictor of postoperative mortality (n=20). Other factors that were found to be independent predictors of septic shock included patient age, ASA class, and preoperative serum albumin level. Wound classification and preoperative serum albumin were found to be independent predictors of sepsis. In addition to operative approach, male gender, patient age, ASA classification, and preoperative serum albumin level were found to be independent predictors of postoperative mortality following appendectomy.

Discussion

The current study is the largest of its kind to focus on outcomes for appendectomy based on operative approach. We hypothesized that laparoscopic appendectomy would have fewer infectious complications, superior perioperative outcomes, and decreased morbidity and mortality when

Table 3 Multivariable statistical analysis calculating odds ratios for the categorical outcomes OP time (> 60 min) and LOS (>2 days)

		Op time (>60min)	LOS (> 2days)
Gender	Male	1.17 (0.01)	0.94 (0.29)
Age		1.01 (0.01)	1.0 (<0.001)
BMI		1.03 (< 0.001)	1.0 (0.11)
Smoker		0.95 (0.21)	1.1 (0.21)
Wound class	Clean/contaminated	Ref	Ref
	Contaminated	0.88 (0.01)	0.77 (<0.001)
	Dirty	1.91 (<0.001)	5.20 (<0.001)
Diabetes	None	Ref	Ref
	Oral	1.22 (0.15)	1.71 (0.001)
	Insulin	1.42 (0.02)	1.75 (0.001)
Emergency		0.91 (0.07)	0.92 (0.20)
ASA Class	4	0.64 (1.10)	< 0.001 (4.56)
	3	0.36 (1.06)	< 0.001 (1.41)
	2	0.10 (1.11)	0.09 (1.16)
	1	Ref	Ref
Albumin		0.80 (<0.001)	0.55 (<0.001)
WBC		1.00 (0.74)	1.03 (0.001)
Laparoscopic		0.80 (<0.001)	0.35 (<0.001)

Op operative, *LOS* length of stay, *BMI* body mass index, *ASA* American Society of Anesthesiologists, *WBC* white blood cell count

Binomial logistic regression model with p values listed in parentheses

Table 4 Postoperative wound occurrences, morbidity and mortality

	Open appendectomy	Laparoscopic appendectomy	*P* value
Total	3,025	14,174	
Superficial surgical site infection (%)	120 (4.0)	170 (1.2)	<0.001
Deep incisional surgical site infection (%)	36 (1.2)	33 (0.2)	<0.001
Occurrences wound disruption (%)	10 (0.3)	8 (0.1)	<0.001
Organ space infection (%)	38 (1.3)	234 (1.7)	0.114
Pneumonia (%)	17 (0.6)	36 (0.3)	0.01
Progressive renal insufficiency (%)	5 (0.2)	10 (0.1)	0.11
Acute renal failure (%)	3 (0.1)	9 (0.1)	0.50
UTI (%)	14 (0.5)	57 (0.4)	0.64
DVT (%)	11 (0.4)	15 (0.1)	0.001
Sepsis (%)	42 (1.4)	135 (1.0)	0.03
Septic shock (%)	10 (0.3)	19 (0.1)	0.02
Deaths (%)	10 (0.3)	10 (0.1)	<0.001

UTI urinary tract infection, *DVT* deep venous thrombosis

compared to open appendectomy. To address this hypothesis we utilized the ACS/NSQIP Participant Use File from 2008, which contains de-identified patient data for over 250,000 surgical cases performed at the 250+ hospitals that participate in ACS/NSQIP at the present time.

Using the CPT codes for open and laparoscopic appendectomy, we identified over 17,000 patients that underwent an appendectomy at an ACS/NSQIP participating hospital in 2008. This study shows that in a large cohort, an overwhelming number underwent laparoscopic appendectomy, suggesting that the laparoscopic approach has become the preferred method for appendectomy at this time. Patients undergoing laparoscopic appendectomy were slightly younger, more commonly Caucasian and female, and had a slightly higher BMI when compared to patients that underwent an open appendectomy.

Although there are statistically significant demographic differences between the patient populations in this study, the sheer number of patients in each group may have led to

Table 5 Multivariable analysis calculating odds ratios for factors affecting wound occurrences

		Wound disruptions	Superficial SSI	Deep SSI	Organ space SSI
Gender	Male	1.1 (0.83)	1.3 (0.18)	1.15 (0.64)	1.11 (0.53)
Age		0.99 (0.66)	1.0 (0.67)	1.0 (0.75)	0.99 (0.81)
BMI		1.0 (0.90)	1.0 (0.32)	1.02 (1.15)	1.0 (0.87)
Smoker		1.1 (0.90)	1.0 (0.75)	0.75 (0.45)	1.16 (0.42)
Wound class	Clean/Contaminated	Ref	Ref	Ref	Ref
	Contaminated	1.39 (0.70)	0.98 (0.89)	0.68 (0.29)	1.9 (0.02)
	Dirty	4.68 (0.07)	1.72 (0.007)	1.0 (0.92)	10.7 (<0.001)
Diabetes	None[15]	Ref	Ref	Ref	Ref
	Oral	1.0 (<0.001)	1.9 (0.07)	0.04 (2.89)	1.1 (0.83)
	Insulin	1.0 (<0.001)	2.1 (0.03)	2.2 (0.22)	0.44 (0.25)
Emergency		4.3 (0.16)	0.95 (0.74)	1.50 (0.27)	1.11 (0.59)
ASA Class	4	26.1 (0.04)	1.7 (0.30)	1.0 (0.99)	0.34 (0.30)
	3	4.8 (0.18)	1.5 (0.08)	2.0 (0.18)	1.23 (0.34)
	2	7.0 (0.08)	1.88 (0.003)	2.5 (0.06)	0.95 (0.82)
	1	Ref	Ref	Ref	Ref
Albumin		0.85 (0.74)	0.85 (0.25)	0.52 (0.01)	0.85 (0.28)
WBC		1.0 (0.83)	1.03 (0.06)	1.04 (0.21)	1.04 (0.03)
Laparoscopic		0.26 (0.03)	0.30 (< 0.001)	0.26 (<0.001)	1.29 (0.27)

BMI body mass index, *ASA* American Society of Anesthesiologists, *WBC* white blood cell count

Binomial logistic regression model with p values listed in parentheses

Table 6 Multivariable analysis of factors calculating odds ratios affecting mortality, sepsis and septic shock

		Mortality[a]	Sepsis	Septic Shock[a]
Gender	Male	4.8 (0.02)	1.1 (0.7)	1.7 (0.21)
Age		1.06 (0.01)	1.0 (0.88)	1.07 (<0.001)
BMI		1.0 (0.94)	1.02 (0.14)	1.02 (0.38)
Smoker		1.3 (0.67)	1.4 (0.11)	1.65 (0.34)
Wound class	Clean/contaminated	Ref	Ref	Ref
	Contaminated	0.21 (0.73)	1.1 (0.75)	0.87 (0.84)
	Dirty	0.56 (0.37)	5.1 (<0.001)	1.85 (0.31)
Diabetes	None	Ref	Ref	Ref
	Oral	1.5 (0.61)	0.85 (0.76)	1.3 (0.71)
	Insulin	0.99 (<0.001)	0.49 (0.33)	0.4 (0.40)
Emergency		1.3 (0.62)	0.23 (0.78)	1.82 (0.26)
ASA Class	4	(0.98)	1.6 (0.46)	(0.98)
	3	(0.98)	1.1 (0.78)	(0.98)
	2	(0.98)	1.1 (0.71)	(0.98)
	1	Ref	Ref	Ref
Albumin		0.36 (0.004)	0.61 (0.01)	0.37 (<0.001)
WBC		1.0 (0.88)	1.0 (0.24)	1.0 (0.39)
Laparoscopic		0.28 (0.03)	0.90 (0.68)	0.51 (0.15)

BMI body mass index, *ASA* American Society of Anesthesiologists, *WBC* white blood cell count

Binomial logistic regression model with p values listed in parentheses

[a] Odds ratios were not reported for mortality (n=20, 0.1%) and septic shock (n=29, 0.2%) given the disproportionately small number of events divided between the four ASA classifications

the statistical differences while the "biological relevance" of these differences is questionable. One potential explanation for the younger age and higher percentage of females undergoing laparoscopic appendectomy is the intraabdominal visualization provided by the laparoscopic approach. This is a major advantage in the case of diagnostic dilemmas that are more common in young females with lower abdominal pain. The difference in race between the two groups is difficult to explain and cannot be definitively answered given the current data set. We show that there was a significant trend towards a higher ASA score and dirty wound classification in patients undergoing an open appendectomy. This data might suggest that the more difficult appendectomies or appendectomies in sicker patients were performed open.

Although there are statistically significant demographic differences between the patient populations in this study, the "biological relevance" is questionable. To more accurately assess the relationship and effects of these demographic factors on perioperative results, we incorporated already established multivariable models on our desired outcomes. We confirm that well-established variables that have been shown to influence surgical outcomes in other studies (e.g., preoperative albumin, wound classification, and ASA score), also significantly influence outcomes for appendectomy in this study, lending credibility to our statistical analysis[8–12].

However, in our multivariable model, we also incorporated operative approach, and found that while intuitive pre-operative factors were still predictive, operative approach was also associated with outcomes. Specifically, we found that the laparoscopic approach was associated with a lower incidence of superficial and deep SSIs, and a lower incidence of wound disruptions in patients undergoing appendectomy. Although organ space infections were slightly higher in the laparoscopic group, this did not reach statistical significance. In a retrospective analysis performed on 11,662 admissions from 22 hospitals comparing open and laparoscopic appendectomy, Brill et al.[13] failed to show any difference in the risk for wound related infection for patients undergoing laparoscopic appendectomy. However, they did show an increase in abscess formation in the laparoscopic group. In a small randomized prospective study of 252 patients, Olmi et al.[14] demonstrated a lower wound infection rate in patients undergoing laparoscopic appendectomy. The infectious complication that has been most frequently associated with laparoscopic appendectomy in many studies is intra-abdominal abscess or organ space infection[5].

The results of this study also show that laparoscopic appendectomy was performed on average 6 min faster than open appendectomy. This contradicts previous prospective studies showing longer operative times for laparoscopic appendectomy[15,16]. This may be due to changing practice patterns and increased laparoscopic skill level in surgeons. This study also demonstrates a significantly shorter LOS that was more than 1 day shorter than the mean LOS for an open appendectomy. Ignacio et al.[17] performed a randomized prospective trial comparing laparoscopic and open appendectomy. The trial was more directed towards evaluating postoperative LOS, pain, and return to work, and did not focus on postoperative complications. The trial was very small in number and failed to show any benefit for LOS, perceived pain postoperatively, and return to work between the two operations. Moberg et al.[18] also performed a

randomized prospective trial comparing laparoscopic to open appendectomy. The primary end-point evaluated was time to full recovery, with secondary endpoints including complications, operating time, LOS and functional status. The study failed to show any significant differences between patients that underwent an open or laparoscopic appendectomy. Although operative time was shorter in the group that underwent a laparoscopic appendectomy, because the study was under-powered, the difference was not statistically significant. A meta-analysis of all randomized prospective trials undertaken between 1995 and 2006 confirmed that laparoscopic appendectomy is safe and results in a faster return to normal activities with fewer wound complications at the expense of a longer operating time[19].

Finally, this study shows that patients undergoing laparoscopic appendectomy have a lower mortality rate and have a lower risk for sepsis and septic shock when compared to patients undergoing open appendectomy, although in the multivariable model laparoscopic appendectomy was only found to be weakly predictive of mortality. This has not been previously described and is likely secondary to the large number of patients included in the current study as compared to most other randomized prospective trials which contain far fewer patients. This question obviously cannot be addressed in a non-randomized, retrospective study. However, our multivariable model attempted to control for perioperative risk factors which may influence mortality and yet these results suggest that the laparoscopic approach is associated with a lower mortality.

The main drawback of this study is that it is retrospective in nature. Because the database is retrospective, we could not control for surgeon preference and experience relative to operative approach which could have an influence on the outcomes for the various procedures. The patient groups are statistically different, although we attempted to control for these differences using our multivariable modeling. In addition, the PUF file does not clearly identify those patients that have undergone a lap-converted to open appendectomy which may have some influence on the outcomes for the entire open appendectomy group. Finally, there is no way to control for operative volume (high volume vs. low-volume centers) or for potential geographic or socioeconomic differences using this database. Clearly a large, adequately powered, randomized prospective trial comparing laparoscopic to open appendectomy would be the best means to definitively examine our hypothesis. Several randomized prospective trials have been undertaken to date and because they have suffered from small numbers of patients, they have failed to definitively resolve the issue. This study, although retrospective in nature, has such a large sample size that the findings add relevant new information to an ongoing debate.

In conclusion, using the ACS/NSQIP PUF file from 2008, we have shown that patients undergoing laparoscopic appendectomy have fewer infectious complications, shorter operative times and hospital LOS, fewer complications, and lower perioperative mortality when compared to patients undergoing open appendectomy. While the choice of operation for treatment of appendicitis will remain surgeon specific, this study lends support to the laparoscopic approach for patients requiring appendectomy.

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ORIGINAL ARTICLE

Large Volume Hepatic Microwave Ablation Elicits Fewer Pulmonary Changes than Radiofrequency or Cryotherapy

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Abstract
Background Lung changes after microwave tissue ablation (MTA) of different volumes of liver were compared with hepatic resection, cryotherapy (CRYO) and radiofrequency ablation (RFA).
Methods Live rats underwent MTA, surgical resection, CRYO or RFA of 15%, 33% and 66% of total hepatic volume and lung samples were collected at the time of death. Lung impairment was assessed directly by examining the tissue specimens for the degree of interstitial pneumonia and by comparing the alveolar thickness in the different groups.
Results All RFA and CRYO rats undergoing 66% of ablations died, but the MTA group had no fatalities. Following 66% RFA or CRYO ablations, the animals had a significantly increased thickness of the alveolar septa compared to 15% or 33% ablations and to 66% ablations in the MTA group.
Conclusions Large volume MTA is associated with a significant reduction in consequent lung damage and is well tolerated compared to RFA and CRYO.

Mr. David Lloyd had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Keywords Microwave · Radiofrequency · Cryotherapy · Pneumonia · Hepatic ablation · Hepatic resection

Introduction

Systemic complications following liver ablation are infrequent but potentially life-threatening and, when they occur, significantly influence the postoperative course. Cryotherapy (CRYO) of small areas of the liver is usually well tolerated, but potentially fatal side effects have been reported following ablation of liver volumes which exceed 30% to 35% of the total volume.[1] The "cryoshock" syndrome is fatal in 0–8% of cases[2] and involves the lungs (pleural effusions, acute respiratory distress syndrome), kidneys (myoglobinuria, acute renal failure) and the hematopoietic system (marked thrombocytopenia).[1–5] The level of the injury and the subsequent clinical manifestation is directly proportional to the volume of liver which is ablated and the quantity of

necrotic debris released. The resultant inflammatory response is due principally the release into the systemic circulation of significant quantities of pro-inflammatory cytokines mainly tumour necrosis factor-α, interleukin 1β (IL-1β) and interleukin 6 (IL-6).[3,6–9]

A number of studies have compared the systemic pathophysiologic and histologic responses of the different ablative techniques and compared them to hepatectomy. NF–κB activation, the production of NF–κB-mediated cytokines (TNF-α and MIP-2), histologic changes and pathophysiologic alterations of the lung perfusion have been observed after CRYO but not after RFA[1] or hepatectomy.[3,10] Hepatic resection resulted in only mild perivascular oedema around lung capillaries without any other significant change.[4] Interestingly, systemic responses similar to those obtained from CRYO following ablation of 35% of the volume of normal liver occurred when 50–60% of the normal liver parenchyma were ablated with RFA.[11,12] These results suggest that hepatic tumour ablation that results from RFA-induced thermal coagulation produces a much lower systemic inflammatory insult than an equivalent ablation produced by cryotherapy.[12]

As far as we are aware, there are no studies to date which have investigated the pulmonary consequences of hepatic ablation by microwave ablation (MTA) which is the most recent technology to be investigated and which is increasingly popular. The aims of the present study were to examine the effects on the lungs of different volumes of liver ablated by MTA and to compare them to the consequences of similar ablations with CRYO, RFA and surgical resection

Materials and Methods

Ethical approval was sought in accordance with the Animals (Scientific Procedures) Act 1986. Adult male Sprague–Dawley rats (350–400 g; Charles River Laboratories, Margate, UK) were allowed to acclimatise in the designated establishment for 1 week and underwent the same diet and handling. The details of the hepatic anatomy in the rat which is used to determine the volume of the ablations has already been described.[8]

Experimental Design

Animals were allocated to one of five groups: simple laparotomy (controls), hepatic resection, MTA, CRYO and RFA (treatment groups). Each treatment group consisted of three further subgroups in which rats underwent ablation of 15%, 33% or 66% of the total liver parenchyma. The same major lobe was used in all rats for 15% and 33% ablations, and the two major lobes for 66% ablations. Seven animals were treated in each subgroup corresponding to 21 for each modality.

Operative Procedures

Anaesthesia The animals were placed in an induction chamber with 3–4% Halothane and oxygen (2 l/min), and anaesthesia was maintained with the same mixture and flow rate by means of a conical mask placed around the head. A digital thermometer was inserted rectally, and the animal was placed on a heated mat. Temgesic (0.7 mg) and 4 ml of normal (0.9%) saline were administered subcutaneously for pain relief and for fluid replacement to compensate for intra-operative blood loss. The skin of the abdominal wall was shaved and treated with an antiseptic solution prior to the incision.

Laparotomy A midline laparotomy facilitated access into the abdominal cavity. The peri-hepatic ligamentous attachments were released using sharp dissection and the liver mobilised. The abdomen was then closed using 5/0 Prolene (Ethicon Inc., Bridgewater, NJ, USA) for a mass muscle closure and 4/0 Vicryl (Ethicon Inc.) for skin closure.

Surgical resection Following the laparotomy a vascular clamp was placed horizontally across the liver tissue, and a blade was used to cut through the parenchyma minimising trauma. Prolene sutures (5/0; Ethicon Inc.) were used to produce haemostasis, and an omental patch was also placed over the exposed edge of the liver to prevent any subsequent blood loss.

Microwave tissue ablation A saline soaked swab was placed between the liver and the surrounding organs to prevent any local heat-induced thermal damage either directly from the probe or through tissue conduction. A 2-mm diameter microwave applicator (Microsulis Medical Ltd, Denmead, UK) was inserted through the hepatic parenchyma (Fig. 1), and energy was delivered at a frequency of 9.2 GHz and a power of 20 W until the required volume of liver was macroscopically ablated. This occurred after 2–3 min (depending on the volume of ablation required) and any bleeding from the probe insertion tract was controlled by reapplying the probe for a further 2–3 s.

Cryotherapy A polystyrene block was used to separate the liver from adjacent peritoneal organs and skin which prevented any collateral damage, and hypothermia was avoided by placing a few drops of warmed saline into the peritoneal cavity. Liver cryotherapy was performed using the Liquid Cryo system 3000 (Spembly Medical, Andover, UK). A 3-mm cryoprobe was applied to the liver edge (Fig. 1), and the generator was used on maximum power until the thermocouple in the probe registered −180°C, following

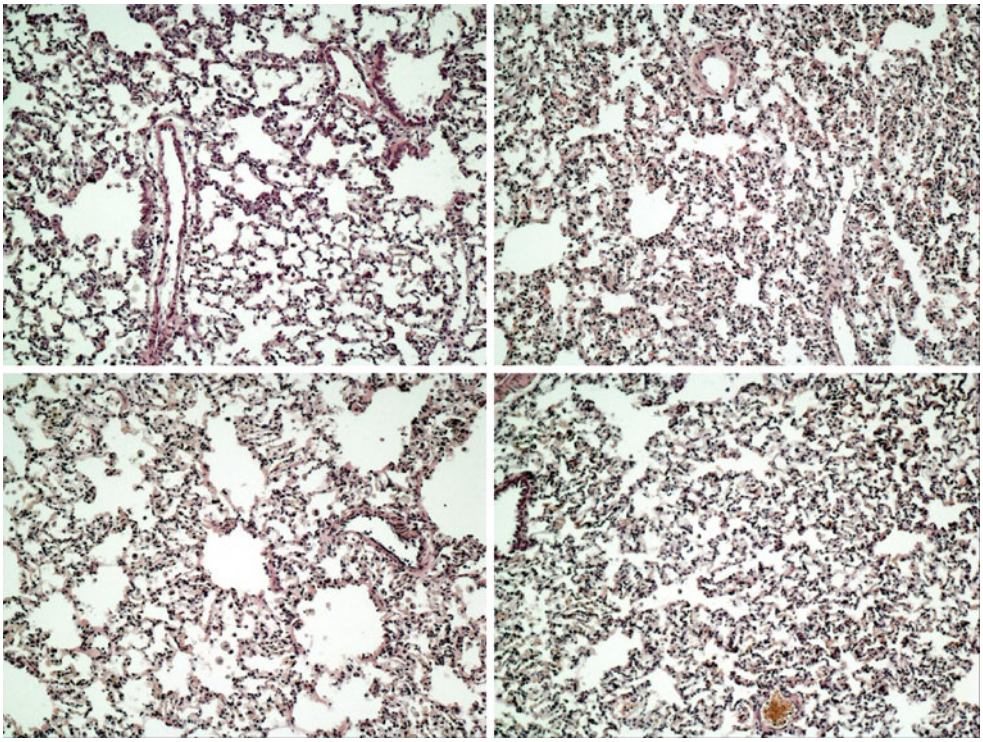

Fig. 1 Specimens obtained after 15% of volume treated with surgical resection (*left upper panel*; AT=0.67 μm, normal appearance of lung parenchyma), MWA (*right upper panel*; AT=1.25 μm, minor collapse with slight compensatory over-expansion of some alveoli), CRYO (*left lower panel*; AT=2.76 μm, slightly more marked over-expansion of some alveoli compared to MWA) and RFA (*right lower panel*; AT=1.24 μm, extensive partial collapse of alveoli with minor over-expansion of some).

which it was turned to minimum output and maintained until the desired volume of liver parenchyma had been ablated. Two cycles of treatment were performed, each lasting 8–14 min (depending on the volume to be ablated), and once the required liver volume appeared macroscopically frozen the cryo-system was switched off and in order to avoid parenchymal fracture and bleeding the probe allowed to completely defrost before removing it.

Radiofrequency ablation A damp swab was used to protect the surrounding structures from thermal damage and the grounding plate was placed on a shaved portion of the back. A 2-mm diameter Cool-tip RF ablation system (Valleylab, Boulder, CO, USA) was used for the energy delivery following insertion into the hepatic parenchyma (Fig. 1). The RFA generator needed constant adjustment to maintain an output of 10 W due to the variable impedance which occurred as increasing volumes of liver were treated. Treatment varied from 7–12 min depending on the amount of liver to be ablated.

Post-Operative Protocol

At the end of the procedures, 2 ml of warmed normal saline were administered subcutaneously. The animals were returned to their cages and kept warm using a lightly heated mat. After 48 h, animals were killed to obtain the pulmonary tissue for the study. Each animal was anaesthetised, the thorax opened and the lungs collected at the time of the animal's death. They were fixed in 10% paraformaldehyde, embedded in paraffin, cut in thin slices (3–5 μm) and stained with standard haematoxylin–eoxin coloration. The alveolar thickness (AT) was quantified by the measuring the thickness of the alveolar septa. All measurements were conducted at a power of ×100 and five different fields examined for each slide to ensure reliable sampling of the entire specimen.

Statistical Analysis

All data analysis was performed using the Statistical Package for the Social Sciences Windows, version 13.0 (SPSS, Chicago, IL, USA). Descriptive statistics consisted of the mean and standard deviation for continuous variables with parametric distribution and median and range for those with non-parametric distributions. Categorical variables were expressed with percentages. The Kruskal–Wallis test was used to compare results for alveolar thickness for each technique (MTA, CRYO and RFA) and for the different volumes (15%, 33% or 66%) of liver ablated or resected. Cut-off values for the risk of death were determined with the receiver operating characteristic curve. A p value of <0.05 was considered statistically significant.

Results

Qualitative Analysis

Histological changes observed ranged from a completely normal appearance of the lung parenchyma through a minor

collapse with slight compensatory over-expansion of some alveoli to extensive partial collapse of alveoli and different degrees of interstitial pneumonia (Figs. 1, 2).

Quantitative Analysis

Results for AT are shown in Table 1, and as can be seen, there are significant differences for AT values between the techniques (Kruskal–Wallis test, $p<0.01$, Fig. 3). In particular, higher values were observed for CRYO and RFA compared to the other three groups. Furthermore, CRYO and RFA conducted at 66% ablation volumes produced significantly higher values when compared to CRYO and RFA conducted at 15% and 33% ablations (Kruskal–Wallis test, $p<0.05$, Fig. 3).

Analysis of Outcomes

Significant differences were present between the groups when comparing animals where the treatment was fatal and those that survived. Treatment was only fatal in the RFA and CRYO groups (Chi-square test; $p<0.05$) following a 66% ablation (Chi-square test; $p<0.001$). All the animals in the other groups (irrespective of the method of treatment or of the volume ablated) survived. A cut-off of 0.87 μm for AT was determined for rats that died (area under the curve=0.866; sensitivity=100%, specificity=68.1%).

Discussion

Pulmonary changes that occur following liver ablation involve both disturbances of the blood–alveolar interface and inflammatory changes consequent upon the release of pro-inflammatory products. The altered capillary permeability is reflected in the increase in the mean pulmonary pressure (20 to 35 cm water), marked increase in the lung lymph–plasma protein clearance and an increase in the lymph–plasma protein ratio.[10] Histological changes between 1 and 2 h following the procedure, resulting from the inflammatory process, consist of airspace oedema and parenchymal haemorrhages[4], multiple foci of perivascular inflammation, activated lymphocytes, foamy macrophages and marginated neutrophils.[1,4] One week following RFA treatment, although the alveolar space was spared, there is a moderate interstitial pneumonia, and the alveolar septum was thickened with an infiltrate of mononuclear cells. Changes after CRYO were more obvious, and there was an additional perivenular inflammation with diffuse infiltration of polymorphs and monocytes into the alveolar and interstitial spaces.[12]

Large-volume MTA has only recently become possible due to significant technological progress resulting in improved generators and probes. Previously incomplete ablations, abscess formations, biliary strictures and bleedings limited its use in the clinical setting.[13,14] These technological advances have meant that it has been possible

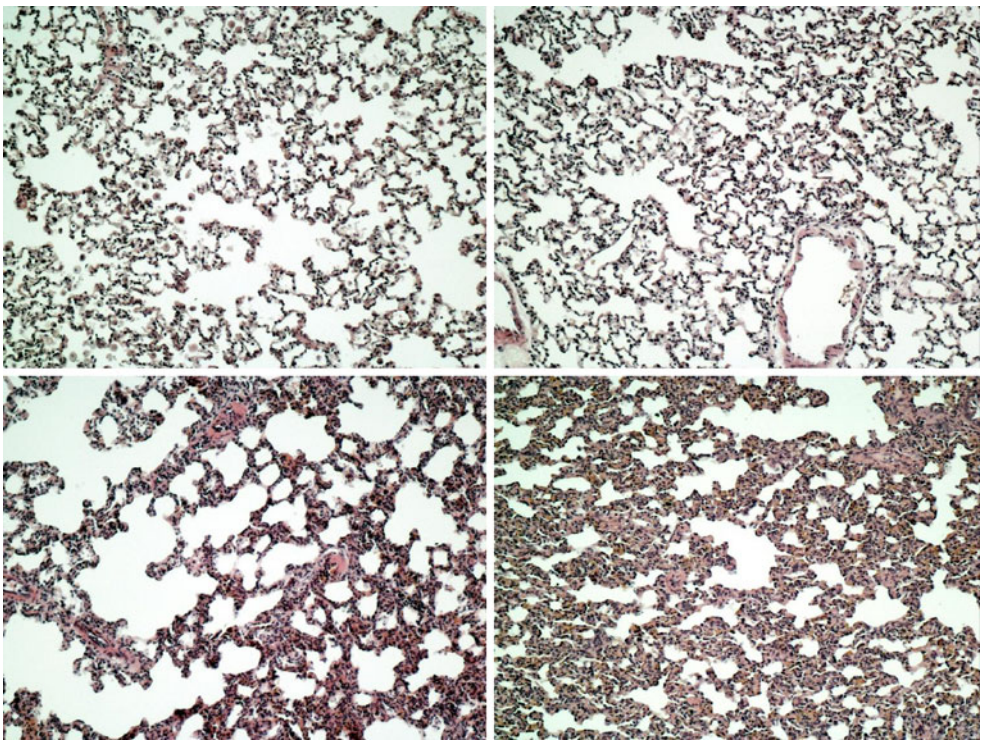

Fig. 2 Specimens obtained after 66% of volume treated with surgical resection (*left upper panel*; AT=0.57 μm, normal appearance of lung parenchyma), MWA (*right upper panel*; AT=0.77 μm, normal appearance of lung parenchyma), CRYO (*left lower panel*; AT=3.71 μm, focal collapse with associated over-expansion of alveoli) and RFA (*right lower panel*; AT=5.90 μm, marked collapse with relatively mild over-expansion of remaining alveoli). Compared to Fig.1, CRYO and RFA show an increase of AT.

Table 1 Results for AT

	AT (μm)		
Laparotomy (controls)	0.93 (0.57–1.66)		
Group of ablation	15%	33%	66%
Resection	0.74 (0.53–1.16)	0.80 (0.44–1.94)	0.73 (0.59–1.37)
MTA	0.88 (0.73–0.98)	0.92 (0.73–1.35)	1.11 (0.77–1.81)
CRYO	0.63 (0.62–0.73)	0.95 (0.55–1.43)	4.51 (1.37–5.60)
RFA	1.28 (0.82–3.93)	1.28 (0.65–2.10)	2.02 (1.35–6.78)

to produce significantly larger ablations, and the duration of treatment required for these larger volumes has been reduced. Over this period, there has not been the same progress with CRYO and RFA, and this is a significant advantage in a clinical setting.[15] The aim of this study was not to investigate the cellular and biochemical changes that occur in the lung following hepatic ablations (previously described in other studies) but to compare the consequences of MTA, CRYO and RFA conducted at extreme volumes of ablation in order to amplify any differences between the different techniques. The results of our study confirm the main histological changes previously described (interstitial pneumonia), and the increased severity of the insult when more than 35–50% of the hepatic parenchyma is ablated with CRYO and RFA. They also confirm the apparent lack of histological changes following surgery as described in the study of Ng et al.[12] In addition, however, our study was also able to demonstrate a lack of significant histological changes in the lung following large-volume MTA compared to controls. This is consistent with our previously reported results in respect of differences in the systemic inflammatory changes elicited following treatment[8] and further confirms the increased safety for large-volume MTA compared to RFA and CRYO. The reasons for such obvious differences when comparing MTA and the other established ablative techniques are still not clear although the different mechanisms which produce tissue destruction are likely to be responsible. Treatment with CRYO preserves tissues and the antigenic properties of the cells and large-volume ablations result in the release of massive amounts of immunogenic products that produce the well documented and frequently severe, systemic reaction.[9] In comparison, MTA is an ablation which relies on heating of the tissue and produces denaturation of cellular proteins consequently decrease their capacity to stimulate the immune system, even when larger volumes are ablated.[9] What remains unclear, however, is why RFA, which is also a technique of ablation by heating, behaves differently from MTA when large volumes (66%) are ablated. One hypothesis involves the more rapid ablation produced by MTA compared by RFA. Kupffer cells within the ablated area would be rendered inactive by the almost instantaneous thermal injury produced by the MTA as opposed to the slower process of tissue heat conduction with RFA and may as a consequence produce significantly less activation of the immune system. This hypothesis will need to be investigated in detail in future studies.

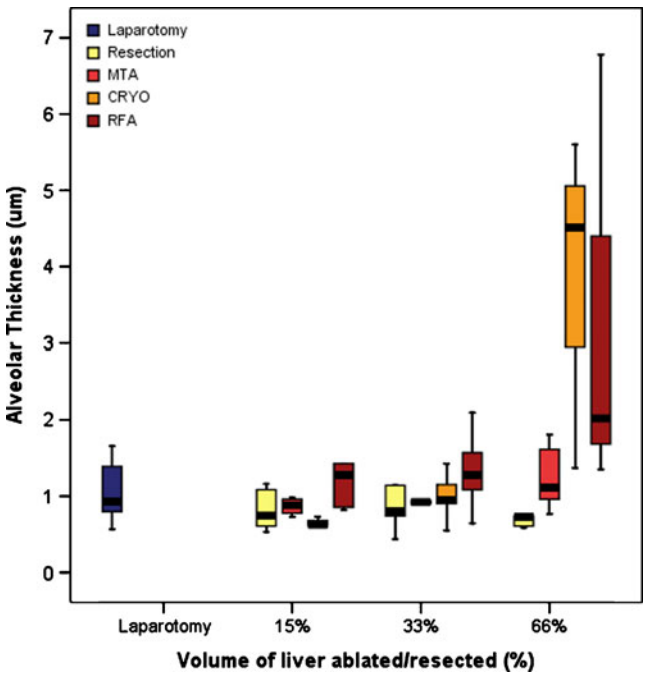

Fig. 3 Box plot graph showing the alveolar thickness values for ablations or resection of 15%, 33% and 66% of the liver parenchyma. *Boxes* represent the first and third quartiles while the *black line* the median values.

All animals in the CRYO and RFA 66% ablations died at 6 h before the time of observation ended. This is contemporarily the main finding and also limitation of the present study because a direct comparison between a histopathologic change after ablation (after 48 h) and a postmortal effect (6 h from ablation) is not possible. From the experimental point of view, in the presence of an important event such as death, it is mandatory to conduct new studies where animals of surviving groups will be killed at 6 h, and their histological samples will be collected at the same time of those that spontaneously die after the ablation. This would allow for a more meaningful comparison between groups. Another important limitation of this study was the treatment of healthy

liver which behaves very differently to malignant or cirrhotic tissue. Cirrhosis is commonly encountered in patients with unresectable liver tumours that are considered candidates for ablative treatments. Studies that compare the different modalities and produce different volumes of ablation in cirrhotic liver and liver tumour models are required to examine the systemic inflammatory reactions after different ablative therapies in tissues which behave differently. Further evaluation in the clinical setting is also required as there are clear and important differences between humans and animals in the innate and specific immune responses.

Conclusions

Large-volume MTA is associated with significantly less lung damage compared to RFA and CRYO and is the only ablative technique which is capable of producing very large ablations with few pulmonary complications. Large-volume ablations with RFA and CRYO are not survivable in this animal model and result from the pronounced systemic response. These findings should be considered when selecting an ablative technique in the clinical setting especially when large inoperable lesions require treatment in elderly patients or those with significant co-morbidity, especially if this includes compromised respiratory function.

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ORIGINAL ARTICLE

Development of a Multimodal Tumor Model for Porcine Liver

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Abstract In our efforts to develop a guidance system for laparoscopic liver surgery, we are working towards a live animal tumor model. The objective of this study was to establish the tumor model for live porcine liver, visible on both computed tomography (CT) and ultrasound images. The tumor model was created by injecting a mixture of agarose, sephadex, and glycerol. Together with water, the mixture was heated to bring its components into solution. Once heating was complete, methylthionine chloride and CT contrast were added. Using laparoscopic ultrasound guidance, the tumor model mixture was injected into in vivo porcine liver. The resulting model tumors were radiolucent, visible on both CT and conventional X-ray. They appeared as hyperechoic lesions on ultrasound images. Compared to the CT images, the model tumors in the ultrasound images showed good correspondence in size. We conclude that our tumor model, due to its clearly identifiable nature on multiple imaging modalities, is a valuable tool for further studies on laparoscopic ultrasound (2D and 3D) and navigated ultrasound in laparoscopic surgery of the liver and other organs in a pre-clinical set-up.

Keywords Tumor model · Laparoscopy · Ultrasound · Navigation · Three-dimensional ultrasound

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Introduction

On a mission to improve the safety and efficacy of laparoscopic liver surgery, navigation systems are being developed to combine and integrate real-time laparoscopic ultrasound (LUS) images with preoperative computed tomography (CT) or magnetic resonance images.[1–5] To develop and evaluate the usability, possible clinical benefits, and the accuracy of these systems, a life-like tumor model in a live animal set-up is both beneficial and necessary. The purpose of this study was to develop a tumor model in an in vivo porcine liver tissue that is visible on multiple imaging modalities. The tumor model would have the following characteristics:

- Discrete, well circumscribed lesions
- Lesions visible on both ultrasound and CT images
- Lesion consistency similar to consistency of liver parenchyma
- Easily identifiable on gross examination

We aimed to achieve a tumor consistency similar to that of liver parenchyma in order to facilitate unbiased targeting of the tumors with tracked surgical instruments in further studies, i.e., the surgeon should be able to rely exclusively on the navigation system for sense of direction and location

of tumor in guidance of procedures and should not be influenced by sensing a different consistency with the surgical instrument. Furthermore, to facilitate further experiments using the tumor model in studies on LUS-guided liver resection, we have compared sample images from CT and ultrasound to demonstrate the feasibility of the model.

Materials and Methods

The animal experiments in this study were approved by the national committee for research on animals. In addition, the study protocol was approved by our hospital research scientific board.

Initial Model

As a first attempt, the tumor model presented by Restrepo et al.[6] was used as inspiration; KY jelly (water-soluble lubricant, Johnsen & Johnsen) with different amounts of CT contrast fluid was used to create tumor mimicking lesions in the liver.

1. Components mixed in open container; resulting mixture was full of air bubbles
   (a) KY jelly+50% CT contrast (Omnipaque 270 mg/ml, GE Healthcare)
2. Components mixed using two syringes connected by a two-way catheter to prevent air bubble formation
   (a) KY jelly+50% CT contrast (Omnipaque 270 mg/ml)
   (b) KY jelly+30% CT contrast (Omnipaque 270 mg/ml)
   (c) KY jelly+20% CT contrast (Omnipaque 270 mg/ml)

Final Model

Our final tumor model, based on Scott et al.,[7] was created by injecting a mixture of 6 g of agarose, 6 g of sephadex, and 14 ml of glycerol with enough tap water to make a 200-ml volume. The mixture was then heated to 95°C using a microwave oven to bring its components into solution. Microwave energy on a high-power setting was applied for a total of approximately 3 min, for 30 s at a time to prevent mixture from overflowing. Once heating was complete, 2 ml of methylthionine chloride (10 mg/ml) was added.

The mixture was divided equally and transferred to four glass jars and sealed with airtight lids. Gradual cooling at room temperature resulted in a solid material with a tough gelatin-like consistency. The jars were stored for up to 4 weeks at room temperature prior to use. When needed for an experiment, the jars were individually reheated in a microwave oven for 30 s at a time until the gelatin was completely re-liquefied. Eight milliliters of the mixture was then drawn up into a 10-ml syringe. Two milliliters of CT contrast (Omnipaque 270 mg/ml) was drawn up into another syringe. The contents of the syringes were mixed, with the help of a three-way catheter to prevent air from entering the mixture, yielding our tumor model mixture. Several syringes with the tumor model mixture were prepared and then maintained at a temperature of 65°C in a hot water bath.

Ex Vivo Model

An ex vivo model was created to establish solidification time of tumor model mixture. A bovine liver was cut into nine 10×10-cm pieces. The liver pieces were placed individually into plastic bags and maintained at 38°C in a water bath. The tumor model mixture was maintained in a water bath at 65°C and then injected approximately 2 cm deep into liver pieces. Syringes were left in place to prevent leakage. Fig. 1 shows a photo of the transected tumor model and the liver parenchyma-like characteristics.

In Vivo Model

With the pig under general anesthesia, three laparoscopic ports were made: one supraumbilical and two in the left upper quadrant. The sites were chosen in order to have proper access to the liver. The needle was placed through the skin and guided into the liver under laparoscopic visualization (Fig. 2a–c). Using ultrasound guidance, the needle tip was advanced to a depth of 1.5 to 2.0 cm in the liver (Fig. 2b–c). Care was taken to avoid injuring vascular or biliary structures with the needle. A 2–3-ml bolus of the tumor model mixture was rapidly injected through an 18-

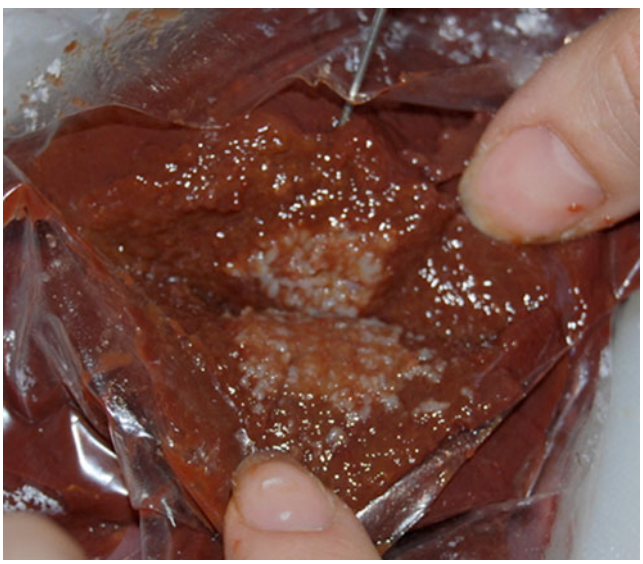

Fig. 1 Photo of a transected model tumor from an ex vivo bovine liver.

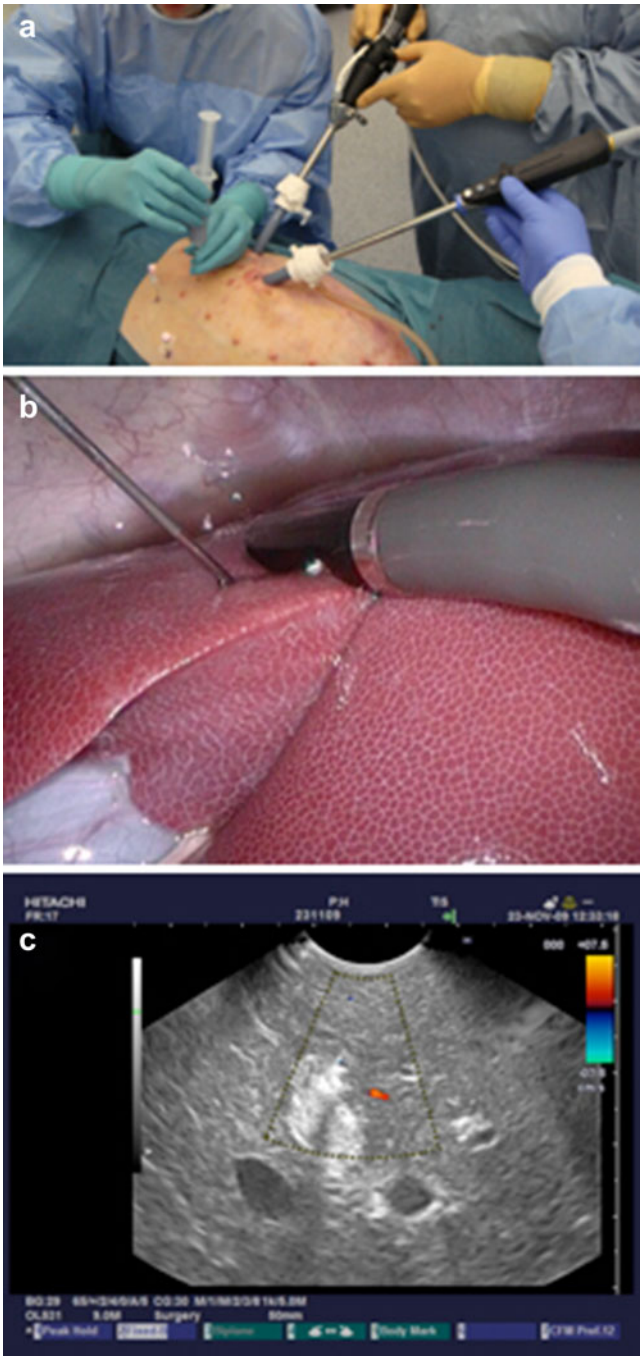

Fig. 2 Laparoscopic ultrasound (LUS)-guided injection of the liver model tumors. **a** Overview showing two needles used to inject tumors and one in progress. Laparoscope and LUS probe are used for guidance. **b** Laparoscope video image showing the LUS probe tip and one needle. **c** LUS image of hyperechoic tumor with color flow imaging. The needle is causing the shadow in the image (in part of the tumor). Color flow is used to avoid blood vessels.

gauge epidural needle into the hepatic parenchyma. The needle was left in place for 45 min to prevent extravasation of the tumor model mixture. The puncture site was cauterized to achieve adequate hemostasis.

Acquisition of Images

Computed Tomography

The operating room (OR) where the experiments were performed contains a roof mounted C-arm fluoroscopy unit (Axiom Artis dTa system, Siemens, Germany; Fig. 3a). In addition to regular fluoroscopy and X-ray imaging, it has cone beam CT (CBCT) functionality. By acquiring approximately 400 X-ray images while rotating 220° around the OR table, it is able to reconstruct CT-like images. The images are reconstructed on a workstation (Leonardo, Siemens, Germany) and can be visualized in the OR. This CBCT imaging modality has some quality limitations compared to regular multislice CT,[8] but the intraoperative imaging possibilities provide great experimental possibilities (and patient logistics).

Ultrasound

The ultrasound images were acquired using an LUS probe (OL531, Hitachi, Japan; Fig. 3b).

Results

In Vivo—KY Jelly Model

Mixture was injected under LUS guidance using an 18-gauge epidural needle. Tacosil® was used for hemostasis and to

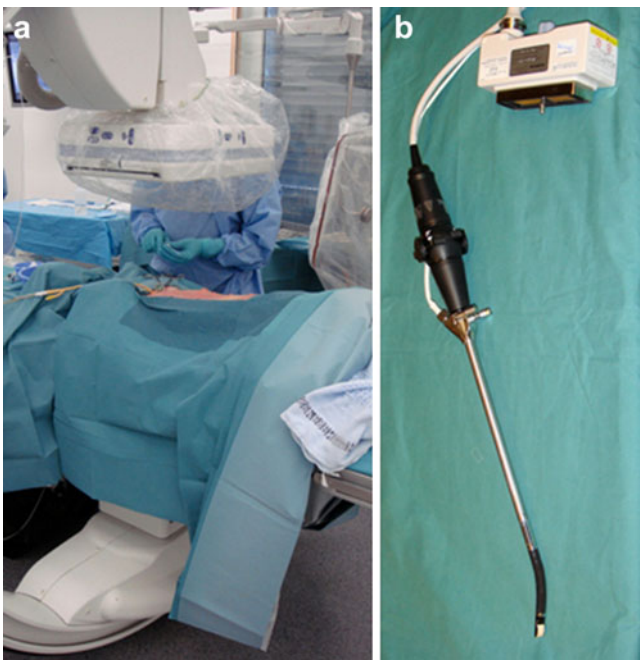

Fig. 3 **a** The C-arm used to acquire 3D cone beam computed tomography data in the experiments. **b** Laparoscopic ultrasound probe used in the experiments to guide the placement of the tumors and to view the final tumor models.

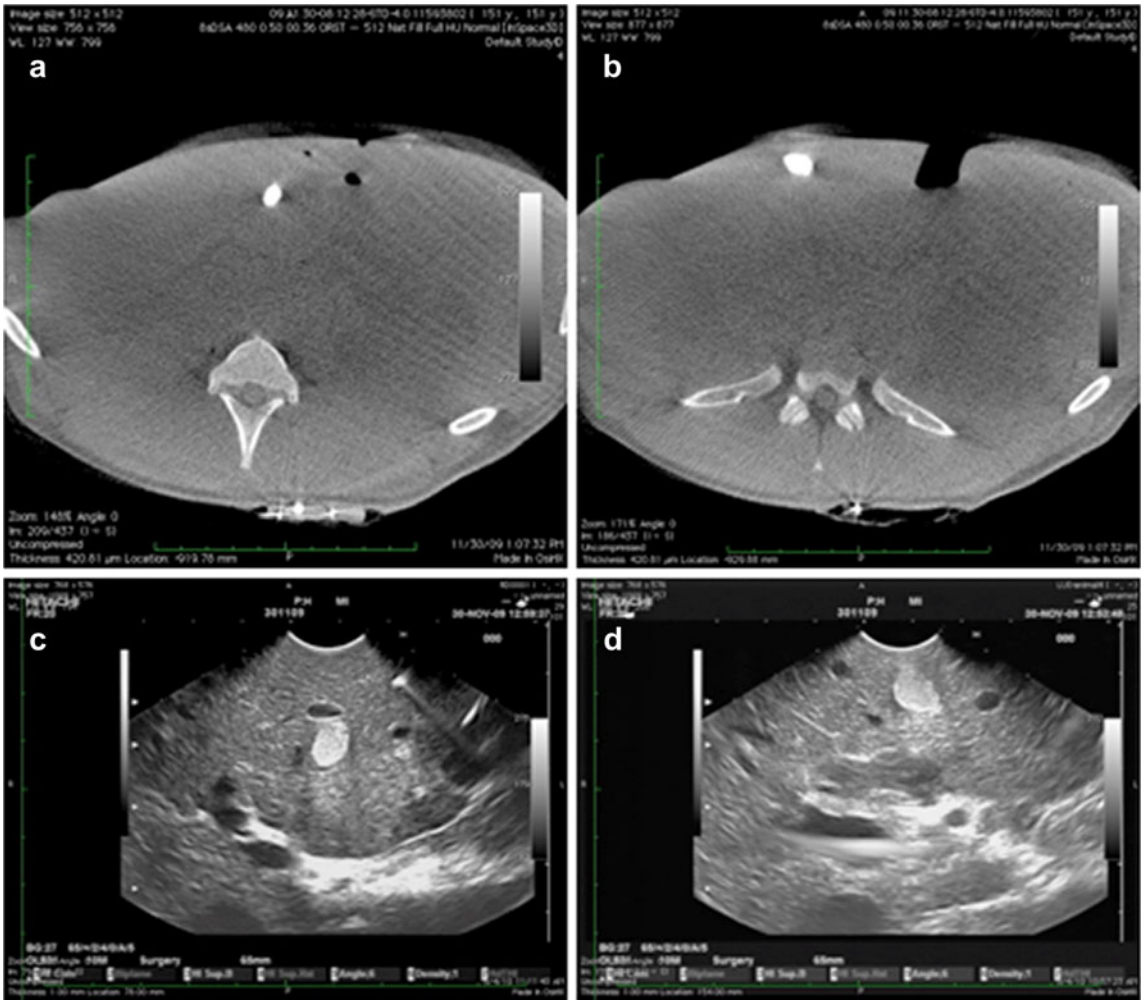

Fig. 4 Sample images of in vivo model tumors. **a**, **b** Computed tomography slices showing two model tumors. **c**, **d** The corresponding tumors seen in laparoscopic ultrasound images.

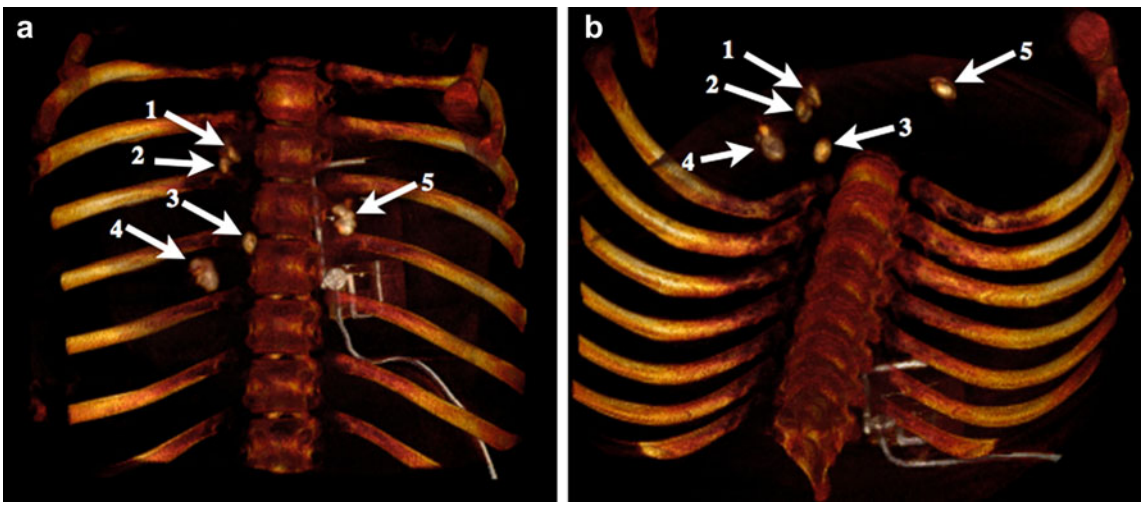

Fig. 5 Volume rendering (thresholded) of a cone beam computed tomography volume showing five tumors in the liver. **a** Approximately anteroposterior view. **b** Volume slightly tilted for better view of the tumors.

prevent leakage of the injected material. The resulting tumors had poorly defined borders, poor visibility on both modalities, and leakage of the injected material could not be prevented sufficiently. The presence or absence of air did not have a significant impact on the resulting tumor models.

Ex Vivo—Agarose Model

The livers were cut open one at a time at 10-min intervals. Optimal solidification time of tumor model mixture was found in the fourth liver; therefore, optimal solidification time was established at 40 min.

In Vivo—Agarose Model

Resulting tumors were well circumscribed with clearly defined borders. They were clearly visible on both CT (Fig. 4a–b) and ultrasound (Fig. 4c–d). Consistency was constant, permanent, and similar to the consistency of the liver parenchyma.

With the 3D CT capability of the C-arm in our OR set-up, we can acquire volume renderings such as the one shown in Fig. 5 for better overview of all tumors injected. This feature will be exploited in further studies.

Discussion

The tumor model was developed primarily with navigation in mind. The intraoperative CBCT was used out of convenience of availability and also as a gold standard for comparison to ultrasound images (particularly in further studies). Navigation systems have the potential to improve the safety and efficacy of laparoscopic surgery. Ultrasound integrated with preoperative CT can help the understanding of the LUS images in correspondence with surrounding anatomy. Solberg et al.[5] have shown that image fusion techniques make it easier to perceive the integration of two or more volumes in the same display (monitor) than mentally fusing the same volumes presented in their own separate displays. The ultrasound data will show updated information that the surgeon relies on during surgery, while the advantages from CT, such as better overview and understanding of the anatomy and pathology, are displayed simultaneously. Herein lies the importance of the tumor model being visible on multiple imaging modalities. Surgical instruments (with integrated tracking technology) can be visualized in these volumes. This opens up the possibility for the laparoscopic surgeon to visualize the exact location of the surgical instruments in relation to the preoperative CT images combined with real-time LUS images. Having an additional image, to the standard image provided by the video laparoscope, provides precision and thus added safety to minimally invasive surgery. Our tumor model due to its multimodal visibility can be used to further develop and perfect navigation systems.

Conclusion

Our tumor model, being equally well visible on both ultrasound and CT, creates a set-up for developing guidance systems in controlled animal trials in order to improve their accuracy and feasibility. We believe that the model can be a valuable tool for further studies on navigation systems and LUS, both 2D and 3D, in laparoscopic surgery of the liver and other organs in a pre-clinical set-up.

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ORIGINAL ARTICLE

Simultaneous Liver and Colorectal Resections Are Safe for Synchronous Colorectal Liver Metastases

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Abstract
Background Hepatic resection (HR) is the only option offering a potential cure for patients with synchronous colorectal cancer liver metastases (SCRLM). The optimal timing of HR for SCRLM is still controversial. This study aimed to determine whether simultaneous HR is similar to staged resection regarding the morbidity and mortality rates in patients with SCRLM.
Methods Four hundred and five consecutive patients with SCRLM were treated with either simultaneous (n=129) or staged (n=276) HR. The postoperative complications were analyzed retrospectively according to the documented records and hepatectomy databases at the Gastrointestinal Institute.
Results Perioperative morbidity and mortality did not differ between simultaneous resections and staged resections for selected patients with SCRLM (morbidity, 47.3% versus 54.3%; mortality, 1.5% versus 2.0%, respectively; both $p>0.05$). Simultaneous liver resections of three or more segments would not increase the rate of complications compared to staged resections (56.8% and 42.4%, respectively; $p=0.119$). Meanwhile, patients with simultaneous resections experienced shorter duration of surgery and postoperative hospitalization time as well as less blood loss during surgery (all $p<0.05$).
Conclusions Simultaneous resections of colorectal cancer primary lesions and hepatic metastases were safe and could serve as a primary option for selected SCRLM patients.

Keywords Colorectal cancer · Complication · Liver metastasis · Surgical resection

Introduction

Up to 50% of patients with colorectal cancer (CRC) might have liver metastases during the course of their disease.[1,2] Of these, 15% to 25% present with synchronous colorectal liver metastases (SCRLM),[3–5] whereas an additional 20% to 25% develop metachronous hepatic tumors.[6–8] In 20% of patients with synchronous or metachronous liver metastases, the liver is the only site of metastatic disease.[9] Without treatment, these patients survived a median of 2.3 to 21.3 months.[10,11]

Hepatic resection (HR) is the main mode of treatment offering a potential cure for patients with colorectal liver metastases (CRLM). Patients with curatively resected CRC with isolated liver metastases can expect a 5-year overall survival of 22% to 65%.[12–15] The 10-year survival rates have been even reported as 22~26%.[15,16]

Yanxin Luo, Lei Wang, and Chuangqi Chen contributed equally to this work.

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Most series reporting on the surgical management of SCRLM have recommended a staged approach with initial resection of the primary lesion followed by HR 2 to 3 months later.[17,18] However, the paradigm for the surgical management of SCRLM has begun to change in two ways. First, the safety and efficacy of simultaneous resection of colorectal and liver tumors has improved,[19–24] and second, we have seen the emergence of neoadjuvant chemotherapy for unresectable metastasis as well as resectable synchronous metastasis.[21,25,26] Thereby, the recommendations calling for the staged management for SCRLM patients are being debated. The optimal timing and indication of surgical resection for synchronous metastasis are still controversial. The primary goal of this study was to investigate whether simultaneous HR is similar to staged resection with regards to morbidity and mortality in SCRLM patients.

Materials and Methods

Subjects

Patients who underwent resections of SCRLM between January 1994 and February 2008 were identified from hepatectomy databases at the Gastrointestinal Institute (Guangzhou, Guangdong, People's Republic of China). This study was approved by the institutional review board at the Sixth Affiliated Hospital of Sun Yat-sen University.

The inclusion criteria for patients to be considered for the study were as follows: (1) liver metastasis/metastases as the first manifestation of M1 disease accompanied by no documented non-hepatic disseminated disease in preoperative imaging; (2) no prior history of liver-directed treatment such as HR, radiofrequency ablation, or other local modalities; (3) histologically proven colorectal carcinoma; and (4) age ≥18 years.

In the present study, SCRLM were defined as hepatic lesions discovered before or during primary tumor resection. Hepatic lesions were typically detected via computed tomography, magnetic resonance imaging, position emission tomography, or at exploration with intraoperative ultrasound before colorectal resection. Whether patients underwent simultaneous or staged resection depended on three primary aspects: (1) the sizes and distribution of the liver metastases, (2) surgeons' own opinion regarding the safety of the resection, and (3) the patients' preferences and physical situation. Demographics, clinicopathologic data, medical and surgical treatments, and postoperative outcomes of patients who underwent simultaneous resections of primary lesions and SCRLM were compared to staged patients who underwent hepatectomy after colorectal resection. Duration of surgery was defined as the time from the initial skin incision to closure. HRs were described according to standard nomenclature.[27]

Potential postoperative complications were reviewed for at least 30 days following partial hepatectomy. Hepatic complications included perihepatic or subphrenic abscess, right-sided pleural effusion, bile leak and/or biloma, liver insufficiency or failure, and the need for reoperation due to bleeding at the transaction edge. Colorectal complications included ileus, anastomotic leak, and pelvic abscess. Complications were graded according to the method described by Dindo et al.,[28] except the need for blood product transfusions was not considered a complication here. Postoperative mortality was defined as any death during postoperative hospitalization or within 30 days after hepatectomy.

Methods

Chi-square and Student's *t* tests for nominal and continuous variables were used to evaluate the association of independent variables to surgical complications. Proportional hazards analyses were performed on all variables determined to be significant by univariate analysis. Differences of $p<0.05$ were considered significant. Statistical analysis was performed using SPSS 13.0 software.

Results

A total of 405 patients were treated for SCRLM. There was an even distribution of women (43%) and men (57%), with a median age of 59 years (range, 42 to 70 years). The primary colorectal adenocarcinoma was located within the anal canal in 22 patients (5.4%), within the sigmoid or rectum in 190 patients (46.9%), within the distal transverse colon or descending colon in 71 patients (17.5%), and within the right colon in 114 patients (28.1%). Additionally, synchronous multiple primary colorectal adenocarcinomas were detected in eight patients (1.98%).

Of 405 patients, 129 underwent simultaneous primary colorectal tumor resection (group I). Compared to the 276 patients who underwent staged resection (group II), patients in group I had fewer numbers of hepatic metastases (Table 1) and were less often treated with chemotherapy before liver resection (Table 2). There was a similar distribution of gender, age, coexisting cardiac and pulmonary disease, numbers of rectal primary tumors, and T3/T4 primary tumors in both groups of patients (Table 1). Overall, patients had equivalent risk levels in terms of long-term prognosis as defined by the clinical risk score (Table 1).[15]

As shown in Table 2, some statistical differences in surgical procedures were found between the two groups.

Table 1 Comparisons of Demographics and Tumor Characteristics Between Patients Who Underwent Simultaneous and Staged Resections of Colorectal Cancer and Hepatic Metastases

Variable	Simultaneous (n=129)	Staged (n=276)	P value
Age (years)	58 (42–69)	60 (43–70)	0.720
Male	76 (58.9%)	156 (56.5%)	0.650
Cardiac disease history	26 (20.2%)	61 (22.1%)	0.657
Pulmonary disease history	22 (17.1%)	69 (25.0%)	0.074
Rectal primary tumor	69 (53.5%)	137 (49.6%)	0.470
T3/T4 primary tumor	104 (80.6%)	241 (87.3%)	0.077
Lymph nodes positive	86 (66.7%)	173 (62.7%)	0.436
CEA >5 ng/mL	41 (31.8%)	75 (27.2%)	0.339
Number of hepatic metastases			
1	81 (62.8%)	97 (35.1%)	<0.0001
>1	48 (37.2%)	179 (64.9%)	
CRS			
1	24 (18.6%)	35 (12.7%)	0.115
2	43 (33.3%)	103 (37.3%)	0.436
3	37 (28.7%)	85 (30.8%)	0.666
4	22 (17.1%)	46 (16.7%)	0.923
5	3 (2.3%)	7 (2.5%)	1.000

More patients in group I received abdominal perineal resections than those in group II (15.0% and 8.3%, respectively; p=0.049). In addition, hepatic wedge resection was more often performed in group I versus group II (35.7% and 4.4%, respectively; p<0.0001), whereas more patients in group II were treated with right hepatectomy (15.9% and 5.4%, respectively; p=0.003) or unisegmentectomy (19.6% and 7.8%, respectively; p=0.002).

The median duration of surgery for group I was 255 min (range, 121 to 575 min). The duration of surgery for group II was significantly longer with a median of 415 min (range, 233 to 712 min; p<0.0001). Similarly, total blood loss was higher in group II, with a median of 650 mL (range, 300 to 1,100 mL) as compared with group I, which had a median of 400 mL blood loss (range, 200 to 1,000 mL; p<0.0001). Additionally, the postoperative hospitalization was significantly shorter after simultaneous resections (group I) than combined postoperative hospitalizations of staged colorectal and HRs (group II; Table 3).

Table 2 Comparisons of Medical and Surgical Treatments Between Patients Who Underwent Simultaneous and Staged Resections of Colorectal Cancer and Hepatic Metastases

Treatment	Simultaneous (n=129)	Staged (n=276)	P value
Chemotherapy before liver resection	51 (40.0%)	169 (61.2%)	<0.0001
Primary resection			
Right colectomy	41 (31.8%)	73 (26.5%)	0.266
Left colectomy	17 (13.2%)	54 (19.6%)	0.115
Low anterior resection	49 (38.0%)	121 (44.0%)	0.266
Abdominal perineal resection	19 (15.0%)	23 (8.3%)	0.049
Total colectomy	3 (2.3%)	5 (1.8%)	1.000
Hepatectomy			
Extended right hepatectomy	6 (4.7%)	21 (7.6%)	0.266
Extended left hepatectomy	11 (8.5%)	37 (13.4%)	0.157
Right hepatectomy	7 (5.4%)	44 (15.9%)	0.003
Left hepatectomy	17 (13.2%)	20 (7.3%)	0.054
Other trisegmentectomy	3 (2.3%)	11 (4.0%)	0.575
Left lateral segmentectomy	4 (3.1%)	7 (2.5%)	1.000
Right posterior sectionectomy	3 (2.3%)	14 (5.1%)	0.199
Other bisegmentectomy	22 (17.1)	56 (20.3%)	0.442
Unisegmentectomy	10 (7.8%)	54 (19.6%)	0.002
Wedge resection	46 (35.7%)	12 (4.4%)	<0.0001

Table 3 Comparison of Outcomes After Simultaneous or Staged Resection

Outcomes	Simultaneous (n=129)	Staged (n=276)	P value
Duration of surgery (min)	255 (121–575)	415 (233–712)	<0.0001
Total blood loss (mL)	400 (200–1,000)	650 (300–1,100)	<0.0001
Postoperative hospitalization (days)	8 (7–15)	14 (11–22)	<0.0001
Laparotomy complications			
Wound infection	5 (3.9%)	7 (2.5%)	0.670
Pulmonary disease	11 (8.5%)	18 (6.5%)	0.532
Cardiac disease	14 (10.9%)	19 (6.9%)	0.174
Colorectal surgery complications			
Ileus	11 (8.5%)	16 (5.8%)	0.305
Anastomotic leak	4 (3.1%)	11 (4.0%)	0.875
Pelvic abscess	8 (6.2%)	19 (6.9%)	0.798
Hepatectomy complications			
Hepatic insufficiency or failure	11 (8.5%)	17 (6.2%)	0.382
Subphrenic or perihepatic abscess	6 (4.7%)	7 (2.5%)	0.411
Bile leak and biloma	8 (6.2%)	21 (7.6%)	0.609
Pleural effusion	10 (7.8%)	11 (4.0%)	0.113
Severity of all complications			
Grade I or II	67 (50.4%)	179 (59.5%)	0.078
Grade III or IV	64 (48.1%)	116 (38.5%)	0.062
Grade V	2 (1.5%)	6 (2.0%)	1.000

Overall, postoperative complications occurred in 211 of 405 patients (53.5%). In group I, 133 complications occurred in 61 patients (47.3%). In group II, 301 complications occurred in 150 patients (54.3%) when considering both hospitalizations. When comparing the morbidity after simultaneous resections to the combined morbidity after staged colorectal and hepatic procedures, the rates of laparotomy and colorectal and hepatic complications were similar between groups (all $p>0.05$). Concerning the severity of all complications, no differences were found in the distribution of mild complications (grade I or II, 50.4% in group I versus 59.5% in group II; $p=0.078$), moderate complications (grade III or IV, 48.1% in group I versus 38.5% in group II; $p=0.062$), and perioperative mortality (grade V, 1.5% in group I versus 2.0% in group II; $p=1.0$; Table 3). No specific factor was associated with overall morbidity after simultaneous or staged colorectal and HRs (Table 4).

Discussion

Surgical resection is the most effective treatment for metastatic CRC isolated to the liver.[1,7] Long-term survival is beyond the scope of this paper and has been the subject of other excellent studies.[12–16,29] Our findings suggested that perioperative morbidity and mortality did not differ between simultaneous resections and staged procedures for selected patients with SCRLM. Meanwhile, patients undergoing simultaneous resections could expect a shorter-duration surgery and postoperative hospitalization as well as less blood loss during surgery.

Although the treatment for patients with SCRLM remains controversial, surgical resection of both the primary tumor and liver metastases is the only option offering a potential cure. Given the natural history of this disease, the majority of untreated SCRLM patients displayed median survival times of 3.8 to 21.3 months.[11,15] Fortunately, due to substantial improvements in chemotherapeutics over the past several decades, greater numbers of patients benefit significantly from adjuvant chemotherapy and/or radiotherapy. Effective treatment with chemotherapy can prolong survival for up to 4 years, with a median survival of around 20 months.[30] Yet, patients who receive curative surgical resections of SCRLM can expect not only a 5-year survival but also a 10- or even a 20-year survival rate of 18% in some studies.[7,15] It appears that surgical resection is an effective treatment option for patients with SCRLM and could even offer a cure.

Both simultaneous and staged resections for patients with SCRLM are associated with similar disease-free survival.[23] Since the perioperative risk of staged resection could be less than that associated with simultaneous resection, some studies have proposed that staged resection is safer and therefore a better option.[17,18] However, this perspective has been under some debate in the last decade due to the significant advancements achieved in surgical techniques and anesthetic management, as well overall

Table 4 Univariate Analysis of Factors Associated with All Complications After Simultaneous or Staged Colorectal and Hepatic Resections

Variable	Simultaneous resection			Staged resection		
	n=129	Overall complications, *n*=61	*P* value	*n*=276	Overall complications, *n*=150	*P* value
Age (years)			0.298			0.548
<60	78	34 (43.6%)		126	66 (52.4%)	
≥60	51	27 (52.9%)		150	84 (56.0%)	
Gender			0.272			0.0578
Male	76	39 (51.3%)		156	77 (49.4%)	
Female	53	22 (41.5%)		120	73 (60.8%)	
Cardiac disease history			0.148			0.531
Yes	26	9 (34.6%)		61	31 (50.8%)	
No	103	52 (50.5%)		215	119 (55.3%)	
Pulmonary disease history			0.223			0.209
Yes	22	13 (59.1%)		69	42 (60.9%)	
No	107	48 (44.9%)		207	108 (52.2%)	
CEA (ng/mL)			0.366			0.250
<5	88	44 (50.0%)		201	105 (52.2%)	
≥5	41	17 (41.5%)		75	45 (60.0%)	
Chemotherapy before liver resection			0.078			0.147
Yes	51	29 (56.9%)		169	86 (50.9%)	
No	78	32 (41.0%)		107	64 (59.8%)	
Primary tumor distribution			0.058			0.114
Rectal	69	38 (55.1%)		137	81 (59.1%)	
Colon	60	23 (38.3%)		139	69 (49.6%)	
Primary tumor stage			0.683			0.098
T4	61	30 (49.2%)		212	121 (57.1%)	
Others	68	31 (45.6%)		64	29 (45.3%)	
Primary nodal status			0.803			0.081
Positive	86	40 (46.5%)		173	101 (58.0%)	
Negative	43	21 (48.8%)		103	49 (47.6%)	
No. of metastases			0.228			0.943
1	81	35 (43.2%)		97	53 (54.6%)	
>1	48	26 (54.2%)		179	97 (54.2%)	
Size of largest metastasis (cm)			0.158			0.313
<5	76	32 (42.1%)		153	79 (51.6%)	
≥5	53	29 (54.7%)		123	71 (57.7%)	
No. of segments removed			0.119			0.369
<3	85	36 (42.4%)		143	74 (51.7%)	
≥3	44	25 (56.8%)		133	76 (57.1%)	

critical care. Those advancements and others make simultaneous resection both readily available and safe.[31]

In this study, in terms of overall perioperative morbidity and mortality, we found that there was no significant difference between simultaneous resection and staged resection of SCRLM in selected patents. Both surgical options appear to share similar severity of total complications, as defined by Dindo et al.[28] Although in this study, those patients who underwent simultaneous liver resections had more wedge resections whereas more patients who underwent staged resections had more extensive resections, neither the number of metastases nor the number of segments removed was found to be associated with the overall morbidity after simultaneous or staged colorectal and HRs in the present set of patients (Table 4). Additionally, the overall mortality in this study was less than 2%. Even with simultaneous HR of equal to or more than three hepatic segments, we noted no differences in complication

morbidity between the two procedures. A similar observation was described in a recent study led by Martin et al.[31] As with their findings, we demonstrated that simultaneous resections are as safe as staged procedures for SCRLM patients and do not increase morbidity, mortality, or severity of complications.

Importantly, staged resections of primary tumors and hepatic lesions require repeated anesthesia as well as surgery. It was expected that staged procedures would have a longer duration of surgery and postoperative hospitalization time as well as more blood loss during surgery. These findings are consistent with previously studies.[19–24] However, even though the magnitude of liver resection alone did not appear to affect mortality or postoperative complication rates in this study, we had to keep in mind that patients with staged resections underwent more extensive liver resections, which could have impacts on increasing the blood loss during surgery and duration of surgery to some extent.

In summary, the present study provides evidence that simultaneous resection of CRC primary tumors and hepatic metastases is safe and is associated with a shorter duration of surgery, reduced postoperative hospitalization time, and decreased blood loss. However, this study does have some limitations. First, our data was analyzed retrospectively, and all the patients enrolled in the study were preselected. Second, outcomes associated with increased follow-up should be documented, as we might have missed additional complications that occurred after 30 postoperative days. Third, there could be surgical bias in the training of different groups, which could affect the clinical outcome to some extent. On consideration of those limitations, better-designed prospective studies are needed to confirm those findings. Finally, although HR is associated with low morbidity and low mortality rates and encouraging survival rates,[13,29] only up to 20% of SCRLM patients are deemed to be resectable with an intent to cure at presentation.[7,21] This fact highlights the importance of not only appropriate SCRLM treatment but also early detection of CRC.

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Conflicts of interest We declare there are no financial or commercial conflicts of interest in this study.

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ORIGINAL ARTICLE

The Effect of Surgical Volume and the Provision of Residency and Fellowship Training on Complications of Major Hepatic Resection

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Abstract
Background Positive volume–outcomes relationships have been demonstrated for hepatic resection using arbitrary criteria to define high-volume centers. The safety of training programs has not been evaluated. The association of surgical volume, as a continuous variable and the influence of a surgical residency and a fellowship program on outcomes after major hepatectomy were determined.
Methods The Nationwide Inpatient Sample (NIS) was queried from 1998 to 2006. Quantification of patients' comorbidities was made using the Charlson index, and mortality, and complication rates were determined. Institutions' annual case volumes were correlated with risk-adjusted outcomes over time, as well as presence or absence of residency or fellowship training program using logistic regression modeling.
Results A total of 5,298 major hepatectomies were recorded, representing a weighted nationwide total of 26,396 cases. In-hospital unadjusted mortality for the study period was 6%. Adjusting for comorbidities, greater major hepatectomy volume was associated with improvements in the incidence of most measured complications, with plateauing of mortality of between 2% and 3% at approximately 50 cases per year. The mortality rate increased once greater than approximately 70 cases were performed per annum. Hospitals supporting a surgical residency program had lower overall morbidity and mortality. A fellowship program however was not associated with overall lower morbidity and mortality and appeared to result in a higher rate of certain complications.
Conclusions Greater annual major hepatectomy volume improves outcomes with reduced mortality up to a certain point. The presence of surgical residency program but not a fellowship program is associated with reduced predicted morbidity and mortality.

Keywords Major hepatectomy · Fellowship · Residency · Mortality · Morbidity · Surgical volume · Volume-outcome · Charlson index

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Introduction

Hepatic resection has previously been associated with high morbidity and mortality.[1–3] Improvements in technique and peri-operative care have resulted in significant reductions in morbidity, with reports of zero mortality in some centers.[4,5] The overall morbidity and mortality associated with hepatic resection however appears to be under-reported, based on large database reviews.[6] Identification of potentially modifiable factors associated with morbidity and mortality following major liver resection is therefore important.

A number of studies identify surgical volume as an important determinant of postoperative mortality following advanced surgical procedures.[7–10] In cases of major hepatic resection, there is a clear association between mortality and surgical volume when arbitrary cut-offs are used to

differentiate high- from a low-volume centers.[6,11,12] There is no consistency or clear reasoning for using certain cut-off thresholds with definitions ranging from 15 to 50 cases per annum used to define a high-volume center.[6,11,12] No previous population studies have examined the association of surgical volume as a continuous variable with inpatient mortality following major hepatic resection.

In addition to surgical volume, it is conceivable that surgical centers offering a residency program or a fellowship in hepatobiliary surgery may also be associated with lower morbidity and mortality. As far as is known, this has not been previously examined. It could be hypothesized that academic centers with a surgical residency or fellowship program provide more focused specialization, which could result in better outcomes, independent of surgical volume and patient comorbidities.[13]

The aim of our study was to analyze a large inpatient database to determine the association of surgical volume, as a continuous variable, with mortality following major hepatectomy. Secondarily, the outcomes of patients following major hepatectomy in centers offering an Accreditation Council for Graduate Medical Education (ACGME)-accredited surgical residency program or a fellowship in hepatobiliary surgery were compared with centers that offered no such programs, controlling for surgical volume and patient comorbidities.

Methods

National Inpatient Study Database

National Inpatient Study (NIS) database covering the years 1998–2006 was queried. This is the largest all-payer inpatient care databases in the USA, containing data from approximately eight million hospital stays each year. The latest release is the 2006 database contains all discharge data from 1,045 hospitals located in 38 States, approximating representing a 20% stratified sample of all non-Federal, short-term, general, and other specialty hospitals in the USA.[14]

Creation of Liver Resection Dataset

A dataset was created by merging the core and hospital files and so that only patients having undergone what was considered a major hepatectomy were included in this study. This was based on ICD-9-CM code 50.3, which defines hepatic lobectomy or greater. Patients undergoing minor hepatectomy or wedge resection (ICD-9 codes 50.2, 50.22, 50.29), and liver transplantation (ICD-9 codes 50.4 and 50.5) were excluded from analysis. Liver operations in patients whose stay in hospital was less than or equal to 23 h are not captured by the NIS database. This compromises mainly minor liver biopsy or minor resectional procedures. Pediatric patients less than or equal to 17 years of age were excluded. To calculate nationwide case volumes, the NIS-supplied discharge-level weight was applied to calculations. At all other times, the unweighted NIS cohort was utilized for calculating standard errors and performing regression analyses.

Identification of Residency and Fellowship Programs

Information regarding the presence of a fellowship program in each year of the study period was taken from the following: (a) The Fellowship Council's (FC) webpage (a total of 89 institutions submitted data in 2006), b) Society of Surgical Oncology (SSO) webpage (11 institutions submitted data) and (c) The International Hepato-Pancreato-Biliary Association (IHPBA) Fellowship listings (ten institutions submitted data).[15–17] The exact years of existence of the fellowship program could be determined for Fellowships listed on the Fellowship Council's webpage. Some programs were listed on both IHPBA and FC websites. In the case of IHPBA and SSO listed programs, the presence of listing on the website was assumed to indicate the presence of such a fellowship throughout all the years of the study. It was also assumed that a Fellowship when listed was actually filled by a fellowship candidate in the year of listing. A teaching hospital was defined within the NIS as a hospital with residents in any specialty and meeting any of the following criteria: Accreditation Council for Graduate Medical Education (ACGME) residency training approval (in any specialty), membership in the Council of Teaching Hospitals, or a ratio of full-time equivalent interns and residents to beds of 0.25 or higher. Hospitals defined as having an ACGME-accredited general surgical residency were defined as a separate group. Details of such a surgical residency program were obtained by combining information from the American Medical Association's FREIDA database and the listings of accredited programs on the ACGME webpage.[18,19]

Identification of Patient Comorbidity

Comorbidity scores were applied to each inpatient stay record, using the Deyo adaptation of the Charlson comorbidity index.[20,21] This validated index allocates a score between 0 and 35, with a higher score indicating more comorbidity. The comorbidities examined include: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, pulmonary disease, connective tissue disease, peptic ulcers, chronic liver disease, hemiplegia, renal disease, diabetes, malignancy, leukemia, metastatic cancer, and acquired immune deficiency syndrome.

Defining Mortality and Morbidity

Peri-operative complications were added based on ICD-9-CM codes, in a similar manner to that described by Santry.[20] The diagnosis of "any complication" was made if the patient "died during hospitalization" field=1, or if any of the NIS's 15 diagnosis fields contained one of the following complications or procedure codes: abdominal drainage procedure (5,491), acute cerebrovascular accident (43100-43191, 4330-4339, 4340-43491), acute dialysis (3,895), acute deep venous thrombosis (4,538, 4,539), acute myocardial infarction (4,100–4,109), acute pulmonary embolism (4,151, 41,511, 41,519), acute renal failure (5,841–5,849), acute respiratory failure (51,881), adhesiolysis (5,451, 5,459), anastomotic leak (9,986), bacterial pneumonia (481, 485, 486, 4,820–4,829), cardiac complications (9,971), central nervous system complications (99,701–99,703), dialysis catheter insertion (3,995), foreign body removal (5,492), intraoperative hemorrhage (99,811), laparotomy (5,412), mechanical ventilation (967, 9,671, 9,672, 9,673), postoperative shock (9,980), reclosure of abdomen (5,461), respiratory tract complications (99,973), small bowel obstruction (5,600–5,609), splenectomy (4,143, 415), splenic injury (8,650–8,651), tracheostomy (311, 3,129), transfusion (9,904, 9,909), urinary complications (9,975), wound dehiscence (9,983, 99,831, 99,832), wound infection (9,985, 99,851, 99,859), wound seroma (99,813).

Statistical Analysis

SAS 9.2 (SAS Institute, Cary, NC) was used to analyze the data. Logistic regression modeling was performed using Generalized Estimating Equations and assuming a binomial distribution of the data. This allowed certain covariables to be controlled for; these included annual improvements in outcomes and Charlson comorbidity index scores. Repeated measure analysis was performed with the experimental unit being hospital identification number clusters. We used logistic regression modeling to model the dichotomous response variables. We used compound symmetric correlation to account for expected correlation within individual hospitals. We used reference cell coding for our parameterization. The model was fit and empirical standard error estimates were generated which in turn were used to generate p values. A p value <0.05 was considered significant. Subsequently, the estimates were exponentiated to calculate an odds ratio and 95% confidence intervals.

We fit the models first with the quadratic terms, for which p values were generated. If statistical significance was determined, then the quadratic term was retained in the model. Otherwise, the quadratic was removed and a linear model was utilized. In interest of simplicity of presentation of our data, tables were presented using the linear model, while graphical representation of the case volume/outcome relationship allowed for demonstration of the model with the quadratic terms, which had reached significance.

Results

Numbers of Major Hepatectomy

A total of 5,298 major hepatectomies were recorded in the NIS database for the study period. NIS weightings indicate this cohort represents 26,396 total major hepatectomies performed in the USA during the 9-year study. With a nationwide weighted total of 2,579 major hepatectomies being performed in 1998 and 2,739 in 2006, it is evident that the annual number of major hepatectomies did not increase over this timeframe (Table 1). The number of cases performed in centers with a surgical residency or Fellowship program did not vary significantly over the study period. The majority of major hepatectomies were per-

Table 1 Unweighted number of major hepatectomy cases performed at various locations (% total hepatectomies)

Year	1998	1999	2000	2001	2002	2003	2004	2005	2006
Overall	470	547	503	517	545	756	676	716	568
All teaching hospitals	385 (82%)	488 (89%)	406 (81%)	424 (82%)	455 (83%)	654 (87%)	543 (80%)	600 (84%)	457 (81%)
ACGME surgical training	268 (57%)	364 (67%)	251 (50%)	309 (60%)	244 (45%)	483 (64%)	355 (53%)	419 (59%)	316 (56%)
Fellowship program	127 (27%)	253 (46%)	44 (9%)	72 (14%)	116 (21%)	431 (57%)	233 (34%)	246 (34%)	149 (26%)
IHPBA	81	192	12	0	44	200	31	84	0
FC	40	84	32	71	82	358	233	211	143
SSO	74	65	0	1	0	29	28	35	6

ACGME Accreditation Council for Graduate Medical Education, *IHPBA* International Hepato-Pancreato-Biliary Association *FC* Fellowship Council, *SSO* Society of Surgical Oncology

formed in centers providing either a surgical residency or Fellowship program. The vast majority of major hepatectomies were performed in institutions classified by the NIS as teaching institutions.

Charlson Comorbidity Score and Unadjusted Mortality Rates Charlson scores during the time period studied are noted (Table 2). Additionally, the unadjusted overall mortality rate during this period is shown, and fluctuated significantly over the study period, with a high of 8.94% seen in 1998 and a low of 4.90% in 2003. Mortality rates and Charlson scores in programs with and without surgical residency or Fellowship programs are shown. Unadjusted mortality rates were consistently lower in hospitals with an ACGME-accredited surgical residency compared with hospitals without, a difference which was statistically significant over the entire study period ($p=0.0003$), with intra-year significant improvements seen in 1998, 1999, and 2004. The same can be said for institutions offering fellowships through the Fellowship Council, the SSO, or the IHPBA; these hospitals had significantly lower mortality rates when compared with non-Fellowship institutions ($p<0.0001$), with approximately a 40% lower risk of unadjusted in-hospital mortality. NIS-designated teaching hospitals showed significantly improved outcomes, with mortality rates in this group averaging 5.92%, while those in non-teaching institutions averaged 8.94% ($p=0.0008$).

The Effect of Case Volume on Morbidity and Mortality

Table 3 examines the independent effect of annual hospital case volume on complication rates, after controlling for year and for comorbidity scores. In contrast to previously

Table 2 Charlson morbidity scores and mortality

	Study year									
	1998	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**All years**
Key: mean Charlson ± SD **mortality (%)**										
Overall	4.76 ±3.11 **8.94%**	4.61 ±3.04 **5.12%**	4.42 ±3.17 **8.75%**	4.02 ±3.29 **7.36%**	4.58 ±3.09 **5.32%**	4.28 ±3.28 **4.90%**	4.40 ±3.02 **6.51%**	4.45 ±3.17 **5.59%**	4.60 ±3.24 **6.87%**	4.45 ±3.16 **6.44%**
Teaching Hospital		– *							– *	
Yes	4.83 ±3.07 **8.31%**	4.47 ±3.03 **3.89%**	4.38 ±3.17 **8.62%**	3.64 ±3.22 **7.09%**	4.40 ±3.08 **5.27%**	4.30 ±3.27 **4.75%**	4.27 ±2.96 **5.89%**	4.34 ±3.13 **5.33%**	4.47 ±3.25 **5.69%**	4.34 ±3.14 **5.92%**
No	4.64 ±3.24 **11.90%**	5.75 ±2.91 **15.25%**	4.56 ±3.17 **9.28%**	5.73 ±3.05 **8.60%**	5.48 ±2.98 **5.56%**	4.12 ±3.37 **5.88%**	4.92 ±3.20 **9.02%**	5.03 ±3.31 **6.90%**	5.19 ±3.18 **10.91%**	4.99 ±3.20 **8.94%**
										$p=0.0008^*$
ACGME surgical residency	– *	– *					– *			
Yes	4.98 ±3.05 **6.34%**	4.37 ±3.05 **3.30%**	4.16 ±3.21 **7.17%**	3.57 ±3.23 **6.49%**	3.92 ±3.11 **5.33%**	3.99 ±3.25 **4.76%**	4.44 ±2.93 **4.51%**	4.18 ±3.16 **6.21%**	4.26 ±3.26 **5.38%**	4.20 ±3.16 **5.39%**
No	4.46 ±3.16 **12.38%**	5.08 ±2.98 **8.74%**	4.67 ±3.11 **10.32%**	4.67 ±3.27 **8.65%**	5.12 ±2.96 **5.32%**	4.78 ±3.29 **5.15%**	4.36 ±3.12 **8.72%**	4.83 ±3.14 **4.71%**	5.03 ±3.18 **8.73%**	4.77 ±3.14 **7.82%**
										$p=0.0003^*$
Any Fellowship Program	– *									
Yes	5.30 ±3.02 **3.15%**	4.15 ±3.15 **3.16%**	5.14 ±3.15 **2.27%**	3.21 ±3.22 **5.56%**	4.34 ±3.19 **4.31%**	4.00 ±3.27 **4.18%**	4.33 ±2.87 **4.29%**	4.62 ±3.07 **6.50%**	4.54 ±3.23 **4.70%**	4.33 ±3.16 **4.37%**
No	4.55 ±3.12 **11.08%**	5.00 ±2.89 **6.80%**	4.35 ±3.17 **9.37%**	4.15 ±3.28 **7.66%**	4.65 ±3.06 **5.59%**	4.65 ±3.26 **5.86%**	4.44 ±3.10 **7.67%**	4.36 ±3.21 **5.11%**	4.62 ±3.25 **7.64%**	4.50 ±3.16 **7.39%**
										$p<0.0001^*$

*Statistically significant

Table 3 The incremental effect of each major hepatectomy on annual outcomes, controlling for year and for Charlson comorbidity scores

Outcome	Odds ratio (95% CI)	*p* value	Effect	Outcome	Odds ratio (95% CI)	*p* value	Effect
Any complication	0.992 (0.987, 0.996)	0.0006	↓	Respiratory tract comps	0.993 (0.986, 1.000)	0.0510	
Death	0.975 (0.967, 0.983)	<0.0001	↓	Acute renal failure	0.989 (0.983, 0.995)	0.0003	↓
Anastomotic leak	0.999 (0.991, 1.007)	0.7466		Acute CVA	0.994 (0.984, 1.004)	0.2184	
Abdominal drainage	0.999 (0.993, 1.005)	0.7720		Bacterial pneumonia	0.986 (0.995, 0.999)	0.0017	↓
Acute DVT	0.993 (0.985, 1.001)	0.0941		Respiratory failure	0.983 (0.977, 0.995)	0.0010	↓
Acute PE	0.996 (0.989, 1.002)	0.2156		Laparotomy	0.992 (0.985, 0.999)	0.0314	↓
Myocardial infarction	0.990 (0.982, 0.998)	0.0134	↓	Transfusion	1.000 (0.990, 1.011)	0.9539	
Cardiac complications	1.001 (0.996, 1.006)	0.6673		Urinary complications	1.007 (0.999, 1.014)	0.0706	
Post-op shock	0.978 (0.958, 0.998)	0.0314	↓	Need to reclose abdomen	0.994 (0.983, 1.006)	0.3288	
Splenectomy	0.989 (0.986, 0.993)	<0.0001	↓	Intraoperative hemorrhage	0.992 (0.986, 0.998)	0.0141	↓
Wound infection	1.000 (0.997, 1.004)	0.8077		Wound dehiscence	0.996 (0.991, 1.001)	0.1410	
Tracheostomy	0.986 (0.977, 0.996)	0.0038	↓				

published studies, artificial case volume groups were not applied and the models were solved for case volume as a continuous variable. An odds ratio <1.0 signifies an inverse correlation between case volume and the complication under review. The effect of each and every case on outcomes is reported.

Nearly all analyzed complication categories trended towards an inverse correlation with volume, with mortality rate and rates of any complication, myocardial infarction, intraoperative hemorrhage, postoperative shock, splenectomy, bacterial pneumonia, respiratory failure, tracheostomy achieving statistically significant improvement. No complication was positively correlated with increasing case volume.

When used as predictors in a logistic regression model, both the case volume ($p<0.0001$) and the quadratic ($p<0.0001$) achieved statistical significance, with the predicted trends plotted in Fig. 1. The improvement in mortality rate observed with increasing hospital case volume seems to level out at approximately 50 cases per year, and then slowly increases after about 70 cases per year.

Relation of Surgical Residency on Morbidity and Mortality

The overall independent effect of surgical residency on morbidity and mortality controlling for Charlson score, case volume, and yearly variations, is shown in Table 4. There was a significant decrease in overall complications and in-hospital mortality associated with hospitals offering an ACGME-accredited surgical residency program. There was no significant increase in any of the complications examined in relation to the presence of surgical residency program.

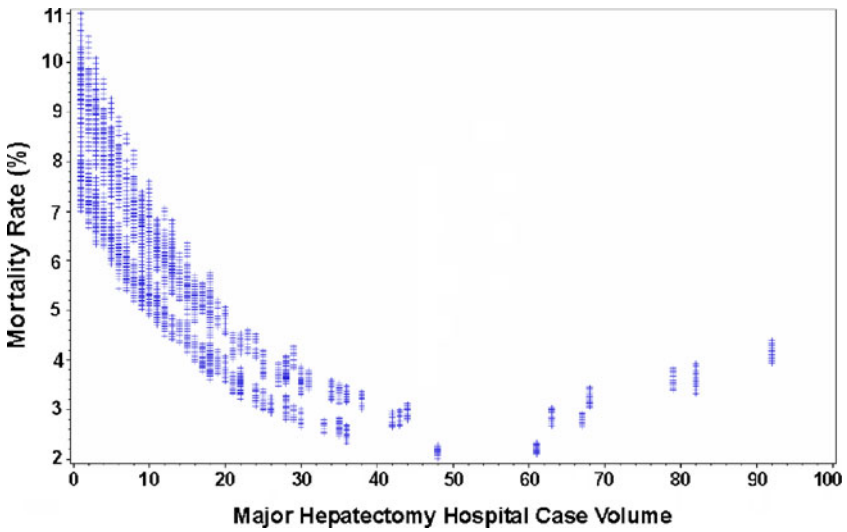

Fig. 1 Predicted mortality rate following major hepatectomy according to annual hospital volume, adjusted for Charlson comorbidity score

Table 4 The effect of surgical residency on major hepatectomy outcomes, controlling for year and for Charlson comorbidity scores

Outcome	Odds ratio (95% CI)	*p* value	Effect	Outcome	Odds ratio (95% CI)	*p* value	Effect
Any complication	0.851 (0.757,0.957)	0.0072	↓	Respiratory tract comps	0.829 (0.683, 1.006)	0.0580	
Death	0.815 (0.706, 0.941)	0.0052	↓	Acute renal failure	0.917 (0.786, 1.070)	0.2713	
Anastomotic leak	1.114 (0.860, 1.443)	0.4136		Acute CVA	1.086 (0.755, 1.562)	0.6548	
Abdominal drainage	1.088 (0.895, 1.323)	0.3972		Bacterial pneumonia	0.715 (0.614,0.834)	<0.0001	↓
Acute DVT	1.090 (0.862,1.380)	0.4707		Respiratory failure	0.840 (0.695,1.015)	0.0706	
Acute PE	1.136 (0.861, 1.500)	0.3673		Laparotomy	1.037 (0.796, 1.351)	0.7877	
Myocardial infarction	0.972 (0.756, 1.250)	0.8276		Transfusion	0.886 (0.687, 1.143)	0.3517	
Cardiac complications	1.168 (0.981,1.391)	0.0819		Urinary complications	1.330 (0.993, 1.780)	0.0554	
Post-op shock	1.029 (0.681, 1.554)	0.8911		Need to reclose abdomen	1.274 (0.839,1.936)	0.2559	
Splenectomy	0.990 (0.897,1.093)	0.8389		Intraoperative hemorrhage	1.046 (0.890, 1.230)	0.5869	
Wound infection	1.013 (0.887, 1.157)	0.8522		Wound dehiscence	1.139 (0.911,1.425)	0.2536	
Tracheostomy	1.038 (0.843,1.279)	0.7233					

Relation of Fellowship Program on Morbidity and Mortality

The overall independent effect of a Fellowship program on morbidity and mortality, controlling for Charlson score, case volume, and yearly variations is shown in Table 5. There was no change associated with a Fellowship program in overall complications or in mortality rates. The specific complications noted to significantly increase with a Fellowship program were acute venous thromboembolic disease, cardiac complications, tracheostomy, and wound dehiscence. There was no significant decrease in any of the complications examined in relation to the presence of a fellowship program.

Discussion

Hepatic resection is effective in the management of various liver tumors. There however continues to be significant morbidity and mortality associated with major hepatic resection based on large populations studies,[6,11,12] despite observations of decreased mortality following liver resection over time.[6] Several studies advocate that advanced surgical operations should be performed in high-volume centers,[7–10] with arbitrary cut-off volumes used to differentiate between high- and low-volume centers. The true extent to which case volume improves outcomes following major hepatectomy has not been previously defined, where case volume is considered as a continuous variable. In addition, the effect of surgical residency and a fellowship training program on outcomes is unknown.

Multiple studies have previously demonstrated reduced mortality associated with advanced surgical procedures in high case volume centers.[7–10] The majority of these studies have utilized the NIS database for analysis. Although not all patients from all States are captured by this database, it is the largest all-payer inpatient database in the USA.[14] The mortality rate following liver resection in high-volume

Table 5 The effect of fellowship program on major hepatectomy outcomes, controlling for year, Charlson comorbidity score, and volume

Outcome	Odds ratio (95% CI)	*p* value	Effect	Outcome	Odds ratio (95% CI)	*p* value	Effect
Any complication	0.931 (0.786, 1.103)	0.4087		Respiratory tract comps	0.878 (0.701, 1.099)	0.2567	
Death	0.855 (0.712, 1.027)	0.0939		Acute renal failure	0.957 (0.797, 1.148)	0.6343	
Anastomotic leak	1.233 (0.884, 1.722)	0.2176		Acute CVA	1.167 (0.780, 1.747)	0.4516	
Abdominal drainage	1.366 (1.112, 1.678)	0.0029	↑	Bacterial pneumonia	0.947 (0.776, 1.155)	0.5919	
Acute DVT	1.375 (1.037, 1.825)	0.0272	↑	Respiratory failure	0.841 (0.667, 1.062)	0.1453	
Acute PE	1.425 (1.074, 1.890)	0.0140	↑	Laparotomy	1.268 (0.954, 1.684)	0.1015	
Myocardial infarction	1.303 (0.983, 1.728)	0.0656		Transfusion	0.977 (0.643, 1.486)	0.9144	
Cardiac complications	1.247 (1.003, 1.550)	0.0474	↑	Urinary complications	1.289 (0.899, 1.847)	0.1672	
Post-op shock	1.034 (0.596, 1.795)	0.9047		Need to reclose abdomen	1.477 (0.937, 2.330)	0.0932	
Splenectomy	1.007 (0.889, 1.14,)	0.9085		Intraoperative hemorrhage	1.090 (0.891, 1.335)	0.4017	
Wound infection	0.969 (0.825, 1.138)	0.6995		Wound dehiscence	1.433 (1.111, 1.848)	0.0056	↑
Tracheostomy	1.334 (1.049, 1.697)	0.0187	↑				

centers based on NIS data from 1998 to 2005 was significantly lower than in low-volume centers (2.6% versus 4.8%).[12] The volume cut-off for a high-volume center was 20 or more cases. Volume cut-offs of 15 and 50 cases has also been previously examined.[6,11] It is proposed that high-volume centers may provide greater overall specialization and care of patients undergoing complex operative procedures.[8,22] The provision of specialized centers that attracts high case volume may be one factor accounting for these differences.

One must consider that mortality rates using the NIS database represent only in-hospital mortality, which is not necessarily reflective of 30–90 day postoperative mortality. It would be expected that the true 30 to 90 day postoperative mortality would be higher than determined from the NIS database. Patients in more specialized high case volume centers may be better streamlined for early home or rehabilitation discharge following surgery. If morbidity and mortality occurs after discharge, this would results in an apparent decrease in postoperative morbidity and mortality.

In our analysis of NIS data from 1998 to 2006, a small decrease in mortality was apparent over the study period. There was also clear reduction in morbidity and mortality following major hepatectomy with increasing case volume when controlling for year and for comorbidities using the Charlson comorbidity scoring system which has been previously validated and shown to be predictive of mortality.[23–25] The greater the number of hepatectomies performed annually, the better the expected outcome, at least up to a point. It appears that at approximately 70 major hepatectomies per year, the mortality rate may rise. This is the first times such a U-shaped curve has been described in the field of hepatic surgery, though this mirrors findings previously reported in other surgical specialties.[13] The argument that the high-volume centers may be tackling higher risk cases is partly rebutted by the aforementioned Charlson score-based risk adjustment data. As previously described, the Charlson score is a validated method of risk-stratification for surgical patients analysis with administrative databases. However, the authors acknowledge that it has not explicitly been validated in patients undergoing hepatic resection, and may therefore introduce some amount of systematic error into the analysis. It is postulated by the authors that at a certain volume, the facilities of the institution, both physical facilities and personnel, may be stretched enough to compromise patient outcomes. Alternatively, these facilities may deal with more advanced cases, requiring larger volumes of hepatic resection and higher risks of postoperative liver failure. These features cannot be determined from the NIS database. This clearly warrants further investigation, and has been undertaken by the authors as a future project. Regardless, it appears clear that case volume cannot be used as a perfect surrogate for surgical quality.

The association of a surgical residency or fellowship program, and morbidity and mortality following major hepatectomy has not been previously examined, although the teaching status of a hospital was not independently associated with mortality in a single reported study.[6] That particular study examined both minor and major hepatectomy combined, but did not specifically examine accredited surgical residency programs and covered the period 1998–2004. According to our data assessing programs offering ACGME-accredited surgical residency, this was independently associated with overall reduced morbidity and mortality. This finding may be reflective of the high specialization of these units that are accredited for a surgical residency program, and has been similarly reported with regard to other operations such as esophagectomy.[13] Given the advanced nature of major hepatectomy, these operative procedures are likely to be performed by attending surgeons than surgical residents. The overall influence of surgical residency on the technical aspects of major hepatectomy operations is therefore likely to be minimal.

The same findings were not apparent with programs offering surgical fellowships as identified by the Society of Surgical Oncology, the Fellowship Council, and the IHPBA listings.[15–17] A Fellowship program was independently associated with an increase in specific complications following major hepatectomy. Our multivariate analysis took into consideration that many programs provide both surgical residency training and a Fellowship program. The specific factors that significantly increased were acute DVT, pulmonary emboli, cardiac complications (other than myocardial infarction), tracheostomy requirement, and wound dehiscence. Interestingly, there was no significant change in mortality or overall morbidity in centers offering a fellowship program. The exact reason for these finding is unknown, is likely to be multifactorial, and may be further evidence of a previous finding that in specialized centers earlier detection and commencement of management of complications lessens the effect of adverse events.[26]

It should be clearly noted that the performance of a hepatectomy in a hospital offering fellowship training does not guarantee that the fellow performed or was even a participant in the procedure. Furthermore, only a subset of Fellowship Council-accredited programs provide training to the Fellow in hepatic resection and similarly some hepatic surgery fellowships are provided outside the studies groups of Society of Surgical Oncology, the Fellowship Council, and IHPBA (for example, those programs accredited by the American Society of Transplant Surgeons). These limitations of the dataset will necessitate caution in the interpretation of associations between Fellowship training per se and outcomes, but will not nullify the association between the parent institution and the outcomes under consideration.

It should be noted that there was variability in the reporting of major liver resections by the various programs during certain time periods. It is possible that during some years, certain programs did not submit cases to the NIS or the NIS did not sample cases from those regions during specific periods.

Fellowship programs may perform more extensive liver resections such as extended lobectomy, which would be coded simply as a major liver resection. Such cases are more complex, take longer to complete and are at higher risk of complications. One may also hypothesize that increased morbidity may occur after advanced liver resections in which the fellow was the primary operator. Fellows may be more likely to be the primary operator for major hepatectomy than surgical residents and inexperience may produce more complications. Increased complications did not however translate to increased mortality that may be reflective of the high standard of postoperative care in such centers.

Socioeconomic status and insurance type was not corrected for in our study, which has previously been associated with mortality following liver resection.[12] Also, our study included patients that had undergone at least a hepatic lobectomy, whereas others have included all patients undergoing hepatic resection.[6] It is possible that not all patients undergoing major hepatectomy were identified based on ICD-9-CM classification as problems of both over- and under-capture of cases with ICD-9-CM-based searches of administrative datasets have previously been reported.[27] Major hepatectomy is generally considered resection of three or more hepatic segments;[28] this may not necessary involve a complete right or left hepatic lobectomy and some patients undergoing a major hepatectomy may have been coded as having a partial hepatectomy (50.22).

Conclusion

The predicted mortality following major hepatectomy decreases with increasing case volume without a specific volume cut-off, though a U-shaped curve exists with upturn at very high annual case volumes. Centers with surgical residency programs appear to be associated with reduced morbidity and mortality. Fellowship-associated programs have increased overall morbidity, without increased mortality. The factors related to these observed differences are only speculative and are worthy of further investigation.

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ORIGINAL ARTICLE

Surgeon Volume Versus Morbidity and Cost in Patients Undergoing Pancreaticoduodenectomy in an Academic Community Medical Center

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Abstract
Background Despite trends toward regionalization of care, the majority of pancreaticoduodenectomies (PD) are performed in community hospitals by surgeons with varying degrees of experience. We analyzed the impact of several variables, including surgeon volume, on outcomes following PD within a high-volume community-based teaching hospital system.
Methods Patients who underwent PD from 2005 to 2008 were reviewed retrospectively. Perioperative data, complications, and hospital financial data was queried. A high-volume (HV) surgeon was defined as an average of 10 or more PD per year.
Results Ninety-four patients underwent PD with an overall operative mortality rate of 9.6% (HV 2.2%, LV 16.0%), major complication rate of 32% (HV 18%, LV 44%), and median cost of $30,860 (HV $27,185, LV $33,007). Factors predictive of death were age ($p<0.02$), body mass index ($p<0.01$), and surgeon volume ($p<0.05$). Factors predictive of major complication were surgeon volume ($p<0.01$) and body mass index ($p<0.01$). Factors predictive for increased length of stay for patients discharged from the hospital were surgeon volume ($p<0.02$) and preoperative ASA classification ($p<0.05$).
Conclusions Surgeon volume and patient body mass index have a significant impact on perioperative morbidity following PD in a community teaching hospital.

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Introduction

Pancreaticoduodenectomy (PD) remains one of the most formidable operative procedures for the surgical treatment of gastrointestinal malignancy. Outcomes after the Whipple procedure have improved over time and this improvement has been attributed to better preoperative patient selection, advances in radiographic imaging, improvements in post-operative management, and regionalization of referrals to high-volume tertiary care centers. Over the past decade, there have been many studies analyzing the impact of hospital volume on outcome after PD.[1–7] Most of these studies have shown decreased morbidity and mortality when PD is performed at high-volume centers. The impact

of surgeon volume, independent of institutional experience, has been more difficult to establish, but several studies have indicated that surgeon volume can be an independent predictor of improved outcome after PD.[8–12] Despite this abundant literature and the demonstration of some trends toward regionalization of care, the majority of PDs are still performed in community hospitals by surgeons with varying degrees of experience.[12–14]

The number of PDs that categorizes an institution as high volume varies within the literature.[1,3,4,7,13,15] Some studies define high-volume centers as hospitals performing >5 PDs/year, while other studies use a cutoff of >50 PDs/year to define a high-volume center. The "Leapfrog Group" defined criteria for evidence-based hospital referral for pancreatic resections as those performing a minimum of 11 resections per year. Even less clear is the number of PDs that defines an individual surgeon as a high-volume (HV) surgeon.[8,9,12] There is little data to support specific volume cutoffs, and attempts at defining centers of excellence based solely on volume cutoffs have been unsatisfactory.[16]

Most studies in the literature looking at volume and cost analysis for PD are from large academic centers or state/national administrative databases, which may not reflect the experience of community teaching hospitals. High-volume pancreas surgery is not limited to large academic centers, and in fact, many community-based teaching hospitals have sufficient numbers of pancreatic resections to be categorized as high-volume centers. Particularly in smaller institutions, there may be one or two high-volume surgeons whose experience places the institution into a high-volume status. Likewise, such a hospital often has surgeons with low volume as well, leading to a wide spectrum of experience within these institutions. Patterns of care for PD at an individual community teaching hospital are probably reflective of the majority of PDs that are performed in the United States each year.

Most studies to date have looked at the impact of hospital and surgeon volume on postoperative morbidity and mortality. However, in today's healthcare system, it is important to analyze other preoperative and operative variables that can impact patient outcome as well as other endpoints such as hospital length of stay and cost of hospital care associated with the procedure. The goal of this study was to analyze the impact of several perioperative variables, including surgeon volume, on morbidity, mortality, length of stay, and cost of PD within a community-based teaching hospital system.

Methods

From the electronic hospital record system and a prospectively maintained pancreatic database, all patients who underwent a PD within Providence Portland Health System from January 2005 to June 2008 were identified. Patient's complete medical records including demographic information, preoperative data, operative procedure, pathology, and postoperative course were reviewed and analyzed. Surgeon experience was categorized as either HV or low volume (LV) based on an average of ten PDs per year.

Demographic and Preoperative Data Collection

Information obtained in the preoperative setting included patient age, sex, race, body mass index (BMI), history of jaundice, preoperative weight loss, cardiopulmonary comorbidities, ASA classification, preoperative biliary drainage, preoperative imaging studies, and preoperative laboratory values, specifically albumin, bilirubin, and creatinine.

Operative Data and Histopathologic Diagnosis

Operative notes and anesthesia records were reviewed to determine the type of surgical procedure performed, the surgeon, operative time, estimated blood loss, and need for intraoperative blood transfusion. Histopathology reports were reviewed to determine the pathologic diagnosis, completeness of resection, size of primary tumor, and evidence of lymph node involvement. Pathologic diagnoses of adenocarcinoma (pancreatic, duodenal, ampullary, and distal cholangiocarcinoma), neuroendocrine tumors, and metastatic disease were classified as malignant. Patients with a diagnosis of IPMN, mucinous tumors, pancreatitis, or other benign pancreatic processes were classified as benign disease.

Postoperative Complications

Surgical complications were obtained by thorough examination of hospital progress notes. Complications were classified as grade 1–5 based on the severity of the complication as previously described in the surgical literature using the Dindo–Clavien classification.[17,18] Grade 1 and 2 complications were considered minor and did not require operative or image-guided intervention, the use of parenteral nutrition or result in an increase in postoperative length of stay beyond 20 days. Grade 3–5 complications were considered major complications and required either operative or image-guided interventions, the utilization of parenteral nutrition, or resulted in a hospital stay beyond 20 days. Operative mortality was defined as death within 60 days of the index operation.

Cost Data

The only cost data that was available for our review was total cost of the hospitalization. In order to determine which

component of the hospitalization was responsible for difference in costs, we had to analyze itemized charge data. Therefore, hospital financial data was queried for total cost, total charges, and itemized departmental charges.

Statistical Analysis

Statistical calculations were performed using SPSS version 11.5 (Statistical Package for the Social Sciences, Chicago, IL). Continuous variables were compared using Student *t* test (two-tailed) and categorical variables with χ^2 test. Cox regression was used to determine independent predictors of outcome, using death, major complications, length of stay, and total cost of hospitalization as the dependent variables. Continuous variables were utilized whenever feasible. Binary logistic regression was used for death and major complications, which are dichotomous variables, while linear regression was used for length of stay and total cost which are continuous variables. p values <0.05 were considered to be significant.

Results

From January 2005 until June 2008, 94 patients underwent PD (mean, 31.3/year). One surgeon consistently met the high-volume cutoff (average 13 PDs/year), for a total of 44 procedures, while the remaining 50 PDs were performed by 15 surgeons (average 1.1 PDs/year; range 0–5 per year). Mean patient age was 66 (44–88), 52% were male, and the mean BMI was 26.3 (22–55). Preoperative albumin levels had a mean of 4.2 mg/dl (range 2.6–4.9) and ASA classification ranged between 1 and 4 with a mean of 2.8. Thirty-seven resections were for benign disease and the rest for malignant disease (Table 1).

Table 1 also shows these patient characteristics stratified by surgeon volume. There was no difference in patient age, gender, body mass index, ASA classification, or preoperative albumin level between high-volume and low-volume surgeons. The only difference identified between these two groups in terms of risk stratification was the percentage of patients with a malignant pathologic diagnoses and the estimated intraoperative blood loss. The high-volume surgeon operated on more patients with benign disease and had a lower intraoperative blood loss compared to low-volume surgeons.

Table 2 depicts the results of the multivariate analysis looking at preoperative variables predictive for several outcome measures. An analysis of preoperative factors found that higher body mass index ($p<0.01$), increased age ($p<0.02$), and PD performed by a low-volume surgeon ($p<0.04$) were the factors predictive of increased mortality after PD. Factors predictive of major complication (grade≥3) were increased body mass index ($p<0.01$) and low-volume surgeon ($p<0.01$). When we analyzed factors that would predict an increased length of hospital stay for PD patients that were discharged from the hospital, we found that higher preoperative ASA classification ($p<0.05$) and PD performed by low-volume surgeon ($p<0.02$) were significant predictors. When we look at the total cost of the hospitalization, we found that the only preoperative factor predictive of increased cost was a higher ASA classification ($p<0.02$).

Table 1 Demographics, Preoperative, Pathology, and Operative Data

Variable	Overall	HV surgeon	LV surgeon	*p* value
Demographics				
Median age (years)	66	64	67	0.200
Gender: male (%)	52	59	46	0.210
Mean BMI	26.3	26.4	26.2	0.860
Mean ASA	2.8	2.7	2.8	0.390
Preoperative albumin (mg/dl)	4.2	4.0	4.5	0.410
Pathology				0.016
Adenocarcinoma	46.0	17.0	29.0	
Neuroendocrine	5.0	2.0	3.0	
Other malignancy	6.0	2.0	4.0	
Pancreatitis	10.0	7.0	3.0	
Benign (other)	27.0	16.0	11.0	
Operative EBL	567.0	434.0	717.0	0.020

When we directly compared the outcomes of patients undergoing PD by high-volume surgeons compared to those undergoing PD by low-volume surgeons at the same institution (univariate analysis), there is a significant difference in terms of mortality, rate of major complication, and postoperative length of stay (Table 3). PDs performed by high volume surgeons had a mortality rate of 2% compared to 16% for low-volume surgeons ($p<0.03$). Major complication (grade≥3) rates were 18% for high-volume surgeons compared to 44% for low-volume surgeons ($p<0.01$). Median and average hospital stay for patients undergoing PD was 10 and 12.6 days for high-volume surgeons and 13 and 15.4 days for low-volume surgeons ($p<0.01$). In addition, although total cost did not reach statistical significance ($p=0.16$), the difference in median total cost per case between high- and low-volume surgeons was $5,820.

A further detailed analysis of deaths and major complications are provided in Table 4. Of the 50 patients operated upon by LV surgeons, 12 patients (24%) had a pancreatic leak that required additional drainage with a 33% mortality (4/12). The high-volume surgeon had four patients (9%) that required additional drainage procedures for a pancreatic leak with a mortality rate of 0% (0/4). The remainder of

Table 2 Multivariate Analysis of Factors Predictive for Mortality, Major Complication, Length of Stay, and Total Cost

Risk Factor	Mortality	Major complication	Length of stay	Total cost
Age	0.02	0.29	0.36	0.4
Gender	0.82	0.07	0.33	0.14
BMI	0.005	0.004	0.17	0.15
ASA	0.1	0.47	0.05	0.02
Albumin	0.45	0.69	0.62	0.94
HV surgeon	0.04	0.009	0.02	0.16

the serious complications and causes of death are outlined in Table 4.

A malignant pathologic diagnosis was not found to be associated with either increased morbidity or mortality on univariate and multivariate analysis (data not shown). Eight deaths occurred in the low-volume surgeon cohort: four in patients with a benign diagnosis and four in patients with pancreatic adenocarcinoma (three patients with LN (−) disease and one patient with (+) LNs). The only mortality in the high-volume surgeon cohort was in a patient with a benign pathologic diagnosis.

Table 5 provides further detailed information on the patients operated upon with a periampullary malignancy including pathologic diagnosis, size of primary tumor, rate of lymph node involvement, and rate of margin positive resections. As we can see from the table, the high-volume surgeon operated on tumors that were larger in size, had higher rate of involved lymph nodes, and had a higher rate of margin positive resection.

Detailed analysis of total hospital cost and charge data revealed a difference in cost of $5,820 between patients in the HV cohort compared to those in the LV cohort (Fig. 1). Review of the itemized hospital charge data reveals that pharmacy charges were responsible for most of this difference, specifically the utilization of antibiotics, TPN, and octreotide.

Discussion

Over the past decade, there has been increasing emphasis on the analysis of outcomes and cost-effectiveness of medical care. There has been a multitude of literature supporting the importance of regionalization (delivery of care at a limited number of selected provider sites) of certain complex operations to high-volume centers.[1,5,19,20] One of the operations that has been extensively studied in this regard is PD. However, despite many reports demonstrating improved outcomes when PD is performed at high-volume institutions by high-volume surgeons, there remains a debate in the literature regarding the feasibility and appropriateness of this concept.[21–29]

Complications following PD can be devastating or even deadly and occur even in the most advanced programs. The ability to predict outcomes, or to at least stratify risk, would be immensely helpful for practitioners, administrators, and patients. The present study, conducted at a single, high-volume institution, identifies several preoperative factors that predict worse outcomes (cost, complications, and mortality) after surgery. These include: obesity, old age, high ASA score, and surgery by a low-volume (<5/year) surgeon.

This study demonstrates a significant difference in PD outcomes when stratified by surgeon case volume. Other studies in the literature have demonstrated an association between surgeon volume and morbidity after PD but most are from state/national administrative databases. One such study analyzed the outcomes of PD within the state of Florida and found improved outcomes for high-volume providers compared to low-volume providers within a high-volume center.[30] A follow-up publication 6 years later found that although there were fewer surgeons performing PDs in state of Florida, the majority of PDs were still being performed by low-volume surgeons (<1 PD every 2 months) with an even greater discrepancy in outcomes compared to high-volume surgeons.[12]

The utilization of large administrative databases is subject to criticism because of differences in patient cohorts from hospital to hospital and between high- and low-volume surgeons. Studies have indicated that low-volume surgeons tend to perform complex surgical resections on more high-risk patients with significant comorbidities, which partially accounts for the difference in outcomes that is observed in most studies.[9,12,13] Risk stratification is typically not available in state/national databases, and this limits their applicability to real world practice.

Table 3 Outcome Stratified by Surgeon Volume

Outcome	All PD patients	High-volume surgeon	Low-volume surgeon	Univariate *p* value
Mortality (%)	9.6	2.2	16	0.024
Major complication (%)	32	18	44	0.003
Median/average length of stay (days)	12/14.1	10/12.6	13/15.4	0.008
Median total cost ($)	$30,860	$27,185	$33,007	0.17

Table 4 Specific Details on Mortality and Major Complications

Variable	High-volume surgeon	Low-volume surgeon
Death		
Pancreatic leak with resultant MSOF	0	4
Pulmonary embolus	0	1
Myocardial infarction	0	1
Upper GI hemorrhage	0	2
Ischemic bowel	1	1
Complications		
Pancreatic leak requiring perc drainage	4	8
Re-operation		
Wound infection	1	0
VATS decortication	1	0
Repair of colon perforation	0	1
Delayed gastric emptying requiring G-tube or prolonged TPN	2	2
Upper GI hemorrhage	0	1
C-diff	0	1
Pneumothorax	0	1

Regional demographics may also play a role. A recent study by Eppsteiner et al. found that HV surgeons were more likely to perform elective pancreatic resections in white male patients of higher socioeconomic backgrounds in teaching hospitals.[9] This study utilized propensity-matched groups to account for these differences. The positive effect of HV surgeons on patient outcomes remained despite controlling for patient factors. In our study, all patients were operated upon in a single medical system and as such were very similar patient populations. In addition, we looked at several preoperative factors that have been shown to be associated with outcome and found no difference in patients operated upon by high- and low-volume surgeons.

The only difference we were able to identify between our patient cohorts was the higher rate of PDs done by low-volume surgeons for a malignant pathologic diagnosis. The most likely explanation for our high-volume surgeon performing PD for patients with benign disease (including IPMN and mucinous tumors of the pancreas) is based on referral patterns to specialty surgeons for complex decision-making processes. The high-volume surgeon operated on tumors that were larger in size, had higher rate of involved lymph nodes, and had a higher rate of margin positive resection in comparison to the low-volume surgeons; however, this was not found to be statistically significant. One could speculate that surgeons with less experience in pancreatic surgery (lower volume) may be less aggressive with bigger tumors or involved lymph nodes and therefore determined these patients to be unresectable, whereas high-volume surgeons may be more aggressive with surgical management.

Table 5 Details on PDs for Periampullary Malignancy

Variable	High-volume surgeon	Low-volume surgeon
Pathologic diagnosis		
Pancreatic adenocarcinoma	15	22
Ampullary adenocarcinoma	1	4
Duodenal adenocarcinoma	1	1
Cholangiocarcinoma	0	2
Average size of primary tumor (cm)	3	2.6
(+) Lymph node involvement	12/17 (71%)	14/29 (48%)
Margin positive resection	6/17 (35%)	5/29 (17%)

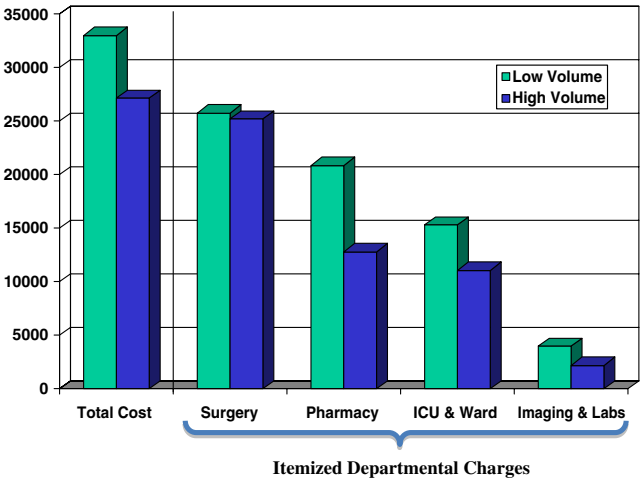

Fig. 1 Hospital costs/charges stratified by surgeon volume. The *column* on the *far left* reveals average total cost of pancreaticoduodenectomy by high- and low-volume surgeons. The *other columns* depict itemized hospital charge data stratified by surgeon volume.

Although there has been a significant amount of literature analyzing the impact of surgeon and hospital volume on morbidity and mortality after PD, there have been few studies analyzing the impact on healthcare cost. Sosa et al. found that hospital charges for pancreatic resections were lowest at high-volume hospitals compared to medium- and low-volume hospitals.[7] However, this study was across many hospitals in the state of Maryland, and as such, it is difficult to compare charge data across hospitals. A more recent study found a statistically significant cost reduction of $5,935 for a PD performed by a HV surgeon (>5 PDs/year) compared to a LV surgeon (1 PD/year), but found no significant cost difference by hospital volume.[11] This cost difference between HV and LV surgeons was close to the cost difference of $5,820 found in our study, although our study did not reach statistical significance likely due to a smaller number of patients.

Interestingly, the cost savings seen when comparing HV and LV surgeons performing PD are similar to those

observed in a study which utilized deviation-based cost modeling to evaluate the economic impact of clinical pathways.[31] This study found that there was a cost saving of $5,542 per patient after clinical pathway implementation with fewer deviations from the expected postoperative course. A similar study from MD Anderson found that a clinical pathway for PD patients dramatically reduced costs with a mean decrease of $10,888 per patient.[32] This raises the question as to whether the cost savings identified in these studies are truly due to surgeon volume or to the presence of clinical pathways and guidelines for complications that are more common in specialty divisions in a hospital.

When we looked at which particular itemized charges were most discrepant between HV and LV surgeons, we found that most of the difference was accounted for by pharmacy charges. Careful review of these itemized charges found that octreotide, TPN, and intravenous antibiotics were most responsible for this difference. This suggests the importance of clinical pathways in establishing postoperative pathways that limit deviation, reduce complications, and guide utilization of these expensive pharmaceutical therapies.

Conclusion

In conclusion, surgeon volume and patient body mass index were found to be most predictive of poor outcome after PD in a community teaching hospital system. Pancreatic surgeons performing >10 PDs per year at a community center can achieve outcomes similar to high-volume pancreatic surgeons at academic medical centers. Patients who undergo PD by a high-volume surgeon can expect to have superior outcomes compared to those patients who have a PD performed by a low-volume surgeon within the same institution.

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ORIGINAL ARTICLE

Evaluation of Cyst Fluid CEA Analysis in the Diagnosis of Mucinous Cysts of the Pancreas

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Abstract
Background Although cyst fluid carcinoembryonic antigen (CEA; >192 ng/ml) is the preferred test for identifying mucinous pancreatic cysts, the data are more robust for mucinous cystic neoplasms (MCN) than for intraductal papillary mucinous neoplasms (IPMN). The role of cyst fluid CEA as a marker for either malignancy or malignant progression is uncertain.
Methods All patients with pancreatic cysts who had undergone endoscopic ultrasound with cyst fluid CEA measurement between 2001 and 2009 were identified. Patient outcomes and pathology from operative resections were recorded.
Results Two hundred sixty-seven patients were identified; pathological diagnosis was obtained in 97. Mucinous cysts were identified in 66 of 97 (68%): benign IPMN, $n=42$; malignant IPMN, $n=10$; benign MCN, $n=12$; malignant MCN, $n=2$. CEA>192 ng/mL had a sensitivity and specificity of 73% and 65% for identifying mucinous cysts; cyst fluid CEA was not associated with malignancy ($p=0.85$). One hundred seventy-eight patients were managed with an initial non-operative strategy. Eight (4%) developed radiographic changes necessitating surgery; pathology demonstrated seven benign mucinous cysts and one retention cyst. CEA was not associated with radiographic progression ($p=0.37$).
Conclusions Cyst fluid CEA is a useful test for identifying mucinous cysts, including MCN and IPMN. In mucinous cysts, cyst fluid CEA is not associated with malignancy or radiographic progression.

Keywords Cystic pancreatic neoplasm · Mucinous cystic neoplasm · Intraductal papillary mucinous neoplasm · Pancreatic cancer

Satish Nagula and Timothy Kennedy contributed equally to the study and are considered co-first authors.

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Introduction

The identification of asymptomatic pancreatic cysts has increased over the last decade, coinciding with the increased usage of high-resolution cross-sectional imaging. Pancreatic cysts can be pathologically divided into non-neoplastic and neoplastic lesions. Non-neoplastic cysts include pseudocysts and retention cysts, and these lesions do not have malignant potential. Neoplastic cysts include serous cystadenoma (SCA), mucinous cystic neoplasms (MCN), intraductal papillary mucinous neoplasms (IPMN), and other rare cystic tumors such as cystic neuroendocrine tumor (NET) and solid pseudopapillary tumor.[1]

Mucinous cysts (MCN and IPMN) are considered premalignant, and it is important to distinguish these lesions

from non-mucinous cysts. Brugge et al. demonstrated cyst fluid carcinoembryonic antigen (CEA) levels (>192 ng/mL) to be more useful than endoscopic ultrasound (EUS) morphology or cyst fluid cytology in the identification of mucinous cysts, with a sensitivity of 75% and a specificity of 84%.[2] Although current guidelines advocate the use of CEA for the identification of both MCN and IPMN,[3] the published literature on cyst fluid CEA has focused primarily on MCN. Many studies have specifically excluded IPMN, including one large meta-analysis.[4] Some have reported a decreased utility of CEA in the diagnosis of IPMN, with one recent study demonstrating that a cyst fluid CEA of 200 ng/mL was 44% sensitive for the diagnosis of IPMN.[5] Data are conflicting about the utility of cyst fluid CEA for distinguishing malignant and benign IPMN.[5,6]

There has been significant investigation into the role of IPMN as precursor lesions in familial pancreatic cancer,[7] and large case series have identified carcinoma within MCNs and IPMNs. Carcinoma within these lesions has been associated with large cyst size, the presence of symptoms, mural nodules, and main pancreatic duct involvement.[8–13] In the absence of these characteristics, serial cross-sectional imaging has been recommended, with resection reserved for radiographic progression. It is currently unknown which mucinous cysts will progress to malignancy. Appropriate risk stratification would lead to a more optimal selection for operative or non-operative management.

The aim of this study was to evaluate the utility of cyst fluid CEA for the diagnosis of mucinous neoplasms in a patient population inclusive of all cyst types. Cyst fluid CEA was evaluated for the ability to distinguish benign from malignant cysts, and to predict future cyst growth. The natural history of unresected pancreatic cysts was also examined.

Methods

Patients

The study was a single-center retrospective analysis of a prospectively maintained registry of patients with pancreatic cysts evaluated at Memorial Sloan-Kettering Cancer Center (MSKCC) between 2001 and 2008. Patients are included in the MSKCC Pancreatic Cyst Registry if they are evaluated by a surgeon or gastroenterologist and coded as having a pancreatic cyst (ICD-9: 577.2). Patients were eligible for inclusion in the current study if they underwent endoscopic ultrasound with fine-needle aspiration (FNA) and determination of cyst fluid CEA. Approval for this study was provided by the Institutional Review Board at Memorial Sloan-Kettering Cancer Center.

Patient demographic data, the results of the initial and most recent radiographic evaluation, cyst fluid CEA level, and pathology results from operative resection (if performed) were recorded. Cyst size was based on radiographic measurements only. Patient management, including the decision to perform operative resection and the interval of serial cross-sectional imaging, was based on patient, radiographic, and endosonographic characteristics as previously reported.[12]

Pathology

All surgical pathology was reviewed by one of three gastrointestinal pathologists. Non-mucinous cysts, including SCA, cystic NET, retention cysts, and inclusion cysts, were identified according to previously established criteria.[1] MCNs and IPMNs were identified according to multiple diagnostic criteria.[14,15] MCNs were distinguished from IPMNs by the lack of both gross and microscopic communication with pancreatic ducts as well as the presence of ovarian-like stroma that is immunoreactive to the estrogen and/or progesterone receptor. IPMNs were identified by their communication with either the main pancreatic duct or its branches and by their mucinous epithelium with intestinal differentiation and intraductal growth pattern. In some cases, the papillary formation is less apparent and the cyst may present as an ectatic ductal lesion with relatively flat mucinous epithelial lining. The cyst wall and septae of an IPMN do not have an ovarian-like stroma. Malignant cysts were defined as having carcinoma in situ (CIS) or invasive carcinoma; benign cysts included those with either low-grade or borderline dysplasia.

Statistical Analysis

Data analysis was performed with SPSS v16.0 and Microsoft Excel 2007. Patients who had a definitive diagnosis made by positive cytology for malignancy along with typical imaging characteristics for a cystic neoplasm were considered part of the surgery group for analysis. Calculations of sensitivity and specificity were based on patients who had a definitive diagnosis. The Mann–Whitney *U* test was used to determine if there was a statistically significant difference between cyst fluid CEA values from resected mucinous and non-mucinous cysts, as well as between resected benign and malignant cysts. Change in cyst size was defined as the difference in cyst size between the first and most recent radiographic evaluation. Spearman's correlation coefficient was used to determine if there was a relationship between cyst size, time, and cyst fluid CEA.

Results

A total of 272 patients were identified who had the diagnosis of a pancreatic cyst and underwent an endoscopic

ultrasound and fine-needle aspiration with cyst fluid CEA measurement. Five patients were excluded: One patient had two pancreatic cysts with an EUS-FNA performed on a pancreatic body cyst, but underwent surgery for a pancreatic head adenocarcinoma; one patient had treatment for a pancreatic cyst with ethanol ablation; one patient was found to have a mesenteric cyst instead of a pancreatic cyst at the time of surgical resection; one patient was diagnosed with cholangiocarcinoma and subsequently discontinued further follow-up of the pancreatic cyst; one patient had an FNA with cytology suspicious for adenocarcinoma and subsequently transferred her care to an outside institution. Of the remaining 267 patients, the median age was 66 years (range 21–84 years) and 180 patients (67%) were female. The median duration of follow-up was 14 months (range 0–167 months; Table 1).

A pathologically proven diagnosis was made in 97 patients (median age 65 years, 68% female; Table 1). Operative resection was performed in 95 patients; one patient had an unresectable tail cyst with typical features of an MCN, cytology revealed adenocarcinoma, and imaging revealed metastatic disease; one patient had an unresectable head cyst with typical features of an IPMN, surgical biopsy revealed adenocarcinoma. Surgical pathology and cyst fluid CEA levels are summarized in Table 2.

Non-mucinous cysts were identified in 31 patients (SCA, $n=9$; NET, $n=10$, and other, $n=12$—retention cysts, inclusion cysts, and pseudocysts). Mucinous cysts were present in 66 patients (IPMN, $n=52$ and MCN, $n=14$). The median cyst fluid CEA was 21 ng/mL for non-mucinous cysts (range 0–60,000 ng/mL), and 895 ng/mL (range 0–38,530 ng/mL) for mucinous cysts ($p<0.001$; Fig. 1). Of the 97 cysts with a definitive diagnosis, 85 (88%) were benign and 12 (12%) were malignant (six IPMN with CIS, four IPMN with invasive CA, one MCN with invasive CA, and one MCN with CIS). Preoperative cytology by EUS-FNA was performed in 11 of 12 patients with malignant cysts: two with positive cytology for malignancy, one with cytology suspicious for malignancy, and eight with no evidence of malignancy. The median CEA for benign cysts was 445 ng/mL (range 0–60,000 ng/mL) and 353 ng/mL (range 8–26,351 ng/mL) for malignant cysts (Fig. 2; $p=0.852$). Sensitivity and specificity of multiple cyst fluid CEA thresholds for the diagnosis of mucinous cysts are shown in Table 3, with increasing cyst fluid CEA levels corresponding with decreasing sensitivity and increasing specificity. A cyst fluid CEA threshold of 192 ng/mL had the highest sensitivity and accuracy of all of the thresholds, with a sensitivity of 73%, specificity of 65%, and accuracy of 70%.

Non-operative management was initially performed in 178 patients, and these patients were followed up with serial radiographic imaging (median age 66 years, 68% female, median follow-up 22 months). Eight patients (4%) underwent subsequent surgical resection after a median follow-up of 38 months: Six patients had cysts which increased in size on follow-up; one patient had a cyst which developed a thickened wall on follow-up; one patient underwent EUS-FNA which revealed suspicious cytology. Pathology from these surgical resections showed benign IPMN in six patients, benign MCN in one patient, and a retention cyst in one patient. Among the remaining 170 patients who did not undergo surgical resection, no patient developed clinical or radiographic evidence of malignancy. The median cyst fluid CEA in these patients was 48 ng/mL (range 0–164,407 ng/mL).

To evaluate the natural history of pancreatic cysts, Fig. 3a shows a plot of change in cyst size over time for all cysts ($r=0.12$); 62% ($n=166$) demonstrated minimal size change, remaining within 5 mm of their original size; 13% ($n=36$) decreased in size by more than 5 mm; and 24% ($n=65$) increased in size by more than 5 mm over time.

Limiting the analysis to suspected mucinous cysts (CEA> 192 ng/mL; $n=50$), a plot of change in cyst size vs. time is shown in Fig. 3b, including only patients with more than 1 year of follow-up ($r=0.09$; median CEA 989 ng/mL, median size 1.8 cm, median follow-up 36 months). Despite the elevated cyst fluid CEA, 76% of these cysts remained stable or decreased in size over time, with 12 cysts (24%) increasing by more than 5 mm, and only six cysts (12%) increasing by more than 1 cm during follow-up. In order to evaluate the association between cyst fluid CEA and cyst growth, a plot of change in cyst size vs. cyst fluid CEA for all cysts with greater than 1 year follow-up ($n=161$) is shown in Fig. 4; there is no correlation between cyst fluid CEA and cyst growth ($r=-0.07$).

Table 1 Demographic Information and Cyst Characteristics

	Unresected ($n=170$)	Resected ($n=97$)	All patients ($n=267$)
Female	114 (67%)	66 (68%)	180 (67%)
Age at 1st scan (median, years)	66 (21–84)	65 (24–86)	66 (21–86)
Initial cyst size (median, cm)	1.9 (0.4–10.8)	2.9 (0.7–9.0)	2.1 (0.4–10.8)
Final cyst size (median, cm)	1.9 (0.0–11.3)	3.0 (1.0–9.0)	2.2 (0.0–11.3)
Follow-up (median, months)	21 (0.2–167)	5 (0–130)	14 (0–167)
Cyst fluid CEA (median, ng/mL)	48 (0–164,407)	437 (0–60,000)	99 (0–164,407)

Table 2 Pathology and Cyst Fluid CEA for Cysts with a Definitive Pathologic Diagnosis

	n	Cyst fluid CEA (median, range) (ng/mL)
Non-mucinous	31	21 (0–60,000)
SCA	9	2 (0–635)
NET	10	3 (1–354)
Other	12	539 (1–60,000)
Mucinous	66	895 (0–38,530)
IPMN	52	574 (0–38,530)
MCN	14	2,844 (2–14,540)
Benign	85	444 (0–60,000)
Malignant	12	353 (0–26,351)

Discussion

Cyst fluid CEA is currently the diagnostic test of choice for the identification of mucinous cysts of the pancreas. The data supporting the use of cyst fluid CEA for the diagnosis of IPMN are not as robust as for MCN, and one recent study demonstrated cyst fluid CEA to not be useful for the diagnosis of IPMN.[5] Our findings demonstrate that cyst fluid CEA is useful in the diagnosis of all mucinous cysts (including both MCN and IPMN) with a sensitivity of 73% if the cyst fluid CEA is greater than 192 ng/mL, consistent with prior reports.[2] Our study is the largest published series of cyst fluid CEA in resected IPMNs and supports the use of cyst fluid for the diagnosis of all mucinous cysts of the pancreas.

A few reports have suggested that the degree to which cyst fluid CEA is elevated is predictive of the presence of malignancy. Each of these studies have identified a different cyst fluid CEA threshold for predicting the risk of malignancy (range between 200 and 5,000 ng/mL) with varied sensitivity and specificity.[5,6,16,17] Given the low incidence of malignancy (12/97) in the current study, we are unable to fully examine the role of cyst fluid CEA in predicting malignancy. However, given the wide range of cyst fluid CEA in the 12 malignant cysts (Fig. 2; 8–26,351 ng/mL), it is unlikely that cyst fluid CEA will be a definitive factor in distinguishing benign from malignant mucinous cysts.

Current guidelines advocate resection for pancreatic cysts with high-risk radiographic characteristics. However, guidelines for the management of the remaining pancreatic cysts are less definitive, recommending surveillance with serial cross-sectional imaging along with possible endoscopic ultrasound and fine needle aspiration.[13,18] The natural history of these lower-risk pancreatic cysts has yet to be defined, but two recent large, prospective longitudinal series demonstrate that radiographic follow-up is a reasonable approach in selected patients. Rautou et al. followed up 121 patients with suspected branch duct IPMNs (BD-IPMN) for a median of 33 months. Twelve patients (10%) demonstrated changes suggestive of malignancy, and five patients (4%) were found to have malignancy at the time of surgical resection. Four of these five patients developed main pancreatic duct involvement on preoperative imaging, highly suggestive of malignancy.[19] Salvia et al. followed up

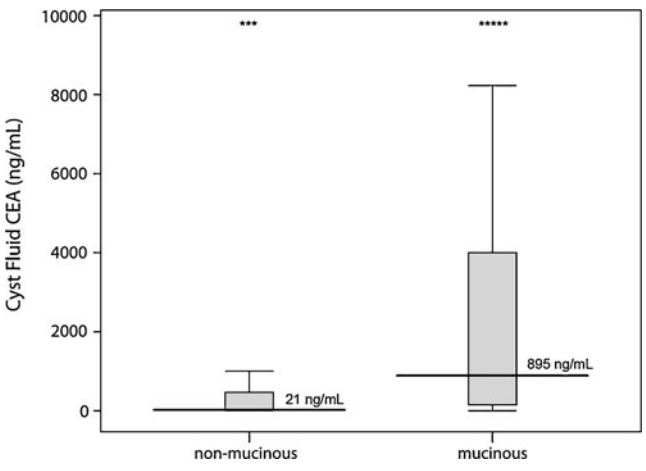

Fig. 1 Box plot of cyst fluid CEA levels for mucinous and non-mucinous cysts. *Asterisks* represent individual patients with cyst fluid CEA levels beyond the scale of this graph.

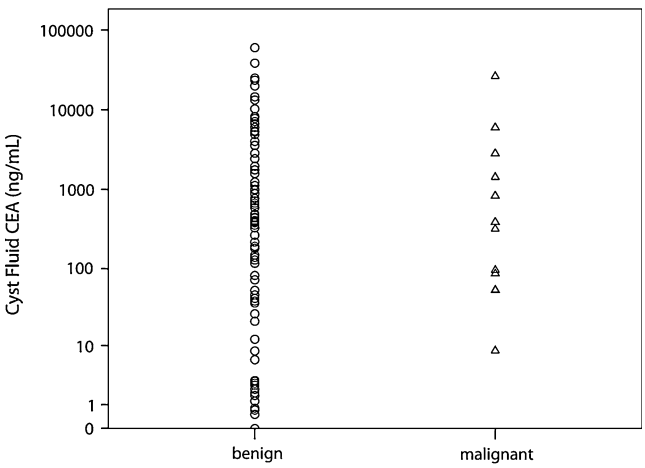

Fig. 2 Scatter plot of cyst fluid CEA levels (logarithmic scale) for benign and malignant cysts.

Table 3 Performance Characteristics of Different CEA Thresholds for the Diagnosis of Mucinous Cysts of the Pancreas

CEA (ng/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
>100	76	55	73	52	69
>192	73	65	76	53	70
>250	71	68	77	53	70
>500	56	77	80	45	63
>1,000	47	87	88	44	60

89 patients with suspected BD-IPMN for a median of 33 months, with five patients (6%) undergoing surgical resection due to increasing cyst size (>3.5 cm). Pathology revealed benign IPMN adenoma in these five patients; no evidence of malignancy was seen in the remaining 84 patients throughout the follow-up period.[20] In both studies, BD-IPMN was diagnosed on the basis of imaging that clearly demonstrated a communication between the cyst and pancreatic ducts. Similar findings were recently illustrated in a long-term retrospective study that demonstrated 89% of suspected MCN and BD-IPMN remained stable in size with a median follow-up of 32 months.[21]

Our study supports the findings of these other long-term longitudinal pancreatic cyst studies. With a median follow-up of 22 months for unresected cysts, we demonstrated that the majority of cysts remained stable in size, remaining within 5 mm of their original size, with a significant percentage of cysts regressing in size as well. None of these patients developed evidence of malignancy on follow-up. Although eight patients developed radiographic changes necessitating surgical resection, pathology revealed benign pancreatic cysts in each patient. The findings from the current study further demonstrate the safety of a non-operative strategy in selected patients, with periodic surveillance with semi-annual or annual cross-sectional imaging.

Given the benign behavior of most BD-IPMNs without initial high-risk characteristics, a diagnostic test that could reliably predict future cyst behavior would allow for an optimized surveillance and management strategy. We examined the role of cyst fluid CEA in predicting cyst growth. Our study demonstrates no clear association between cyst fluid CEA and cyst growth, regardless of the degree of elevation of cyst fluid CEA. Although higher cyst fluid CEA is more specific for mucinous cysts (specificity

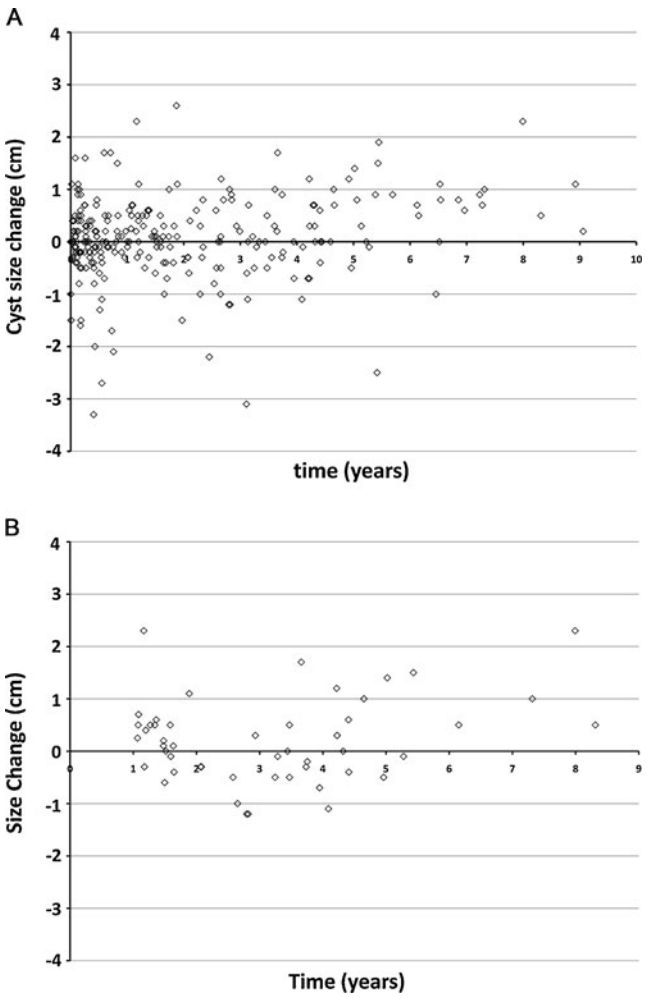

Fig. 3 **a** Scatter plot of change in cyst size vs. time for all cysts (r= 0.12). The majority of cysts remain within 5 mm of their original size. **b** Scatter plot of change in cyst size vs. time for suspected mucinous cysts (cyst fluid CEA>192 ng/mL), with greater than 1 year of follow-up (r=0.09).

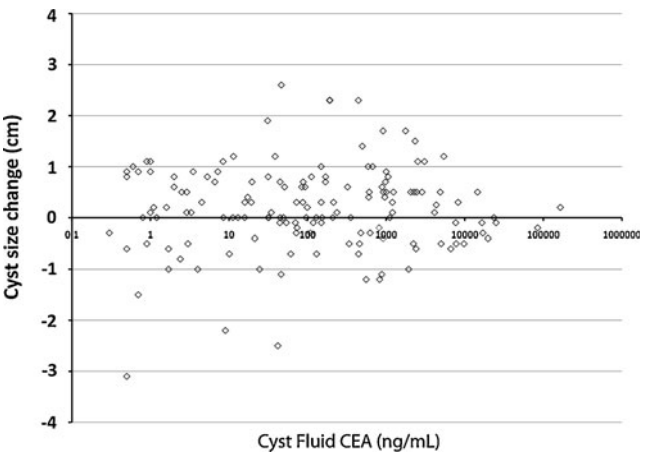

Fig. 4 Scatter plot of change in cyst size vs. cyst fluid CEA (logarithmic scale) for all cysts with greater than 1 year of follow-up (r=−0.07).

of 87% for CEA>1,000 ng/mL), these cysts remained relatively stable in size over longitudinal follow-up.

Accurate identification of cysts with malignancy or cysts with significant malignant potential (high-grade dysplasia) would allow for an optimal management strategy. The lack of association between the degree of cyst fluid CEA elevation and dysplasia or cyst growth limits the value of CEA beyond that of identifying a mucinous lesion. While cyst fluid CEA has some utility in guiding patient management, it is not a marker for identifying cystic lesions that require operative resection. A recent unblinded study examining cyst fluid DNA markers, including k-ras mutations, allelic loss, and DNA quantity, shows some potential diagnostic utility.[22] However, the incremental benefit of this DNA analysis over the current criteria for operative resection is unknown, as this DNA analysis was not compared to current criteria, and no follow-up was provided for unresected cysts with "positive" DNA markers. Preliminary studies on proteomic analysis of cyst fluid shows potential for the accurate identification of malignant mucinous cysts, yet further large-scale studies are needed to evaluate the diagnostic utility.[23,24] Until further studies on molecular and proteomic analyses are performed, the presence of malignancy or high-grade dysplasia within branch duct IPMN must remain one that is suspected radiographically by cyst size and the presence of a solid component.

This study represents an interim report of our pancreatic cyst registry at Memorial Sloan-Kettering Cancer Center. The median duration of follow-up presented in this study is somewhat limited, but our wide range of clinical follow-up provides substantial information. This study was limited to patients who underwent EUS-FNA with cyst fluid CEA determination, and thus, high-risk cysts, such as main duct IPMNs or cysts with solid nodules, are not included in this study, as these often were referred for immediate surgical resection without EUS evaluation. The unique distinction between our study and other longitudinal series is that this series represents an all-inclusive list of all pancreatic cysts that underwent EUS-FNA, not just limited to suspected mucinous neoplasms. Thus, the findings from this study are widely applicable to a broad range of patients who present for clinical evaluation.

Although CEA is not predictive of malignancy or radiographic progression, cyst fluid CEA remains an important tool in the diagnosis of pancreatic cysts without high-risk features. Extreme values of cyst fluid CEA have considerable utility; CEA levels less than 5 ng/mL is diagnostic of a non-mucinous cyst, and CEA levels greater than 1,000 ng/mL are highly specific for a mucinous cyst. These extremes in cyst fluid CEA can aid in the diagnosis of cysts with ambiguous morphology, such as distinguishing a large macrocystic serous cystadenoma from a large multiloculated BD-IPMN or differentiating a simple retention cyst from a small MCN.

In conclusion, the current study confirms previous reports of the accuracy of CEA in identifying IPMN and MCN. Elevated cyst fluid CEA (>192 ng/mL) was found to have a high sensitivity for the diagnosis of mucinous cysts, including both MCN and IPMN. Higher levels of cyst fluid CEA are highly specific for mucinous neoplasms, but not predictive of malignancy. Radiographic follow-up of selected patients who do not meet criteria for immediate resection every 6 months to 1 year is a safe management strategy; these cysts did not develop any evidence of malignancy and were often stable in size or regressed over time. Cyst fluid CEA is not useful for the risk stratification of pancreatic cysts and is not predictive of future radiographic progression. Beyond its role in the identification of mucinous cysts, cyst fluid CEA levels do not have any additional prognostic value and generally should not be used to guide future therapeutic strategies.

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HOW I DO IT

Alternative Port Site Selection (APSS) for Improved Cosmesis in Laparoscopic Surgery

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Abstract The use of laparoscopy can be associated with improved cosmesis following a variety of gastrointestinal procedures versus standard open surgery. The placement of laparoscopic ports in less visible areas of the body such as the bikini line, termed alternative port site selection (APSS), may result in further improved cosmesis. Performance of laparoscopic procedures from such alternative port placement areas may be associated with increased technical challenge. This manuscript discusses APSS approaches for two common laparoscopic procedures, cholecystectomy and gastric banding. Familiarity and implementation of these techniques can allow select patients to undergo procedures with less visible scarring and is less challenging than laparoscopic single site approaches.

Keywords Laparoendoscopic single site surgery · Laparoscopic cholecystectomy · Laparoscopic adjustable gastric banding · Laparoscopy · Cosmesis

Introduction

Conventional laparoscopic port placement leaves scars that are visible in the mid-abdomen. Herein, we report alternative port site selection we utilize for laparoscopic cholecystectomy and gastric banding procedures to improve cosmesis for patients. We believe that the port site selection preserves the technical ease with standard laparoscopic instrumentation and remains easier to perform than those that utilize laparoendoscopic single site surgery (LESS).[1,2]

Technique

Laparoscopic Cholecystectomy

The standard four-trocar sites, two 12-mm trocars and two 5-mm trocars (Fig. 1a), are modified to three trocars including one 12-mm trocar at the umbilicus and two 5-mm trocars. A number of centers routinely perform laparoscopic cholecystectomy (LC) utilizing three-trocar sites.[3,4] As proficiency improved with three trocars, we have adjusted their placement for better cosmesis in patients that had no previous scars on the abdomen. Initially, the right-sided site was moved much more laterally to hide it in the patient's flank. The next step was to move the 12-mm trocar away from the umbilicus, down to the suprapubic area below the pubic hairline. This allowed us to move the 5-mm subzyphoid trocar to the umbilicus (Fig. 1b). More recently, we have further modified the procedure by also dropping the right flank 5-mm trocar below the pubic hairline, thus leaving the patient no visible scars once the procedure is completed (Fig. 1c, d). Of note is that the second modification increases the technical challenge of laparoscopic cholecystectomy, and surgeons considering trying such an approach are encouraged to first try the port placement detailed in Fig. 1b.

The laparoscopic cholecystectomy procedure was carried out in a normal fashion using the left-hand instrument as a grasper and retractor and the right-hand instrument for the dissection. We generally have performed this procedure utilizing a 30° laparoscope, but have also successfully completed it using a 0° scope. Grasping the gallbladder in different points can significantly improve visualization of the triangle of Calot. Much of the early dissection is done from the lateral side of the duct (as opposed to medially as in a standard LC). The lateral

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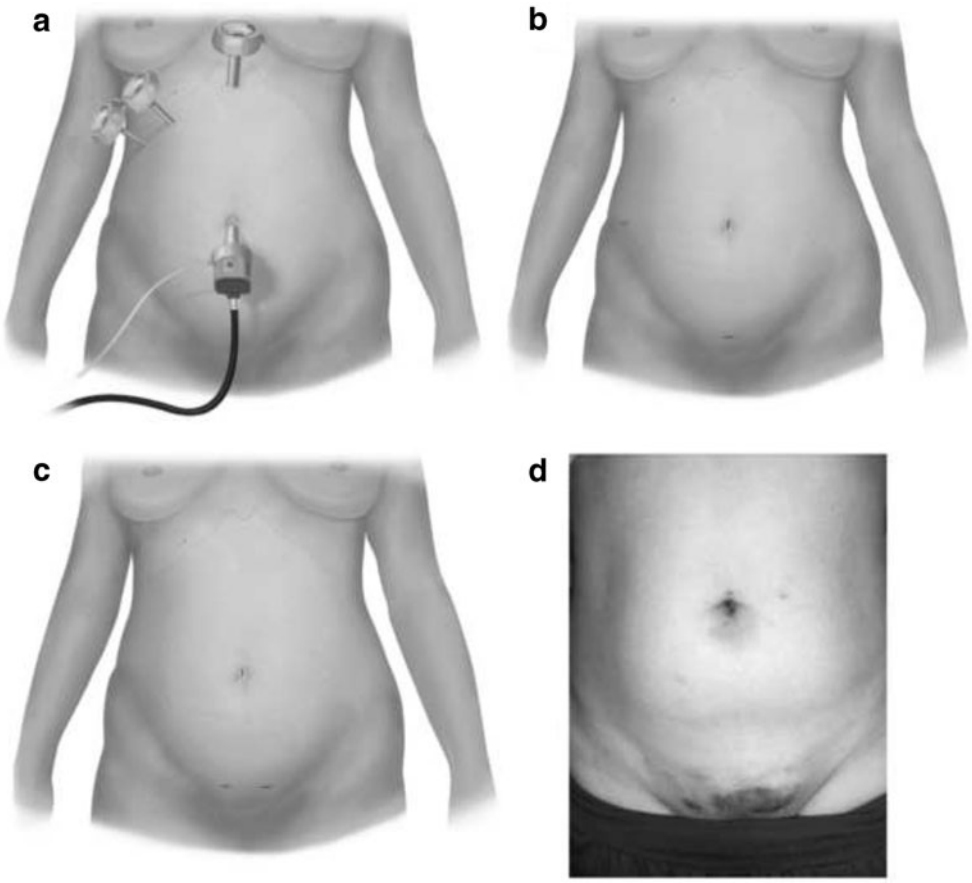

Fig. 1 Port placement of the 5-mm subzyphoid trocar to the umbilicus and below the pubic hairline.

visualization is easier when using only one retracting instrument. Once some dissection has been accomplished, it becomes easier to move medially into the triangle. The 5-mm clip applier is used through the right-hand trocar site at the umbilicus. There are some other minor adjustments the operative surgeon should make in performing this alternative approach for laparoscopic cholecystectomy. It must be noted that placing the camera in the suprapubic position changes the angle of visualization. It is important to gain the critical view of the ducts prior to transection. This was routinely accomplished by grasping the infundibulum of the gallbladder with the left-hand instrument and pulling laterally while grabbing the fundus with the right-hand instrument and pulling cephalad and medially. With this exposure, the triangle of Calot can be very clearly visualized. Having the camera in such a low position causes a slight rotation of the contents within the triangle of Calot. The cystic artery moves from its normal position and will appear behind the cystic duct rather than slightly superior to the duct when the camera is placed in the umbilicus. Thus, the area has to be approached carefully as indiscriminant use of the scissors while clipping the cystic duct can cause bleeding from the cystic artery if that relationship is not recognized.

All patients who underwent laparoscopic cholecystectomy with the suprapubic ports had Foley catheters placed after induction of anesthesia as the port sites were very low in the anterior abdominal wall. The fascia at the 12-mm trocar site was closed using 0 Vicryl, a figure eight suture on the anterior rectus sheath. There have been no hernias in any of the patients. Their most common complaint was of tenderness at the suture site within the fascia.

Laparoscopic Adjustable Gastric Banding

Laparoscopic adjustable gastric banding is routinely performed with five port sites using one large incision (approximately 2 in.), which allows for the insertion of the band and placement of the port, and four smaller 5- or 12-mm trocars. Our standard port sites for laparoscopic adjustable gastric banding include a 15-mm trocar and four other 5-mm incisions placed across the upper abdomen (Fig. 2a). For cosmesis, the port sites for laparoscopic adjustable gastric banding have been adjusted in patients whose anatomy allows it (no previous scars, lower BMI, less central obesity, and smaller gastric fat pads). We enter the abdomen through a 5-mm optical trocar through the umbilicus. Two 5-mm trocars are then placed in the far right and left flanks. A 15-mm trocar is placed below, and just medial to, the left anterior superior iliac spine, which should be covered by most pants (Fig. 2b). This allows inserting the port and the band without any visible scars within the anterior upper abdominal wall, which is the most visible aspect of the

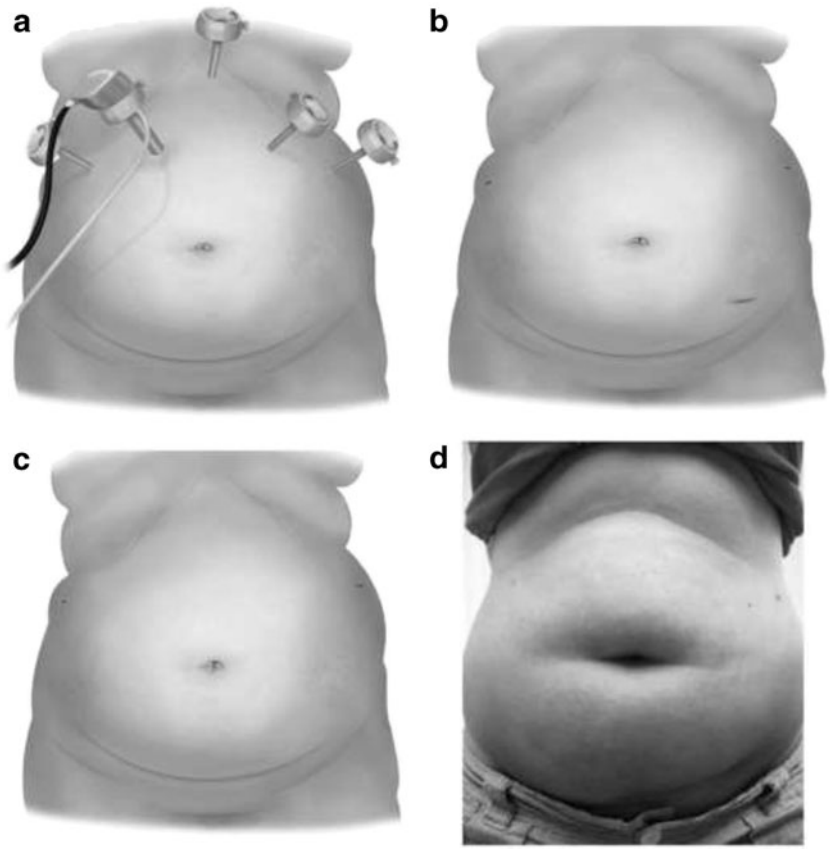

Fig. 2 Standard port sites for a 15-mm trocar and four other 5-mm incisions placed across the upper abdomen.

abdomen. We have also performed a variant of the above positioning by placing the 15-mm trocar (and the band's port) through the umbilicus (Fig. 2c, d).

All patients who underwent laparoscopic adjustable gastric band with the low trocar sites voided just prior to entering the operating room. The 15-mm skin site was below the anterior superior iliac spine, but the trocar was tunneled under the subcutaneous tissues to enter the fascia higher within the abdominal wall. The 15-mm trocar site was the site where the band tubing was brought out, and this fascial defect was tightened with a 0 Vicryl suture to decrease a ventral hernia at this site in the future.

Results

Laparoscopic Cholecystectomy

The laparoscopic cholecystectomy described above in its final variation (Fig. 3) has been performed in 23 patients. These procedures have taken an average of about 35 min (as compared to 20–25 min for standard laparoscopic cholecystectomies and nearly an hour in our LESS procedures). All the patients were discharged after a 23-h observation. There were no conversions to open surgery. Indications for laparoscopic cholecystectomy in this group of 23 patients included 13 patients with acute cholecystitis. These patients were chosen by the following criteria: they were all female with a BMI <30 with no previous abdominal incisions, except for laparoscopic bilateral tubal ligations (three patients).

Laparoscopic Adjustable Gastric Banding

There have been eight patients who have had their laparoscopic adjustable gastric banding done with the alternative port site selection (APSS) approach. The left lower quadrant 15-mm trocar allows us to use a 10-mm, 30° scope which gives us adequate visualization of the surgical field. The surgeon is able to triangulate his instruments well using both the left flank and right flank instruments, and we have used the umbilical port as a retractor port either pulling the stomach inferiorly or lifting the liver cephalad, depending on the situation. The procedure steps themselves were standard. The procedures took an average of 38 min (as compared to 30 min for standard laparoscopic adjustable gastric banding), and all patients have been treated as outpatients, with no complications postoperatively from either group. The patients have been pleased with the outcomes as well as with the cosmesis and are losing weight at the same rate as our standard banding patients. For band adjustments, we have found it easier for the patients to lift their legs off the examination table to tighten their lower abdominals for better access to the port. This seems to work

better than the abdominal crunch that is normally used for an upper abdominal port site. The patients have not complained of any discomfort in this lower abdominal port site either at rest or with exercise. It seems better hidden in these patients as there is slightly more abdominal fat in the lower abdomen. We have performed one laparoscopic adjustable gastric banding with the 15-mm trocar in the umbilicus.[8] We inserted a grasper through the same incision to use as a retractor. The intra-abdominal portion of the procedures took approximately 25 min, and placing the port took us another 15–25 min.

Discussion

APSS as described allows the use of instrumentation that is readily available and allows for less visible scars than are encountered following standard laparoscopy.[5–7] It follows the basic laparoscopic principle of triangulation of the instruments to give the best ease of use and is likely considerably easier to apply than LESS approaches. Using LESS, the angles of the working ports are narrowed; it becomes more difficult to adequately expose tissues and perform the necessary moves for dissecting, suturing, and knot tying.[1,8–10] Even with the articulating instrumentation available today, there is a significant increase in the difficulty in performing tasks, and, at least in our hands, we find that such procedures take a much longer time.[11]

There also may be a potentially lower hernia rate with APSS versus LESS. LESS combines several fascial defects within one small area, which could potentially weaken that area by decreasing the vascular supply and predispose it to ventral hernias. Also, increased manipulation of the trocars, increased torque on the fascia, and increased surgical time have been shown to increase the occurrence of incisional hernias.[12,13] The LESS technique increases all of those risk factors. Individual non-bladed trocar sites have a very low incidence of herniation (0.14% for 12-mm trocars and <0.05% for 5-mm trocars). Making a larger fascial incision will increase the rate to incisional herniation.[12] The hernia rate for an open Hassan approach to the midline fascia (even smaller than would be performed in a LESS procedure) has been reported at 3%.[14]

The APSS laparoscopic adjustable gastric band provides a significant cosmetic improvement over a LESS laparoscopic adjustable gastric band (when not performed from the umbilicus) as there is not a large scar in the upper abdomen. Given the choice, after both approaches were discussed, all the patients preferred to have their large trocar incision in the lower abdomen and all felt that the 5-mm trocar sites in the flanks were much more acceptable than a much larger incision in the upper middle abdomen.

The operative time for the APSS procedures was approximately 10 min longer than following standard port placement approaches. We believe that this minimal increase in time supports that the laparoscopic technical skill required to perform an APSS procedure was not significantly more than that used for patients undergoing standard laparoscopic port placement.

We believe that APSS for cosmesis is a technique that can be easily utilized by all surgeons currently performing laparoscopy without the need to purchase additional laparoscopic instruments or a substantial learning curve. In our practice, decreasing the appearance of incisions by placing them farther into the flanks, within the umbilicus, and suprapubically seems very well accepted by patients. We submit that the upper, mid-abdomen is the most visible area in most patients' minds, and avoiding scars in this area is preferable. We believe that the addition of the technique modifications described will be useful for surgeons who perform either laparoscopic cholecystectomy or laparoscopic adjustable gastric banding procedures.

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REVIEW ARTICLE

Epiphrenic Diverticulum of the Esophagus. From Pathophysiology to Treatment

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Abstract
Introduction Epiphrenic diverticula of the esophagus are usually associated with a concomitant esophageal motility disorder. The main symptoms experienced by patients are dysphagia, regurgitation, and aspiration. The best surgical treatment is still debated, particularly the need for a myotomy in addition to resection of the diverticulum.
Discussion While for many decades the traditional approach was through a left thoracotomy, more recently, minimally invasive techniques have been successfully used and are now the procedure of choice in most cases. The purpose of this article was to review (a) the current understanding of the pathophysiology of epiphrenic diverticulum, (b) how this understanding should guide the surgical treatment, and (c) the surgical approach.

Keywords Epiphrenic diverticulum · Esophageal diverticula · Primary esophageal motility disorders · Esophageal achalasia · Dysphagia

Epiphrenic diverticulum is a pulsion diverticulum, usually located in the distal 10 cm of the esophagus. It is due to the herniation of mucosa and submucosa through the muscle layers of the esophageal wall. Historically, the first description in which pulsion forces were implicated as possible causes for the diverticulum formation was done by Mondiere in 1833.[1] The first excision of an epiphrenic diverticulum is attributed to Roux, who used a trans-abdominal approach.[2] The first transthoracic resection was performed by Stierling in 1916 and resulted in patient's death secondary to a leak and mediastinitis.[2] Resection of the diverticulum with primary closure of the esophageal wall and coverage by a pleural flap was commonly performed in the first half of the twentieth century.[3,4]

More than 40 years ago, Effler et al.[5] and Belsey[6] suggested that an esophageal diverticulum was not a primary problem but that it was rather secondary to an underlying esophageal motility disorder. Therefore, they emphasized the need to address the underlying esophageal motility disorder by performing a myotomy in addition to resecting the diverticulum. This brilliant intuition was confirmed in the following decades, and it still constitutes the basis for the modern treatment of epiphrenic diverticulum.

Pathophysiology of Epiphrenic Diverticulum: Implications for Treatment

While most authors feel that a primary esophageal motility disorder (PEMD) underlies the development of the diverticulum in almost all patients,[7,8] others believe that this relationship is not as frequent.[9,10] The implications are very important for the answer governs the decision as to whether a myotomy should be performed as a routine part of the operation.

Recent studies of patients with epiphrenic diverticulum have shown the presence of a PEMD in 75% to 100% of

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patients (Table 1).[7,8,11–15] Achalasia and diffuse esophageal spasm are the disorders most commonly documented by manometry and barium swallow, but nutcracker esophagus and a hypertensive lower esophageal sphincter (LES) are also found to be associated with these diverticula. A possible explanation for the finding of normal esophageal motility by manometry may be due to the intermittent nature of diffuse esophageal spasm. During a conventional esophageal manometry, LES function and esophageal peristalsis are usually assessed by observing ten wet swallows of 5 ml of water at 30 s intervals.[16] Therefore, it is possible that, during the 300 s of the test, spastic activity is not present. The hypothesis that PEMD is present in virtually all the patients with an epiphrenic diverticulum was tested by Nehra and colleagues by using ambulatory manometry in addition to stationary manometry.[7] Ambulatory manometry allows recording of about 1,000 swallows over a 24-h period, recording motility as stimulated by both liquid and solid food. Among 21 patients tested with stationary manometry, a PEMD was documented in 15 (71%). When tested by ambulatory manometry, the remaining six patients were also found to have a PEMD, which was identified as DES in 5. These findings corroborate the rationale for performing a myotomy in all patients with an epiphrenic diverticulum, regardless of the findings of conventional stationary manometry.

Table 1 Esophageal Manometry in Patients with Epiphrenic Diverticulum

Author	# of patients	PEMD	Diagnosis
Nehra et al.[7]	21	21 (100%)	Achalasia—9 DES—5 Hypertensive LES—3 NE—2 NSMD—2
Melman et al.[8]	13	11 (85%)	NSMD—5 Achalasia—4 DES—2
Del Genio et al.[11]	13	13 (100%)	Achalasia—6 Hypertensive LES—3 NSMD—3 NE—1
Tedesco et al.[12]	21	17 (81%)	NSMD—5 Achalasia—2 DES—5 NE—5
Fernando et al.[13]	20	15 (75%)	NSMD—7 Achalasia—8
Varghese et al.[14]	20	17 (85%)	NSMD—1 Achalasia—5 DES—5 NE—6
D'Journo et al.[15]	23	20 (87%)	DES—9 LES disorders—7 NE—1 Achalasia—3

PEMD prevalence of a primary esophageal motility disorder, *NSMD* nonspecific esophageal dysmotility, *DES* diffuse esophageal spasm, *NE* nutcracker esophagus

Clinical Presentation and Preoperative Evaluation

Symptomatic Evaluation

The most common symptoms in patients presenting with an epiphrenic diverticulum are dysphagia and regurgitation of undigested food.[12] Chest pain and weight loss are also common. As pointed out by Belsey and others, these symptoms are usually caused by the underlying esophageal dysmotility more than the diverticulum per se.[6,7,14] Indeed, the size of the diverticulum correlates poorly with the severity of the symptoms.[9] Respiratory complains, such as nocturnal cough, asthma, laryngitis, and pneumonia, may be due to episodes of aspiration and can be the presenting symptoms in some patients.[12,17] Heartburn, when present, is usually due to stasis and fermentation of the food as in patients with esophageal achalasia rather than real gastroesophageal reflux.[18] Malignant transformation of an epiphrenic diverticulum and other complications such as bleeding and perforation are exceedingly rare.[19–21]

Barium Swallow

The barium swallow is probably the most important test not only in the evaluation of the symptoms but also in the planning of the operation. This test defines the size of the diverticulum and of its neck, the location, and the distance from the gastroesophageal junction. The size of an epiphrenic diverticulum ranges from 1 to 14 cm, with a median size of about 4–7 cm.[12,14,22] In approximately 70% of patients, the diverticulum is on the right side of the esophageal wall[12,22] (Fig. 1). While the majority of patients have a single epiphrenic diverticulum, about 15% of patients may have two or more diverticula.[7,22] The distance of the diverticulum from the diaphragm is variable, but by definition, the epiphrenic diverticulum is located in the distal 10 cm of the esophagus. Diverticula located more than 10 cm above the diaphragm (mid-esophageal diverticula) are rare (Fig. 2). In some patients in whom the manometry is normal, an underlying

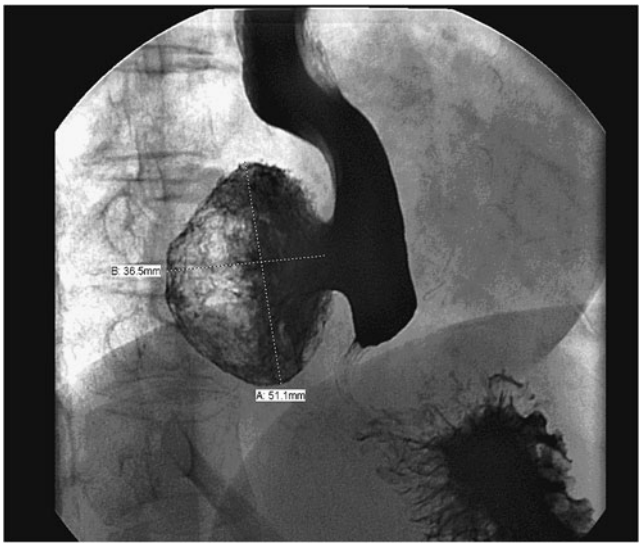

Figure 1 Epiphrenic diverticulum protruding from the right wall of the esophagus.

motility disorder can become apparent during fluoroscopy (Fig. 3).

Endoscopy

Because most of these patients are old and dysphagia is a frequent complain, endoscopy is necessary to rule out a neoplastic process of the distal esophagus. In addition, endoscopy allows proper placement of the catheter if esophageal manometry is to be performed.

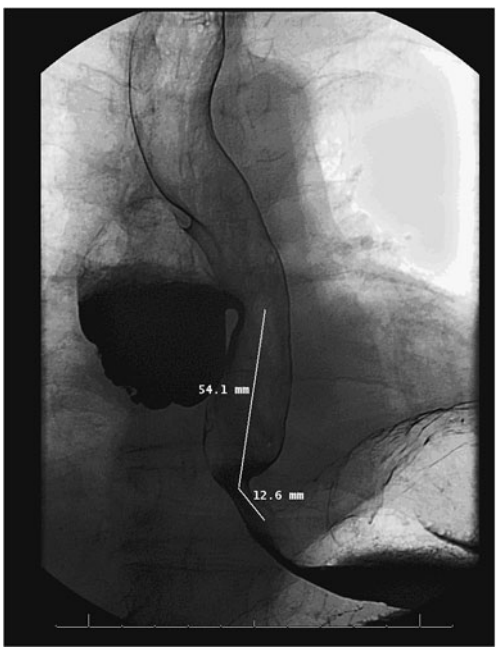

Figure 2 Large midesophageal diverticulum, about 13 cm above the gastroesophageal junction.

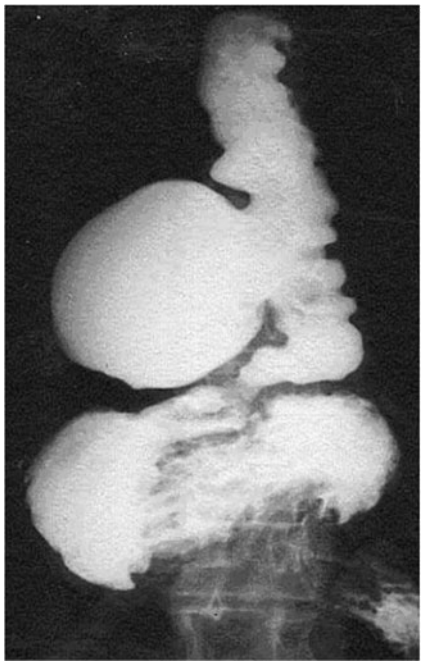

Figure 3 Barium swallow showing an epiphrenic diverticulum and diffuse esophageal spasm in a patient with normal esophageal manometry.

Esophageal Manometry

In order to avoid curling of the manometry catheter inside the esophageal lumen or in the diverticulum, endoscopy or fluoroscopy can be used.[12] However, in view of the data presented in the pathophysiology section, it can be argued that this test is often of academic interest but does not affect management.

Indications for Surgery

While there is a consensus on the need for surgical treatment for patients with severe symptoms, the indications for surgery in patients with mild or absent symptoms are still controversial. The percentage of symptomatic patients is variable and ranges from 37%[9] to 63%,[22] as in the remaining cases the diverticulum is mostly an incidental finding on a chest X-ray.

However, before classifying as asymptomatic patients in whom the diverticulum was incidentally discovered, it is very important not only to evaluate for esophageal symptoms such as dysphagia but also to determine whether respiratory symptoms suggestive of aspiration are present. In a patient with regurgitation, night cough, asthma-like symptoms, laryngitis, or pneumonia, aspiration should be assumed to occur and surgical treatment is indicated to avoid potentially fatal complications. For instance, Debas and others[23] reported that among 29 symptomatic patients with epiphrenic diverticulum who were not treated, four suffered aspiration and two subsequently died from pulmonary complications.[23]

Other authors advise operative intervention even in the absence of symptoms, to protect patients from the risk of aspiration.[17] Overall, it is our policy to operate only on symptomatic patients for two reasons: (1) fewer than 10% of asymptomatic patients eventually develop symptoms due to the diverticulum[24] and (2) even in experts hands the operation carries a significant morbidity and mortality.[13,14]

Technical Steps

Dissection This step is relatively simple when a left transthoracic approach is chosen. The diverticulum is easily identified and its neck isolated. However, dissection with identification of the upper border of the diverticulum and of its neck is probably the most challenging aspect of the laparoscopic approach. It is useful to pass a Penrose drain around the gastroesophageal junction early in the course of the operation as it allows traction and facilitates the dissection in the posterior mediastinum.

It is important to dissect the neck of the diverticulum free of the surrounding tissue and to clearly identify the muscle layers before the stapler is applied. Usually the esophageal hiatus is quite wide at the end of the dissection so that the crura should be approximated before the fundoplication is performed.

Table 2 Open Approach for Epiphrenic Diverticulum

Series	Number of cases	Technique used	Morbidity rate (%)	Mortality rate (%)	Excellent/good results (%) follow-up
Streitz et al.[10]	16	Left thoracotomy—15 Right thoracotomy—1 Diverticulectomy alone—3 Diverticulectomy, long myotomy—3 Myotomy LES alone—10	Leak—6% Overall—37.5%	0%	87% (f/u—7 years)
Fékéte et al.[31]	27	Diverticulectomy alone—10 (5—rigth thoracotomy; 5—left thoracotomy) Resection, myotomy, fundoplication (left thoracotomy)—10 Other—3	Leak—15% Reflux esophagitis—15% Reoperation—22%	11%	72% (f/u: NA)
Altorki et al.[17]	17	Left thoracotomy for all the patients Myotomy, diverticulectomy, Belsey—13 Myotomy, diverticulopexy, Belsey—1 Myotomy, Belsey—2 Myotomy, Nissen—1	Leak—0%	5.9%	93% (f/u—7 years)
Benacci et al.[9]	33	Left thoracotomy—32 Right thoracotomy—1 Myotomy, diverticulectomy—22 Diverticulectomy alone—7 Myotomy alone—1 Esophagectomy—3	Overall 33% Leak—21%	9%	75.8 (f/u—6.9 years)
Nehra et al.[7]	17	Left thoracotomy for all the patients Diverticulectomy, myotomy, fundoplication—13 Diverticulopexy, myotomy, fundoplication—4	Leak—6% Reoperation—11%	6%	82% (f/u 2 years)
Varghese et al.[14]	35	Left thoracotomy for all the patients Diverticulectomy, myotomy, fundoplication—33 (Belsey—29, loose Nissen—4) Diverticulopexy, myotomy, fundoplication—1 Diverticulectomy, myotomy—1	Leak—5.6%	2.8%	76% (f/u—33 months)
D'Journo et al.[15]	23	Left thoracotomy for all the patients Long myotomy for all the patients Diverticulectomy—13 Diverticulopexy—2 No resection, no suspension—8	Leak—0 Overall—8.7%	0%	Symptoms decreased at a f/u of 61 months

Type of operation, morbidity rate, mortality rate, and symptomatic outcome

Transection of the Diverticulum After the entire diverticulum is freed from surrounding structures and the neck is clearly identified, a 50- to 56-F bougie is placed inside the esophagus to avoid narrowing of the lumen when the stapler is applied. Reticulating staplers should be used with the transabdominal approach to facilitate optimal positioning across the neck of the diverticulum, and the staple height should be appropriate for the thickness of the tissue at the transection site. The coaxial orientation of the stapler in relation to the esophagus during laparoscopy significantly aids in the proper orientation of the stapler as compared to the more perpendicular orientation required with the thoracoscopic approach.[12] When the transection is done through the chest, a TA-style stapler rather than an endo-GIA is used. After careful inspection for hemostasis and staple formation, the muscle layers should be approximated over the staple line with interrupted stitches.[25]

Myotomy Because it is thought that the epiphrenic diverticulum is secondary to a functional obstruction of the distal esophagus, a myotomy should be routinely performed. The myotomy should start at the level of the neck of the diverticulum and extend onto the gastric wall as in a Heller myotomy for achalasia.[26,27] The myotomy should be done 180° opposite the diverticulum to avoid interference with the resection and with the muscle closure at that site. This can be easily done either laparoscopically or through a left chest approach.

Fundoplication There are no data in the literature comparing the incidence of reflux with and without fundoplication after myotomy in patients with epiphrenic diverticulum. However, many studies have shown that, when a fundoplication is not performed after a myotomy for achalasia, gastroesophageal reflux occurs in 50% to 60% of patients.[28–30] On the other hand, the incidence of postoperative reflux is significantly reduced when a fundoplication is added.[28–30] Because of the abnormal peristalsis, a partial rather than a total fundoplication (Dor, Toupet, Belsey Mark IV) should be chosen, as a total fundoplication may cause too much resistance at the level of the gastroesophageal junction causing staple line disruption and dysphagia.[11]

Transthoracic Approach

The transthoracic approach through a left thoracotomy remains the standard of care for most patients and surgeons.[7,9,14,15] This approach provides the best access to the distal esophagus and the diverticulum. It allows excellent exposure for the dissection, for the resection of the diverticulum with oversewing of the staple line, for a myotomy, and for either a Belsey or a Dor fundoplication (Table 2).[7,9,10,14,17,31] Even in the hands of expert thoracic surgeons, this approach is associated to a high morbidity rate with leaks present in up to 21% of patients and a mortality rate between 0% and 11%.[9,10,14,17] Varghese and others reported the results in 35 patients operated between 1976 and 2005.[14] Relief of symptoms was obtained in 74% of patients while 21% required periodic esophageal dilatations for treatment of dysphagia. There were two leaks (6%) and one patient died (3%). The authors stated that "these data should serve as a benchmark against which newer surgical techniques can be measured".[14]

Table 3 Laparoscopic Approach for Epiphrenic Diverticulum

Series	Number of cases	Technique used	Morbidity rate (%)	Mortality rate (%)	Excellent/good results (%) follow-up
Rosati et al.[31]	11	Laparoscopic diverticulectomy, myotomy, partial fundoplication	Leak—9%	0%	100% (f/u—36 months)
Klaus et al.[33]	11	Laparoscopic diverticulectomy, myotomy, partial fundoplication	Leak—9%	0%	100% (f/u—26 months)
Del Genio et al.[14]	13	Laparoscopic diverticulectomy, myotomy, Nissen–Rosetti fundoplication	Leak—23%	7%	100% (f/u—58 months)
Fernando et al.[13]	20	Diverticulectomy, myotomy, partial fundoplication—12 Diverticulectomy, myotomy—4 Diverticulectomy alone—2 Other—2	Overall—45% Leak—20%	5%	83% (f/u—15 months)
Tedesco et al.[12]	7	Laparoscopic diverticulectomy, myotomy and Dor fundoplication	Leak—14.3%	0%	100% (f/u—6 months)
Melman et al.[8]	13	Laparoscopic diverticulectomy, myotomy and Dor fundoplication	Overall—15.4% Leak—7.7%	0%	85% (f/u—13 months)

Type of operation, morbidity rate, mortality rate, and symptomatic outcome

From the Transthoracic to the Laparoscopic Approach

In 1998, Rosati et al. first reported the results of a diverticulectomy, myotomy, and Dor fundoplication through a laparoscopic approach in four patients with epiphrenic diverticulum.[25] There were no intra- or postoperative complications, and all patients had good symptomatic relief. A few years later, the same authors confirmed the good outcome in seven additional patients, although a thoracotomy was required to treat an esophageal leak in one patient.[32] Subsequently, many studies have shown excellent results with this approach[8,12,33] (Table 3).[8,12–14,31,33] For instance in 2009, Melman et al.[8] reported good results in 13 patients, using the technique described by Rosati et al.[25] A leak occurred in one patient and required a thoracotomy for repair. At a mean follow-up of 14 months, 85% of patients were asymptomatic and two had mild dysphagia.

As compared to the transthoracic approach, the laparoscopic approach has some technical disadvantages. The dissection of the upper part of the diverticular neck is more complex and a pleural tear may occur. For this reason, diverticula that are 8 to 10 cm above the gastroesophageal junction are perhaps best approached transthoracically or left in situ after the myotomy.[34] Finally, it is more difficult to approximate the muscle layers laparoscopically when the diverticular neck is high in the mediastinum.

Despite these shortcomings, the laparoscopic approach has some advantages, including superior orientation of the stapler to resect the diverticulum, easy approximation of the crura, and better exposure of the gastroesophageal junction for performing both the myotomy and the fundoplication. A partial rather than a total fundoplication should be performed to avoid the creation of a high pressure zone with the risk of dysphagia and leaks of the staple line. This was the case in the report of Del Genio et al. in which the performance of a Nissen fundoplication was followed by a leak rate of 23%.[11] Finally, as shown for patients with achalasia, the operation is associated to less postoperative pain, a shorter hospital stay, and faster recovery as compared to the transthoracic approach.[28]

Conclusions

An operation should be offered only to symptomatic patients with epiphrenic diverticulum. The laparoscopic approach to epiphrenic diverticula, although technically challenging, should be considered today as the surgical treatment of choice for most patients. The transthoracic approach should be used for patients who have giant or very high diverticula, or when the technical expertise with minimally invasive techniques is not available.

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GI IMAGE

An Unusual Cause of an Acute Abdomen—a Giant Colonic Diverticulum

David Beddy · Catherine DeBlacam · Brian Mehigan

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Abstract A giant colonic diverticulum (GCD) is a rare presentation of diverticular disease of the colon that usually necessitates surgery. The case described is of a GCD that became symptomatic due to rapid enlargement caused by an intracolonic bleed. GCD usually presents with abdominal pain and a palpable periumbilical or pelvic mass. Radiological imaging shows a large gas-filled cyst associated with the colon. Surgical resection with sigmoid colectomy is usually performed to alleviate symptoms and prevent later perforation.

Keywords Giant · Sigmoid · Colonic · Diverticulum

Case Report

A 75-year-old man was admitted to the surgical department in a stable condition with a 1-day history of bright red bleeding per rectum. The abdomen was soft and non-tender on examination. Blood tests revealed the haemoglobin of 7.4 g/dL. Within 24 h of admission, the patient became acutely unwell with abdominal pain, distension and confusion. On physical examination, he was hypotensive with tenderness and a large mass palpable in the left iliac fossa. A plain X-ray of the abdomen showed a large lucency in the mid-abdomen with distension of the surrounding colon (Fig. 1). A spiral computed tomography (CT) scan confirmed a 17-cm cystic lesion containing air and gas that was in continuity with the sigmoid colon (Fig. 1). An emergency laparotomy was performed where a large anti-mesenteric cyst was found in continuity with the sigmoid colon. The colon and anti-mesenteric cyst contained fresh blood. A Hartmann's procedure was performed with resection of the sigmoid colon and contiguous cyst and formation of end colostomy in the left iliac fossa. The patient spent 24 h in the intensive care unit post-operatively because of hypotension and then made an uneventful recovery being discharged at 2 weeks after admission. Pathology of the sigmoid colon showed several small diverticula and one extremely large diverticulum that was inflamed and diffusely ulcerated (Fig. 2). The wall of the giant diverticulum consisted of inflamed granulation tissue with fibrosis.

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Discussion

Giant colonic diverticulum (GCD) is a rare entity first described in the French literature in 1946 and classified as a diverticulum greater than 4 cm in size.[1] Diverticula up to 40 cm in diameter have been reported.[2] More than 90% are anti-mesenteric, arise from the sigmoid colon and occur in isolation.[3] GCDs can be pseudodivertuculae—consisting of only fibrous tissue and inflammatory cells—or true diverticula, which contain all bowel wall layers. Several theories have been proposed for their aetiology. The most accepted of these is the ball–valve mechanism, whereby a small communication between the bowel lumen and the herniated diverticulum allows air to enter but not exit, thus permitting progressive enlargement. Alternately, a focal subserosal perforation of the colonic mucosa may lead to a contained abscess cavity, which gradually enlarges to form the GCD. It has also been suggested that gas-forming bacteria may contribute to enlargement of a subserosal cyst.[4] The true GCD consists of all four bowel wall layers and is thought to be a congenital form of communicating bowel duplication cyst. It usually presents in childhood and accounts for only 13% of GCDs.[1]

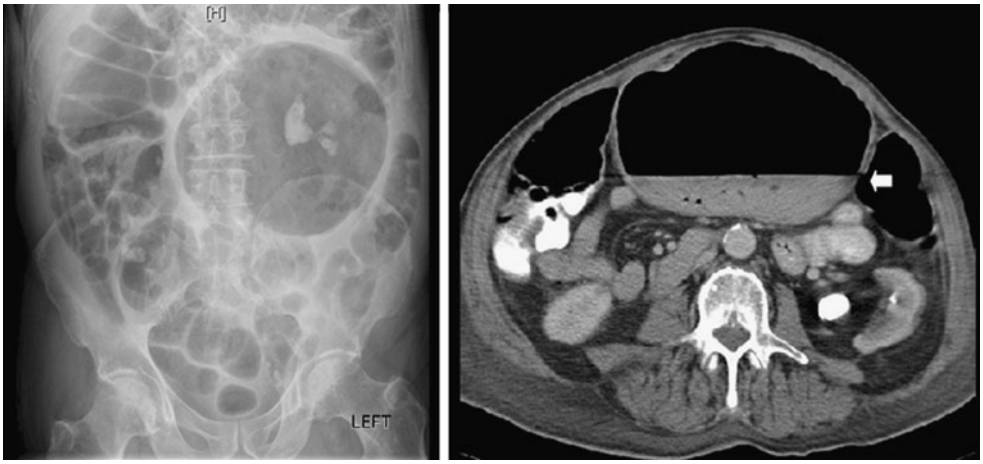

Fig. 1 Plain abdominal X-ray demonstrating a large lucency in the mid-abdomen with distension of the surrounding colon (*left*). CT scan of the abdomen shows a 17-cm cyst containing an air fluid level in continuity with the sigmoid colon (*arrow*) (*right*).

Patients may present acutely, complaining of abdominal pain and distension with a palpable periumbilical or pelvic mass. The lump can fluctuate and may enlarge rapidly due to raised intracolonic pressure.[4] This would account for acute enlargement as was the case in our patient and may have been precipitated by bleeding from the ulcerated lining of the diverticulum. The patient may be septic with features of acute diverticulitis, abscess formation or perforation. Alternately, symptoms may be less severe and chronic. One case of carcinoma within a GCD has been reported.[5] Ten percent are asymptomatic and are picked up incidentally either as an abdominal mass on clinical examination or on X-ray.[6] Differential diagnosis includes sigmoid or caecal volvulus, a duplication cyst or giant meckel's diverticulum and pneumatosis cystoides intestinalis.

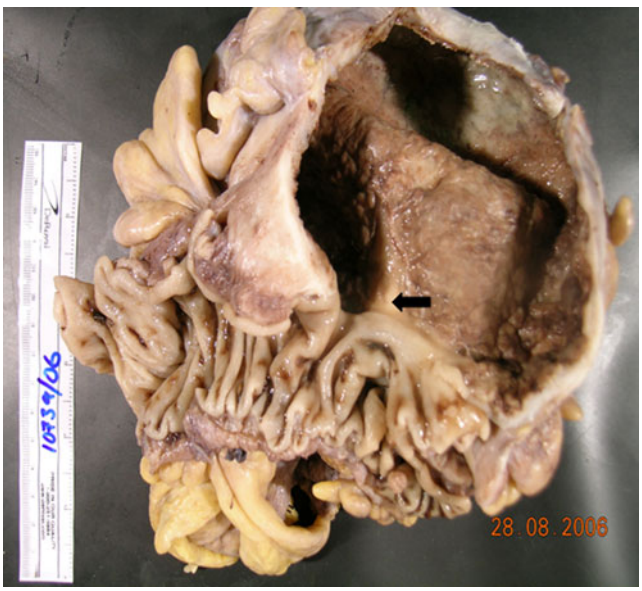

Fig. 2 Gross pathology of Hartmann's specimen demonstrating the inflamed and ulcerated lining of the giant diverticulum and its connection to the sigmoid colon (*arrow*).

Investigation includes plain radiography, which reveals a balloon sign (a large gas filled cyst).[7] An air fluid level may be seen. Barium enema demonstrates communication with the large bowel lumen in the majority of cases.[4] Computed tomography shows a smooth, thick-walled, air-filled structure intimately associated with the colon.[6]

In order to alleviate symptoms and prevent complications, GCDs need to be surgically excised. In most cases, this means a sigmoid colectomy. If the adjacent colon is healthy, a diverticulectomy may be undertaken.[4] For cases complicated by perforation or in a haemodynamically unstable patient, a Hartmann's procedure is indicated. Alternately, percutaneous drainage may provide a bridge to definitive surgical resection of the GCD. Only extremely high-risk patients, who would not tolerate surgery. should be managed conservatively.

GCD is a rare complication of a common condition. It is an important differential to consider when a large dilatation of bowel is seen on radiological imaging. Definitive surgical management is necessary to prevent serious complications.

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LETTER TO THE EDITOR

Emergence of Secondary Resistance to Imatinib in Recurrent Gastric GIST

Naga Venkatesh Gupta Jayanthi

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Dear Sir

I read the case report 'Emergence of Imatinib Resistance Associated with Downregulation of C-Kit Expression in Recurrent Gastrointestinal Stromal Tumor (GIST): Optimal Timing of Resection'[1] with interest.

Thanks to the authors for reporting this case of recurrent gastric GIST and development of secondary resistance to imatinib. This case shows the importance of a multidisciplinary approach to the treatment of a recurrent gastric GIST. This case emphasises the importance of close liaison between the surgeons, oncologists and pathologists in successful treatment of such tumours.

However, there are a number of points which are not clear in the report. The primary tumour was 7 cm in size with <5 mitoses/50 high power fields. This puts this tumour into an 'intermediate risk' category based on guidelines proposed by National Institute of Health GIST Workshop 2001[2] as mentioned in the paper. This tumour falls into the 'low risk' category according to the criteria obtained from long-term follow-up of a large cohort of patients with GISTs.[3–5]

The paper does not give any details of the initial surgery. Did initial surgery for the primary tumour achieve a R0 resection margin? With the tumour classified as an 'intermediate to low risk' of aggressive behaviour/malignancy, it is surprising that the tumour should recur within a year of resection. If the resection margins were positive, this patient could have been treated with further resection. If no further resection was performed, was he treated with adjuvant chemotherapy?

I am not certain if the patient was fully investigated after the recurrence was detected. Did the patient have a gastroscopy? Was a specimen obtained either endoscopically or radiologically for histological analysis? The paper does not mention carrying out a histopathological or an immunohistochemical evaluation of the tumour before the commencement of chemotherapy with imatinib. This is important because firstly, this would have confirmed the diagnosis of a recurrent GIST. Secondly, cKIT expression in the recurrent tumour could have been assessed and confirmed before commencement of any treatment. If the patient did receive adjuvant therapy with imatinib after the first operation, this could have led to downregulation of cKIT. Thirdly, if the tumour was in fact negative for cKIT before the start of imatinib therapy, an alternative therapeutic agent may have been more appropriate in this patient.[6–8]

Up to 5% of primary GISTs do not express cKIT.[3] cKIT expression patterns of a recurrent tumour are not well known. After an incomplete resection of the primary tumour, the tumour cells may have undergone further mutation resulting in a tumour that was not expressing cKIT. Therefore, without histopathological and immunohistochemical analysis, it is impossible to be certain if absence of cKIT expression in the recurrent tumour after 10 months of imatinib treatment was the case from the outset or if it emerged as a result of imatinib therapy.

If cKIT was not expressed in the recurrent GIST before commencement of imatinib, this would mean either the cKIT was downregulated automatically or raises the question if this is a new tumour. If the recurrent tumour was found to be expressing cKIT before the commencement of imatinib therapy and cKIT was downregulated, this would have confirmed the authors' conclusion. Understanding the behaviour of cKIT expression in recurrent tumour has obvious implications to the understanding of the biology and optimising treatment of recurrent GISTs. Furthermore, if tyrosine kinase inhibitors are to be used as neo-adjuvant therapeutic agents, the benefits of

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this should be balanced against the chances of the tumours developing secondary resistance to imatinib.

In summary, details of the initial surgery and surgical margins are not mentioned in the paper. In addition, the recurrent tumour was not adequately analysed.

Yours truly,
Dr. N Venkatesh Jayanthi

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LETTER TO THE EDITOR

Response to Reader's Queries

Vikas Dudeja · Panjak Gupta · Waddah B. Al-Refaie

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Dear Sir,

We thank our reader for showing interest in our case report and raising pertinent questions. We are in agreement with the reader that multidisciplinary approach is the key to the management of gastrointestinal stromal tumor (GIST) as the evidence-based guidelines continue to expand. Further, the decision to offer adjuvant or neoadjuvant targeted therapy (not chemotherapy) for GIST should be done in a multidisciplinary setting. The reader's questions have been answered below point by point.

1. Did initial surgery for the primary tumor achieve an R0 resection margin?

The patient underwent a prereferral R0 resection of a c-KIT-positive gastric GIST at an outside facility. While the histopathologic features of the primary tumor are that of low to intermediate risk, the pattern of disease recurrence in this case is unusual. The patient did not receive adjuvant imatinib (not chemotherapy) at the outside hospital, as this preceded the recently published American College of Surgeon Oncology Group trial (Z9001). Beyond this point, we cannot offer any definitive reasons for this decision.

With regard to extent of diagnostic workup for this locally advanced unresectable recurrent GIST, this was initially detected on cross-sectional imaging (computed tomography (CT) scan). An upper GI endoscopy with EUS capabilities was performed which showed normal-appearing stomach with postsurgical changes. It also showed no intramural lesion but showed a large mass abutting the antrum of the stomach with two satellite lesions inferior to the left hemiliver. Typical appearance on the CT scan and no intramural involvement strongly suggested a recurrence; thus, no biopsy was obtained. Given that the primary tumor was c-KIT positive as are most recurrent GISTs, our multidisciplinary decision was to offer neoadjuvant imatinib therapy for this locally advanced unresectable GIST. Further, the patient underwent a positron emission tomography (PET) scan before initiation of imatinib, which confirmed the presence of a large, highly PET-avid recurrent tumor and satellite nodules. A repeat PET scan done shortly after initiation of imatinib showed considerable decrease in the size and FDG uptake of the masses. These features are quite typical of GIST and, together with the early radiological (PET) response to imatinib, indicate that the masses did indeed represent GIST and further that the tumor remained kit positive at that time. While the possibilities of a c-KIT-negative recurrent GIST or newly developed primary mutations exist, the early and continued radiographic response is strongly suggestive of a c-KIT-positive recurrent GIST.

2. Our reader states that the benefit of using tyrosine kinase inhibitors in the neoadjuvant setting should be balanced against the probability of the tumors developing secondary resistance to imatinib. We are in agreement that this treatment analogy should be considered in the setting of a resectable recurrent GIST. However, and as we discussed in our case, the patient presented with radiographic features of locally advanced unresectable GIST and it was imperative to use neoadjuvant imatinib.

Again, we thank our reader for his interest in this case.

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ERRATUM

Erratum to: The Long-Term Results of Distal Gastrectomy by Mini-laparotomy in Early Gastric Cancer Patients

Hun Jung · Hae Myung Jeon · Han Hong Lee · Kyo Young Song · Cho Hyun Park

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Due to author oversight, there were errors in the row "OP Name (%)" within Table 1. The percentages have been corrected, and the revised table is printed below.

Table 1 Characteristics of the Enrolled Patients

Factors		Mini-laparotomy (n=22)	Conventional (n=31)	P value
Age		52.9±13.4	58.7±11.6	0.085
Sex (%)	Male	17 (77.3)	20 (64.5)	0.376
	Female	5 (22.7)	11 (35.5)	
Body mass index (kg/m^2)		22.2±2.7	23.1±3.9	0.356
OP name (%)	B-I STG	12 (54.5)	4 (12.9)	0.002
	B-II STG	10 (45.5)	27 (87.1)	
Operation time (min)		188.6±29.0	200.5±41.6	0.216
Hospital stay (days)		8.09±0.9	11.8±1.4	0.002

B-I STG subtotal gastrectomy with gastroduodenostomy, *B-II STG* subtotal gastrectomy with gastrojejunostomy

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