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SSAT POSTER PRESENTATION

Intraoperative Assessment of Pancreatic Neck Margin at the Time of Pancreaticoduodenectomy Increases Likelihood of Margin-Negative Resection in Patients with Pancreatic Cancer

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Abstract
Background The utility of intraoperative assessment of surgical margins is often debated by experienced pancreatic surgeons. We sought to review our experience with pancreaticoduodenectomy (PD) for pancreatic cancer to determine the impact of intraoperative frozen section (FS) analysis on margin-negative resection and long-term outcome.
Material and Methods Between 1992 and 2007, 310 consecutive patients underwent PD at our institution; 223 of these were for pancreatic cancer. Seven patients who underwent R2 resection were excluded. Charts were reviewed to determine demographics, final pathology, perioperative course, and long-term outcome. Data were compared by Fisher's exact and Student's *t* tests. Survival curves were created using the Kaplan–Meier method and compared by log-rank analysis. Predictors of margin-negative resection were determined by logistic regression analysis and predictors of survival determined by Cox proportional hazards analysis.
Results FS analysis of pancreatic neck resection margins was obtained in 75, while no intraoperative assessment was done in 141. Although patients who underwent FS were younger (median, 62 vs. 67 years, $p=0.01$), the two groups were similar in terms of gender, comorbidities, preoperative stenting, pylorus preservation, tumor differentiation, nodal status, tumor size, length of stay, and complication rate. Margin-negative resection was more common when FS was undertaken (99% vs. 81%, $p=0.0001$). However, intraoperative FS did not significantly increase overall survival (median, 21.7 vs. 14.6, $p=0.20$). Only nodal metastasis was predictive of poor survival (median, 21.7 vs. 13.3 months, $p=0.001$).
Conclusions Intraoperative assessment of the pancreatic neck margin status at the time of PD for pancreatic cancer increases the likelihood of obtaining a margin-negative resection. Noteworthy is that final margin status was not predictive of survival, while only nodal metastasis was, suggesting that tumor biology is the most important factor in patients with pancreatic cancer.

Keywords Pancreatic Cancer · RO Resection · Pancreaticoduodenectomy

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Introduction

Pancreatic cancer is a lethal disease, with nearly all patients dying within 2 years of diagnosis. It is the fourth leading cause of cancer-related deaths in the USA, and it is nearly uniformly fatal with its mortality approaching its incidence. An estimated 37,000 new cases of pancreatic cancer were diagnosed in 2007, and over 33,000 succumbed to their disease.[1] Since the 1970s, the incidence of pancreatic cancer has continued to increase dramatically, with little improvement in survival. Current chemotherapy has shown only modest responses. As such,

resection remains the only hope for cure, though overall survival remains dismal.[2,3]

In the surgical treatment of pancreatic cancer, it makes sense that obtaining a margin-negative resection should be associated with improved survival.[4] Surgeons often unreliably predict the completeness of resection, and therefore frozen section (FS) has been debated and recommended by some.[5,6] Nevertheless, a paucity of data exists on the utility of FS analysis during pancreaticoduodenectomy (PD) for pancreatic cancer. In fact, experienced pancreatic surgeons openly disagree about the role of FS analysis during resection of pancreatic cancer. In this study, we reviewed our experience with PD for pancreatic cancer to determine the impact of FS analysis on margin-negative resection and long-term outcome. We hypothesized that failure to obtain a margin-negative resection along the surgical neck of the pancreas at the time of PD was indicative of a biologically more aggressive tumor, thus making FS analysis fruitless.

Material and Methods

Data Collection

Between 1992 and 2007, 310 consecutive patients underwent PD at the Ohio State University. After approval from the Institution Review Board, 223 patients who underwent PD for histologically confirmed pancreatic adenocarcinoma were analyzed, 89 female (41.2%) and 127 male (58.8%) with a median age of 66.0 (range, 30–84). Data were retrospectively obtained from electronic medical records, hospital and clinic charts, and pathology records. Data collected included patient age, gender, comorbidities, clinical presentation, intraoperative findings, FS findings (when applicable), degree of differentiation, tumor size, nodal status, perioperative course, complications, long-term outcome, and survival. FS margins were obtained by shaving a parallel section

Table 1 Demographic and Clinicopathologic Characteristics in Patients Undergoing PD with or without Intraoperative Frozen Section Assessment of Surgical Margin

	Frozen, n=75	No frozen, n=141	p value
Age, median (range)	62.0 (39–81)	67.0 (30–85)	0.01
Gender	F 28 (37%)	F 61 (43%)	N.S.
	M 47 (63%)	M 80 (57%)	
Comorbidities	47 (63%)	91 (65%)	N.S.
Jaundice	67 (89%)	122 (87%)	N.S.
Pain	34 (45%)	57 (40%)	N.S.
Pylorus preservation	21 (28%)	26 (18%)	N.S.
Differentiation			
Well	5 (6.7%)	10 (6.8%)	
Moderately	43 (57.3%)	70 (59.6%)	N.S.
Poor	22 (29.3%)	49 (34.8%)	
Unknown	5 (6.7%)	12 (8.5%)	
Tumor size (cm)	3 (0-8)	3.5 (0.8-8)	N.S.
T stage[a]			
T1/T2	12 (16%)	23 (16.3%)	N.S.
T3	55 (73.3%)	20 (70.9%)	
Node positive	48 (64%)	92 (65.2%)	N.S.
LOS (days)	12.9	14	N.S.
Post-op death	3 (4%)	8 (5.7%)	N.S.
Complications			
Total No.	53	98	
Patients	32 (42.6%)	63 (44.7%)	N.S.
Chemotherapy			
Yes	33 (44%)	49 (34.8%)	
No	12 (16%)	43 (30.5%)	N.S.
Unknown	30 (40%)	49 (34.8%)	
Radiation			
Yes	24 (32%)	33 (23.4%)	
No	17 (22.7%)	48 (34.0%)	N.S.
Unknown	34 (45.3%)	60 (42.6%)	
Follow-up (mean, SD, median) (months)	34.1, 32.4, 18.9	33.5, 39.3, 16.6	N.S.

SD Standard deviation

[a] T stage was unknown in 25 (seven in FS group and 18 in no FS group) and were excluded from this analysis

Table 2 Predictors of Negative Pancreatic Neck Margin Resection in Patients Undergoing PD

Variable	Univariate p value	Multivariate *p* value
Frozen section	0.001	0.001
		RR 27.9 (95% CI 43.7–209)
Age	0.856	–
Gender	0.955	–
Comorbidities	0.346	–
Preoperative stent	0.960	–
Tumor size	0.055	0.209
Differentiation	0.647	–
T stage	0.859	–
Node positivity	0.981	–
Pylorus Preservation	0.060	0.110

Only variables with greatest potential to affect overall survival (i.e., $p \leq 0.2$) were included in multivariate logistic regression analysis

RR Relative risk, *CI* confidence interval

along the cut edge of the neck of the pancreas. Conferential deeper tissue sections were reviewed after formalin fixation and paraffin embedding of the cut margin. Similarly, in specimens where no FS was obtained, pancreatic resection margin status was determined after formalin fixation and paraffin embedding by shaving a parallel section from the cut edge of the pancreatic neck and staining with hemotoxylin and eosin. Overall survival was determined by the time from operation to death as determined by hospital records and by the Social Security Death Index (http://www.ssdi.rootsweb.ancestry.com as of 8/2007).

Statistical Analysis

Chi-square or Fisher's exact test was used for comparison between categorical variables. For continuous variables, Student's *t* test was utilized. Survival curves were constructed using the Kaplan–Meier method and compared by log-rank analysis. Patients who died in the immediate postoperative period were excluded from all survival analyses. Predictors of margin-negative resection were determined by logistic regression analysis, and associations of variables with survival were determined by multivariate Cox proportional hazards. Data are presented as median (range) unless stated otherwise.

Results

FS analysis was completed in 75 patients, while no intraoperative assessment was done in 141. In seven patients, complete extirpation of all macroscopic disease was not possible. These R2 resections were excluded from analysis. Those who did not undergo FS were significantly older than the FS group (Table 1). FS was undertaken in 12 of 25 (48%) patients age 50 or younger compared to 63 of 191 (33%) over the age of 50 (p=0.18). The gender distribution was similar in both groups as was comorbidites. All operations were undertaken for ductal adenocarcinoma arising in the head/uncinate process of the pancreas, and 22% of patients underwent pylorus preservation while the remaining 78% underwent standard PD with antrectomy. The two groups were similar with respect to differentiation, tumor size, T stage, and nodal status (Table 1). Postoperative length of stay was 1 day longer when no FS was undertaken, though this was not statistically significant. As well, complication rates between groups were similar. Fourteen patients required reoperation for hemorrhage (seven), wound revision (one), or intra-abdominal sepsis (six) accounting for three perioperative deaths. There was no difference in the incidence of reoperation in those in which FS was or was not undertaken (p=0.15, 3% vs. 8.5%, respectively). Overall mortality was 5.4% and not influenced by FS. The administration of adjuvant chemotherapy and radiation was also not influenced by FS and, hence, margin status. In the 190 patients

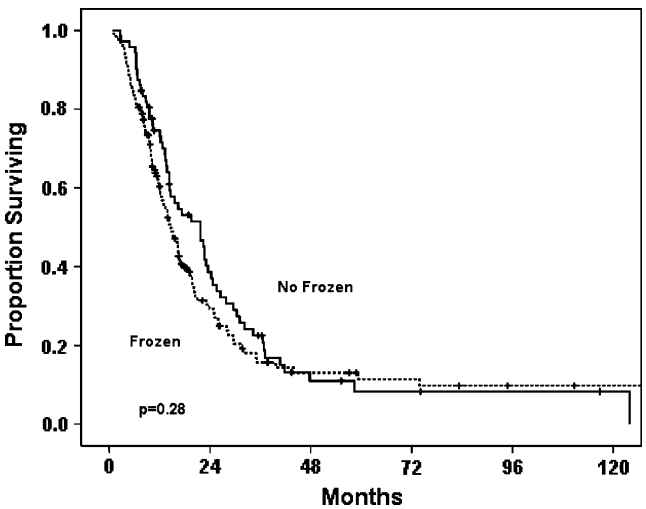

Figure 1 Overall survival in patients with pancreatic cancer following PD. No significant differences in overall survival was seen when frozen section was undertaken.

Table 3 Median, 2 and 5-Year Overall Survival in All Patients with Pancreatic Cancer Following PD

	Median survival (months)	2 year survival (%)	5 year survival (%)
Frozen section	21.7	38.6	8.2
No frozen section	14.6	29.2	11.4

The use of frozen section analysis did not significantly improve overall survival (p=0.28)

with evaluable T stage, there was no statistical difference in the number of tumors that were confined to the pancreas (i.e., T1 and T2) vs. those that invaded beyond that pancreatic parenchyma (i.e. T3).

Negative pancreatic neck margin was obtained in 74 (99%) of those undergoing FS compared to 115 (82%) with no FS (p=0.0001). In five of these latter cases, uncinate margin was also microscopically positive. In seven (9%), the initial FS margin was positive, and further resection was undertaken. In one patient, this required total pancreatectomy. A final negative margin was achieved in six, with one having extension of his resection far to the left of the mesenteric vessels but felt to be a poor candidate for total pancreatectomy, thus leaving a microscopically positive margin along the cut edge of the pancreas. This patient represented the only patient with a positive surgical "neck" margin on final pathology when FS was undertaken. An additional 17 patients in which FS was not undertaken had a microscopically positive retropancreatic/uncinate margin on final pathology, compared to none in the FS group. In total, complete resection (i.e., R0) was obtained in 74 (99%) when FS was undertaken compared to 99 (67%) when FS was not done (p<0.0001).

The size of the tumor and the tendency to undertake pylorus preservation showed a trend toward predicting R0 resection, but only intraoperative FS analysis was predictive of margin-negative resection by univariate and multivariate analysis (Table 2).

During the entire follow-up period, 59 (82%) of those in which FS was undertaken died compared to 107 (77%) in the no FS group, not including those who died in the perioperative period. Median follow-up for all remaining living patients was 16.6 months and similar in each group (Table 1). FS did not significantly increase overall survival (Fig. 1 and Table 3). Median overall survival was also similar between groups with a median of 21.7 vs. 14.6 months (Table 3). We further compared overall survival in all patients in each group found to have a margin negative, i.e., R0, resection and no significant improvement in survival when FS was obtained. Nodal status and poor differentiation of the tumors were predictive of poor survival on multivariate analysis (Table 4). FS did not significantly influence overall survival.

Discussion

Pancreatic cancer is generally considered a fatal disease with most being unresectable at diagnosis. The utility of FS analysis during PD has been debated by pancreatic surgeons. For those who have resectable lesions, this study supports the use of intraoperative assessment of margin status to ensure an R0 resection. Evaluating the margin intraoperatively may allow the surgeon to more effectively manage a positive margin before final pathology and thus achieve an R0 resection. However, the effect of achieving an R0 resection may not be as beneficial to survival as previously thought.

Table 4 Univariate and Multivariate Analysis of Variables to Predict Overall Survival

Variable	Univariate p value	Multivariate p value
Frozen section analysis	0.278	–
Age	0.258	–
Gender	0.949	–
Comorbidities	0.428	–
Complications	0.415	–
Pre-operative stent	0.166	0.596
Tumor size	0.442	–
Differentiation	0.034	0.014
		RR 2.23 (95% CI 1.18–4.24)
T stage	0.420	–
Nodes	0.001	0.003
		RR 1.79 (95% CI 1.20–2.43)
Margin status	0.099	0.228
Pylorus preservation	0.106	0.716

Only variables with potential to affect overall survival (i.e. $p \leq 0.2$) were included in Cox proportional hazards model.

RR Relative risk, *CI* confidence interval

Our population of pancreatic cancer patients who underwent resection is typical of those previously reported, in their seventh decade of life with a male predominance and jaundice. Commensurate with their advanced age, more than half of patients had significant comorbidities. Patients who underwent intraoperative FS analysis of the resection margin tended to be younger. There is no clear reason for this disparity, although it does introduce the possibility of a bias that we were unable to detect in the data we collected. FS analysis in younger patients may be symbolic of a more aggressive surgical approach to complete extirpation of the tumor. As such, FS was undertaken in nearly half of patients 50 years old or younger compared to one third of patients over the age of 50, but this was not statistically significant. Otherwise, patients in each group were well matched by all other parameters measured including operative approach, tumor characteristics, perioperative events, and postoperative adjuvant treatment.

Intraoperative margin assessment significantly increased the likelihood of obtaining a negative margin at the surgical neck of the pancreas. As well, for reasons that are not clear from the data presented, the retropancreatic/uncinate margin was also more likely to be involved on final pathology when FS was not done. The retropancreatic and uncinate margins are not routinely assessed intraoperatively, since, arguably, they do not represent truly surgical margins. In other words, a microscopically positive margin in this region identified in the operating room is not likely to be surgically correctable. Interestingly, overall survival was not increased in the FS group even though a R0 resection was obtained in 99% compared to only 67% when FS was not done (Fig. 1 and Table 4). The incidence of positive margin is similar to those reported previously.[7] Margin status was not associated with survival by univariate or multivariate analysis. As expected, poor differentiation of the tumor and positive nodes were predictive of poorer survival.

While it is well established that advances in imaging, surgical technique, and perioperative care have reduced postoperative morbidity and mortality of PD, most patients do not achieve long-term disease-free survival, even with the best of surgical care.[8] Previous studies have indicated that an R0 resection increases long-term survival after PD, and thus, FS analysis at the time of surgery would seem to be beneficial and lead to better long-term outcomes.[9,10] In fact, it has even been emphasized that achieving an R0 resection is one of the most powerful independent predictors of long-term survival.[8,11] Similarly, Willett et al.[12] reported that patients in whom negative surgical margins were obtained achieved significantly longer 5-year survival (22%) than the group as a whole (13%). Similarly, results from the ESPAC-1 trial demonstrated poorer survival in patients undergoing R1 resection.[13] However, after our review of 216 patients, we did not find an increase in overall survival, even when margin-negative R0 resection was achieved. As such, intraoperative margin assessment as a means of tailoring resection in order to achieve negative margins does not appear to impact outcome, an observation that has not been described previously. More recently, Raut et al.[14] has reported similar results to our study, suggesting R0 resection does not necessarily translate into improved survival. While this may be due to underestimation of margin status due to inconsistent pathologic analysis,[15,16] it comes as no surprise as survival is notoriously poor given the lack of effective adjuvant therapy.

We recognize the difficulty in making definitive conclusions about the true utility of intraoperative margin assessment given the retrospective nature of this study. During the 15-year time period covered, the surgeons who undertook the majority of resections did not routinely obtain intraoperative FS analysis of the surgical neck margin. This alone could introduce a selection bias. Still, the dramatic improvement in the ability to achieve negative surgical margins with intraoperative assessment is undeniable. The impact on survival, however, is less clear.

The extension of a tumor arising from the head of the pancreas into or to the left of the surgical neck is likely indicative of a more aggressive tumor. Therefore, inability to achieve an initially negative margin after transecting the pancreas at the surgical neck during PD may be more reflective of poor biology rather than poor surgical technique. Intraoperative margin assessment, however, does play a role in providing real time feedback on the adequacy of resection allowing the surgeon the option of extending the resection to achieve negative margins for the purpose of proper stratification into clinical trials and outcomes research.

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Cannabinoid Receptor-1 Blockade Attenuates Acute pancreatitis in Obesity by An adiponectin Mediated Mechanism

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Abstract
Background Obesity is a risk factor for increased severity of acute pancreatitis. Adipocytes produce adiponectin, an anti-inflammatory molecule that is paradoxically decreased in the setting of obesity. We have shown that adiponectin concentration inversely mirrors the severity of pancreatitis in obese mice. Cannabinoid receptor CB-1 blockade increases circulating adiponectin concentration. We, therefore, hypothesize that blockade of CB-1 would increase adiponectin and attenuate pancreatitis severity.
Methods Forty lean (C57BL/6J) and 40 obese (Lep^{Db}) mice were studied. Half of the mice in each strain received intraperitoneal injection of the CB-1 antagonist rimonabant (10 mg/kg daily for 7 days); the others received vehicle. Pancreatitis was induced by intraperitoneal injection of cerulein (50 μg/g hourly ×6). Pancreatitis severity was determined by histology. Pancreatic chemokine and proinflammatory cytokine concentrations were measured by ELISA.
Results Rimonabant treatment significantly increased circulating adiponectin concentration in obese mice ($p<0.03$ vs. vehicle). After induction of pancreatitis, obese mice treated with rimonabant had significantly decreased histologic pancreatitis ($p<0.001$), significantly lower pancreatic tissue levels of monocyte chemoattractant protein-1 ($p=0.03$), tumor necrosis factor-α ($p<0.001$), interleukin-6 ($p<0.001$), and myeloperoxidase ($p=0.006$) relative to vehicle-treated animals.
Conclusions In obese mice, cannabinoid receptor CB-1 blockade with rimonabant attenuates the severity of acute pancreatitis by an adiponectin-mediated mechanism.

Keywords Pancreatitis · Cannabinoid · Adiponectin · Obesity

Introduction

Obesity currently affects over 50 million American adults, and the incidence continues to rise at an alarming rate.[1] The detrimental effect of adipose tissue infiltration into visceral organs such as the heart, liver, and kidneys are well documented.[2–4] Emerging evidence supports the concept that obesity affects the pancreas in a similar manner. We have recently shown that pancreata of congenitally obese mice contain more fat and elevated concentrations of proinflammatory cytokines relative to those of lean wild-type animals.[5,6] Our group and others have also shown that obese rodents sustain significantly more severe acute pancreatitis than lean animals.[7,8] The latter experimental observations are consistent with the human situation, in which obesity has clearly been identified as an independent risk factor for increased severity of pancreatitis.[9–12]

The mechanisms by which obesity worsens the inflammatory insult of acute pancreatitis are largely unknown. However, an intriguing observation in our recent experiments was that the severity of acute pancreatitis in obese mice was inversely mirrored by circulating concentrations of the

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adipokine adiponectin.[7] Adiponectin is produced predominantly by adipocytes; however, it is paradoxically decreased in the setting of obesity. This pleiotropic molecule has a number of metabolic regulatory effects. Importantly, adiponectin is also a potent anti-inflammatory agent.[13,14]

The surge in obesity research has fueled an increased interest in the endocannabinoid system. Endogenous cannabinoids are small molecules produced by cleavage of fatty acids from cell membranes.[15] Over the past decade, cannabinoids have been increasingly recognized to play an important role in modulating metabolic and inflammatory pathways. Endogenous cannabinoids are ligands for two receptors: CB-1 and CB-2. Two recent large prospective randomized studies demonstrated that administration of a CB-1 antagonist (rimonabant) to obese adult humans led to significant weight loss and improvements in metabolic parameters such as lipid profile and insulin resistance.[16,17] Interestingly, patients in the treatment arm also showed dose-dependent increases in circulating adiponectin concentration. We, therefore, hypothesized that CB-1 blockade would increase circulating adiponectin and that increased concentrations of this anti-inflammatory molecule would, in turn, attenuate the severity of pancreatitis in obese mice.

Materials and Methods

All studies were performed with approval of the Indiana University Institutional Animal Care and Use Committee and were in accordance with the National Research Council guide for the care and use of laboratory animals.

Animals and Diet

Forty lean (C57BL/6J) and 40 obese leptin-resistant (Lep^{Db}) female mice were obtained from Jackson Laboratories (Bar Harbor, ME, USA) at 7 weeks of age. Mice were housed in a light (12 h light/dark) and temperature (22°C) controlled room. During 1 week of environmental adjustment, mice were fed a standard low fat chow diet (Ralston Purina, St. Louis, MO, USA). At 8 weeks of age, mice were fed a diet containing 25% fat (soybean oil + corn oil), 55% carbohydrate (sucrose and cornstarch), and 20% protein-derived calories (Dyets Inc., Bethlehem, PA, USA) ad libitum for a total of 4 weeks. Animals and food were weighed weekly to monitor growth and dietary intake.

Chemicals

Rimonabant (Zydus/Cadila, Ahmedabad, Gujrat, India) was a kind gift from Professor Surendra Kumar Mathur (Wockhardt Hospital, Mumbai, India). Rimonabant was dissolved in ethanol/cremophor/NaCl (1:1:18). Other chemicals were obtained from Sigma Aldrich (St. Louis, MO, USA) unless otherwise noted.

Experimental Design

Figure 1 depicts a schematic of the experimental design. At 11 weeks of age, 20 mice from each strain were randomly placed into one of two groups. The first group (RIMONABANT) received rimonabant at a dose of 10 mg/kg via intraperitoneal injection daily for 7 days. The other group (VEHICLE) received intraperitoneal injection of saline vehicle daily for 7 days. At 12 weeks of age, after an overnight fast with water available ad libitum, half of the mice in each group (RIMONABANT/VEHICLE) were subjected to acute pancreatitis using the well-characterized method of cerulein hyperstimulation (PANCREATITIS group). Briefly, cerulein (50 μg/kg) was administered hourly via intraperitoneal injection for a total of 6 h. The remaining mice (CONTROL group) received intraperitoneal injection of vehicle (0.5% NH_4/NaCl) on the same schedule. This design resulted in four groups of mice (n=10) in each strain.

Tissue Collection

Nine hours following induction of pancreatitis, mice were sedated with isoflurane and anesthetized with an intraperitoneal injection of xylazine (15 mg/kg) and ketamine (50 mg/kg). The animals then underwent laparotomy and total pancreatectomy. A portion of each pancreas was preserved in formalin for histologic analysis, and the remainder was snap frozen in liquid nitrogen and stored at

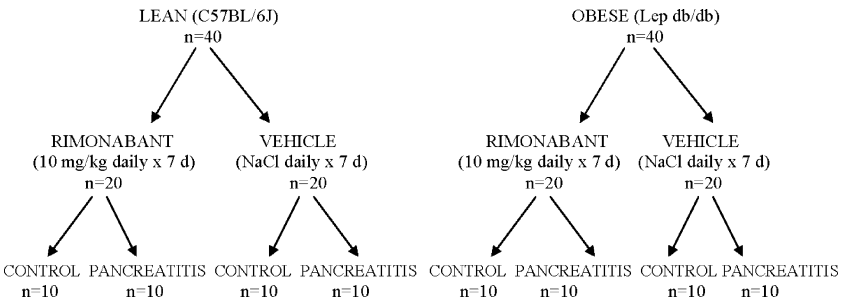

Figure 1 Experimental design.

−80°C for subsequent analysis. Blood was collected by direct ventricular puncture and centrifuged at 15,000 rpm for 5 min to separate serum. Serum was stored at −20°C for subsequent analysis. Animals were then euthanized by exsanguination.

Histologic Analysis

Pancreatic specimens were fixed in formalin, embedded in paraffin, and sectioned into 5-μm sections. Counterstaining was performed with hematoxylin and eosin. Three individual observers who were unaware of the treatment arm reviewed each slide via light microscopy (Lecia DM 5000B, Wetzlar, Germany). Pancreatitis severity was determined using a validated scoring method.[18] Scores for the degree of edema, inflammation, and vacuolization were summed to yield a total pancreatitis score.

Biochemical Analysis

Serum adiponectin concentration was determined by an ELISA technique according to manufacturer instructions (LINCO Research, St. Charles, MO, USA). Pancreatic tissue was homogenized in buffer containing 50 mM Tris, 250 mM NaCl, 5 mM EDTA, 1 mM NaF, 20 mM $Na_4P_2O_7$, 0.02% NaN_3, proprietary detergent, and protease inhibitor (Sigma, St. Louis, MO, USA) at a volume of 50 μL/g tissue. Homogenates were centrifuged at 10,000 rpm at 4°C for 15 min, and protein concentration of the supernatant was assayed (Bio-Rad, Hercules, CA, USA). Pancreatic tissue levels of the cytokines tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and the chemokine monocyte chemoattractant protein-1 (MCP-1) were determined with commercially available ELISA kits (R & D Systems, Minneapolis, MN, USA) according to manufacturer's instructions. Pancreatic tissue concentration of myeloperoxidase (MPO) was determined by ELISA from Cell Sciences (Canton, MA, USA). All analyses were performed in serial duplicates.

Cannabinoid Receptor Gene Expression

Total RNA was isolated from the pancreata of three lean and three obese mice with RNeasy (Qiagen, Valencia, CA, USA) according to manufacturer's instructions. An Agilent 2100 Bioanalyzer (Agilent, Santa Clara, CA, USA) was used to determine concentration, quality, and integrity of total RNA. First strand cDNA synthesis was performed with Superscript III Platinum two-step kit (Invitrogen, Carlsbad, CA, USA), and real time polymerase chain reaction was performed with ABI 7500 (Applied Biosystems, Foster City, CA, USA). The following specific primers were obtained from Applied Biosystems: *CB-1sense*: CACAGGCCTCTGGCCTATAAAGA; *CB-1 antisense*: GCAATAGTCCACATCAAGCAAAAG; *CB-2 sense*: GCCTTGTTAACTCTATGGTCAATCC; *CB-2 antisense*: TGGGCAGCAGAGCGAATC.

Statistical Analysis

Statistical analyses were performed using Sigma Stat Statistical Software (Jandel Corp., San Rafael, CA, USA). Data are expressed as mean ± SEM. ANOVA, Student's *t* test, and the Tukey test were applied where appropriate; $p<0.05$ was accepted as statistically significant.

Results

Animal Weight

Animal weight before and after treatment with rimonabant are shown in Table 1. Consistent with prior observations, at 11 weeks of age, the body weight of obese mice (45.8±0.5 g) was more than twice that of lean wild-type animals (18.8±0.7 g; $p<0.001$). Treatment with rimonabant did not affect the weight of lean animals (RIMONABANT=19.3±0.2 g; VEHICLE=18.9±0.2 g; $p=0.06$). In contrast, obese mice treated with rimonabant for 1 week had significantly lower body weight (41.5±0.6 g) than those treated with vehicle (46.2±0.5 g, $p<0.001$). This change represents a total body weight loss of 10.2%.

Serum Adiponectin Concentration

Serum concentration of adiponectin is shown in Fig. 2. Similar to previous observations, serum adiponectin concentration was significantly lower in obese mice compared to lean animals ($p<0.03$). Treatment with rimonabant did not alter circulating adiponectin levels in any group of lean animals ($p=0.2$). In obese animals, however, rimonabant treatment significantly increased circulating adiponectin concentration by 79% in the CONTROL group ($p<0.03$ vs. vehicle) and by 63% in the PANCREATITIS group ($p=0.03$ vs. vehicle). Induction of pancreatitis did not alter circulating adiponectin concentration in mice treated with either vehicle ($p=0.53$) or rimonabant ($p=0.56$).

Table 1 Weight in Grams of Lean and Obese Mice before (Pretreatment) and after 1 Week of Treatment with Vehicle or Rimonabant

	Lean	Obese
Pretreatment	18.8±0.1	45.0±0.3
Vehicle	19.3±0.2	46.2±0.5
Rimonabant	18.9±0.2	41.5±0.6*

*$p<0.001$ vs. obese/vehicle

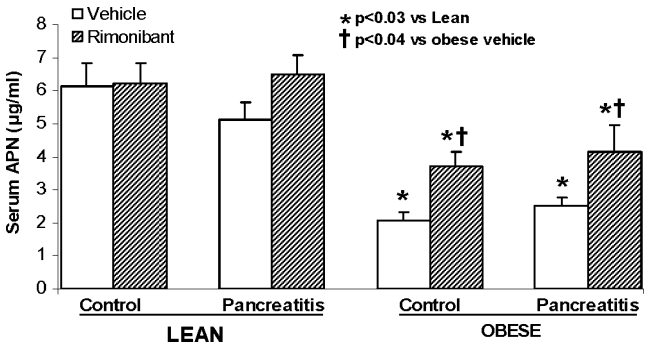

Figure 2 Serum adiponectin concentration in lean (C57BL/6J) and congenitally obese (Lep^{Db}) mice treated with either vehicle (open bars) or the CB-1 antagonist rimonabant (*hatched bars*). Serum adiponectin was significantly lower in all obese animals compared to lean mice. Rimonabant treatment significantly increased serum adiponectin in obese mice.

Histologic Pancreatitis Severity

Lean and obese mice in control groups did not manifest histologic changes of acute pancreatitis (data not shown). Representative photomicrographs demonstrating pancreatitis severity in lean and obese mice treated with either vehicle or rimonabant are shown in Fig. 3. The histologic total pancreatitis score was higher in obese mice than in lean mice (Fig. 4); however, this difference did not reach statistical significance ($p=0.12$). Treatment with rimonabant did not affect pancreatitis severity in lean mice ($p=0.95$). In sharp contrast, obese mice treated with rimonabant showed significantly decreased histologic changes of pancreatitis compared to those treated with vehicle ($p<0.001$; Fig. 4).

Pancreatic MCP-1

Pancreatic tissue concentrations of the chemoattractant protein MCP-1 are shown in Fig. 5. Rimonabant administration did not change the baseline (control) concentration of MCP-1 in either lean ($p=0.71$) or obese ($p=0.88$) mice. Induction of pancreatitis led to a significant increase in pancreatic MCP-1 concentration in both lean ($p<0.001$) and obese ($p<0.001$) mice versus control animals. As we have reported in prior experiments, this increase in MCP-1 was significantly greater in obese as compared to lean animals ($p=0.002$). In animals subjected to pancreatitis, rimonabant administration resulted in a significant decrease in pancreatic MCP-1 concentration in both lean ($p=0.03$) and obese ($p<0.001$) mice.

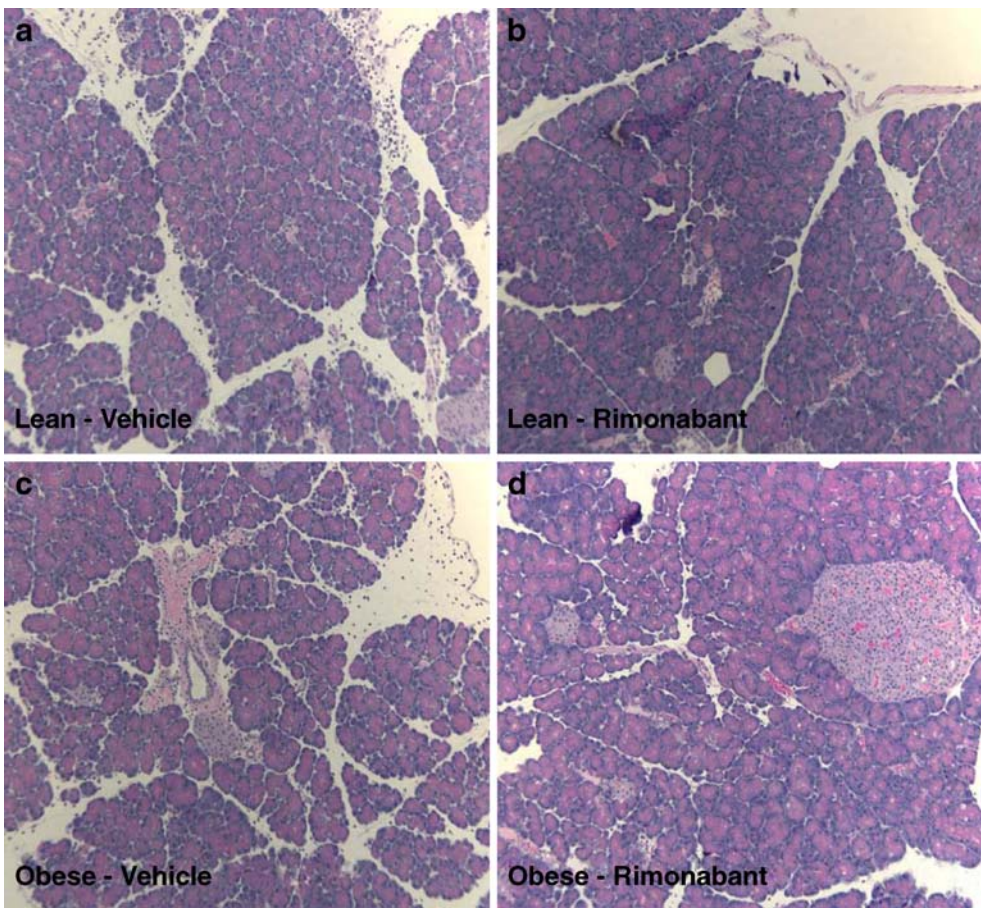

Figure 3 Representative photomicrographs (H&E, ×10) demonstrating histologic severity of acute pancreatitis in lean and congenitally obese mice. **A** Lean mouse treated with vehicle; **B** lean mouse treated with rimonabant; **C** obese mouse treated with vehicle; **D** obese mouse treated with rimonabant.

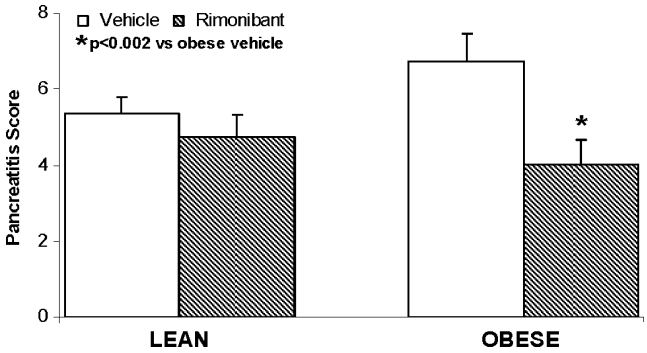

Figure 4 Histologic pancreatitis score in lean and obese mice treated with vehicle (*open bars*) or rimonabant (*hatched bars*). Obese mice treated with rimonabant had a significantly decreased pancreatitis score compared to those treated with vehicle.

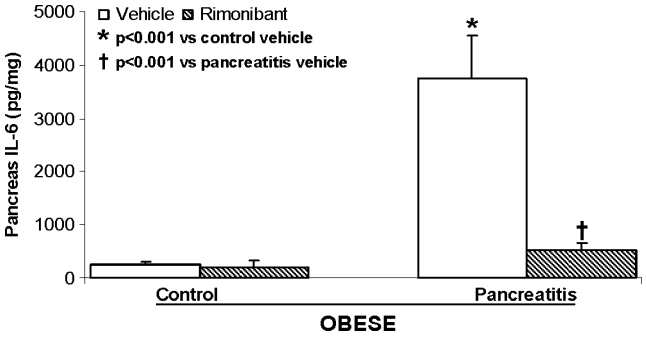

Figure 6 Pancreatic concentration of the proinflammatory cytokine IL-6 in obese mice treated with vehicle (*open bars*) or rimonabant (*hatched bars*). Induction of pancreatitis significantly elevated pancreatic concentration of IL-6. Rimonabant treatment significantly decreased pancreatic concentration of IL-6 in mice subjected to pancreatitis.

Pancreatic IL-6

No difference in pancreatic tissue concentration of IL-6 was observed in any group of lean animals ($p=0.6$): control/vehicle=433±100 pg/mg ($n=5$); control/rimonabant=430±107 pg/mg ($n=8$); pancreatitis/vehicle=395±65 pg/mg ($n=10$); pancreatitis/rimonabant=517±134 pg/mg ($n=9$). No differences in pancreatic tissue concentration of IL-6 were observed between lean and obese animals in the control group (vehicle $p=0.09$; rimonabant $p=0.2$). In obese animals, induction of pancreatitis resulted in a significant increase in pancreatic IL-6 (Fig. 6; $p<0.001$). Rimonabant administration completely abrogated this effect ($p<0.001$ vs. pancreatitis/vehicle group).

Pancreatic TNF-α

Similar to IL-6, no difference in pancreatic concentration of TNF-α was seen in any group of lean animals ($p=0.3$): control/vehicle=814±140 pg/mg ($n=10$); control/rimonabant=984±119 pg/mg ($n=10$); pancreatitis/vehicle=777±129 pg/mg ($n=10$); pancreatitis/rimonabant=873±119 pg/mg ($n=10$). In obese animals, induction of pancreatitis resulted in a significant increase in pancreatic tissue concentration of TNF-α ($p<0.001$; Fig. 7); this effect was significantly decreased in animals treated with rimonabant ($p<0.001$).

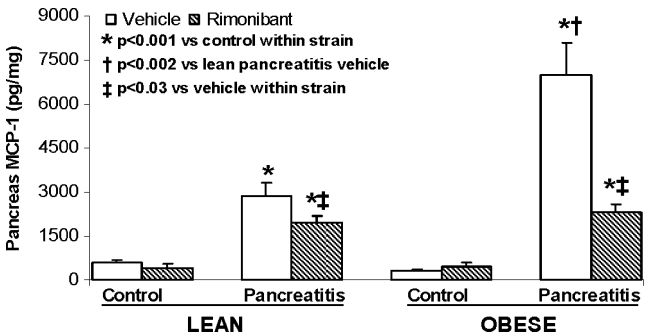

Figure 5 Pancreatic concentration of the chemokine MCP-1 in lean and obese mice treated with vehicle (*open bars*) or rimonabant (*hatched bars*). Control groups and groups subjected to pancreatitis are shown. Induction of pancreatitis significantly increased pancreatic concentration of MCP-1 in lean and obese mice. Rimonabant treatment significantly decreased pancreatic MCP-1 concentration in both lean and obese mice subjected to pancreatitis.

Pancreatic MPO

Pancreatic concentration of MPO was measured in obese mice (Fig. 8). Induction of pancreatitis led to a significant increase in pancreatic MPO concentration in vehicle treated mice ($p=0.006$). Treatment with rimonabant completely abrogated this effect ($p=0.006$).

Cannabinoid Receptor Gene Expression

Gene expression of the cannabinoid receptor CB-1 was not detected in the pancreata of either lean or obese mice. In contrast, cannabinoid receptor CB-2 Mrna was expressed in

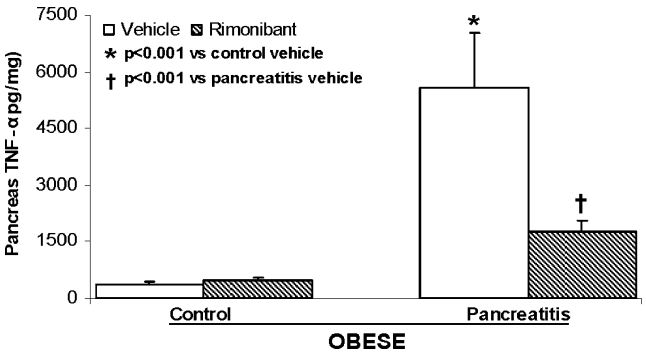

Figure 7 Pancreatic concentration of the proinflammatory cytokine TNF-α in obese mice treated with vehicle (*open bars*) or rimonabant (*hatched bars*). Induction of pancreatitis significantly increased pancreatic concentration of TNF-α, an effect that was significantly attenuated by rimonabant treatment.

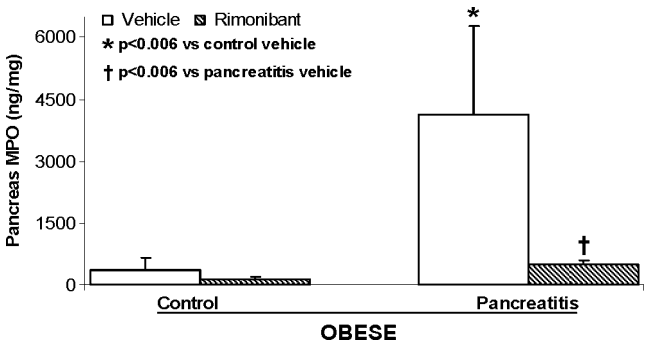

Figure 8 Pancreatic concentration of the marker of neutrophil activation MPO in obese mice treated with vehicle (*open bars*) or rimonabant (*hatched bars*). Induction of pancreatitis significantly elevated pancreatic concentration of MPO, an effect that was completely ameliorated by rimonabant treatment.

the pancreata of both strains. Relative to lean C57BL/6J mice, pancreatic gene expression of CB-2 was decreased by 71% in Lep^{Db} animals.

Discussion

These experiments were designed to test the hypothesis that central blockade of the cannabinoid receptor CB-1 would increase serum adiponectin and attenuate the severity of pancreatitis. We found that 1 week of treatment with the CB-1 antagonist rimonabant significantly increased circulating adiponectin concentration and significantly decreased the histologic severity of pancreatitis in congenitally obese (Lep^{Db}) mice. In addition, rimonabant treatment significantly decreased pancreatic concentrations of the chemoattractant molecule MCP-1, the proinflammatory cytokines IL-6 and TNF-α, and the marker of neutrophil activation MPO in obese mice subjected to pancreatitis by erulean hyperstimulation. These findings suggest that the mechanisms by which CB-1 antagonism attenuates the severity of pancreatitis are mediated by increasing the circulating concentration of the potent anti-inflammatory adipokine adiponectin. Furthermore, the fact that pancreatic tissue concentration of both MCP-1 and MPO were significantly decreased in rimonabant treated animals suggests that adiponectin directly modulates the inflammatory cell response to the insult of acute pancreatitis.

Acute pancreatitis represents a significant problem, accounting for over 240,000 hospital admissions yearly in the USA at a cost of over $2.3 billion.[19] Eighty percent of patients with acute pancreatitis will have a relatively mild, self-limiting course of the disease; 15% to 20% of patients, however, will suffer from severe acute pancreatitis with necrosis of pancreatic parenchyma and peripancreatic soft tissue. Patients with severe acute pancreatitis commonly require protracted hospitalization, including extended intensive care treatment and operative intervention to address local complications such as infected necrosis.[20] Importantly, no specific therapy for acute pancreatitis currently exists, and treatment remains entirely supportive.[20,21] Despite major advances in critical care, patients with severe acute pancreatitis still suffer from significant mortality. Current series report mortality rates ranging from 4% to 20%.[22–24] Studying the pathogenesis of acute pancreatitis from different contexts such as obesity, therefore, offers the opportunity to discover or uncover unique physiologic mechanisms that may ultimately lead to the development of novel directed therapy that is much needed.

An improved understanding of the endocannabinoid system has recently begun to emerge. Endogenous cannabinoids such as anandamide are produced by cleavage of fatty acids (particularly arachidonic acids) primarily from cell membranes.[15] Cannabinoids modulate the inflammatory response in a complex and pleiotropic manner and can upregulate or downregulate inflammatory cytokine production based on the nature of stimulus and the specific cannabinoid involved.[15] Two cannabinoid receptors—CB-1 and CB-2—have been described though it is likely that others exist. CB-1 receptors are highly expressed throughout the brain primarily in the cerebellum and hippocampus.[15] CB-1 receptors also exist in the periphery to a far lesser degree, principally on adipocytes, but also in the liver, murine islet cells, and human acinar cells.

Three studies have evaluated the endocannabinoid system in the setting of acute pancreatitis.[25–27] Data from all three of these studies indicate that the endocannabinoid system is active in the setting of acute pancreatitis; however, attempts to manipulate the endocannabinoid system have produced results that are less clear and in some cases, frankly, conflicting. Using a rodent model, Matsuda et al. found no change in pancreatitis severity but a decrease in mortality after CB-1 blockade.[27] In contrast, Dembinski and colleagues found that CB-1 blockade significantly decreased the severity of acute pancreatitis in a murine model.[26] Finally, Michalski et al. showed upregulation of CB-1 receptor by immunohistochemistry and Western blot in the pancreata of humans with acute pancreatitis.[25] In separate experiments by this same group, CB-1 blockade did not affect severity of pancreatitis in a murine model of erulean hyperstimulation. Interestingly, though, administration of the cannabinoid receptor agonist HU210 significantly reduced pancreatic inflammation in the same model. These somewhat discordant findings may be explained in part by different doses, timing, and methods of administration (intravenous, subcutaneous, intraperitoneal) of these cannabinoid modulators as well as by the use of different animal models of acute pancreatitis. Importantly, none of these studies investigated the impact of obesity on alterations of the cannabinoid system.

In the present study, we found that administration of CB-1 antagonist rimonabant significantly decreased the severity of acute pancreatitis in congenitally obese mice. The fact that these mice did not have pancreatic gene expression of CB-1 makes it unlikely that this effect was mediated directly through CB-1 receptors (at least at the level of the pancreas). It is, therefore, most likely that these effects were mediated by mechanisms remote from the CB-1 receptor blockade, specifically increased circulating concentration of adiponectin. CB-1 blockade also led to a significant increase in circulating adiponectin in obese mice. This finding is consistent with clinical and experimental studies.[16,17,28,29] Adiponectin is produced by adipocytes but is paradoxically decreased in the setting of obesity. Adiponectin is an anti-inflammatory molecule in many models of acute inflammation.[13] Adiponectin modulates inflammatory response through a variety of different mechanisms: downregulation of the chemokine and adhesion model production, alteration of lymphocyte or macrophage function, suppressing production of proinflammatory and upregulating production of anti-inflammatory cytokines.[13,30–32] The finding that CB-1 blockade downregulated pancreatic concentrations of the chemokine MC P-1 and the marker of neutrophil activation myeloperoxidase as well as decreased the proinflammatory cytokines TNF-α and IL-6 is consistent with the paradigm that increased adiponectin decreases pancreatic inflammatory cell infiltration in the setting of acute pancreatitis. We recently observed that circulating adiponectin concentration inversely mirrored the severity of acute pancreatitis in obese mice, suggesting a relative decrease in this anti-inflammatory agent may potentiate the severity of acute pancreatitis in the setting of obesity.[7] This hypothesis is further substantiated by the current findings. A more direct method to test this hypothesis is systemic administration of adiponectin. Unfortunately, the current cost of recombinant adiponectin ($150 per ten micrograms) prohibits achievement of physiologic concentrations in an in vivo model.[33] Therefore, indirect methods of adiponectin upregulation such as central cannabinoid receptor blockade are more practical when using in vivo models.

CB-1 blockade led to weight loss of 10% in obese mice. Severity of pancreatitis in obese mice is not related directly to the volume of fat per se. In previous experiments, we have shown that Lep^{Ob} mice, while significantly heavier than obese Lep^{Db} animals, sustained significantly less severe pancreatitis when challenged with cerulean hyperstimulation.[7] Thus, it is unlikely that this modest weight loss in and, of itself, was responsible for the decrease in pancreatitis severity in obese mice treated with rimonabant. Further study using a pair feeding technique might clarify these observations.

The experimental model of acute pancreatitis induced by hyperstimulation with the cholecystokinin analog erulean is well established, easily performed, and easily reproducible. A disadvantage of this model is that it results in a relatively mild interstitial form of pancreatitis, particularly in lean animals. The fact that there was no change in severity in acute pancreatitis with CB-1 blockade in lean mice, in conjunction with the observation that pancreatic concentrations of the inflammatory mediators IL-6 and TNF-α, were unchanged in lean control animals is likely related directly to use of this model of mild pancreatitis. CB-1 blockade did not increase circulating adiponectin or decrease the severity of acute pancreatitis in lean mice. This interesting finding highlights potential mechanistic differences in the development of acute pancreatitis and severity of subsequent inflammatory response between lean and obese subjects and may at least in part explain the conflicting data from prior reports.[25–27] Continued investigation into the mechanisms by which obesity specifically impacts development of pancreatic disease is therefore clearly warranted.

In summary, antagonism of the central CB-1 receptor significantly decreased the severity of acute pancreatitis in obese mice. This effect is likely mediated at least in part by an increase in the circulating concentration of anti-inflammatory adipokine adiponectin. CB-1 antagonists and/or adiponectin administration may, therefore, represent a promising new therapy for the treatment of acute pancreatitis.

Acknowledgement The authors thank Kimberly Hoffman for excellent administrative assistance.

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SSAT POSTER PRESENTATION MANUSCRIPT

Contemporary Surgical Management for Ileosigmoid Fistulas in Crohn's Disease

Genevieve B. Melton · Luca Stocchi · Elizabeth C. Wick · Kweku A. Appau · Victor W. Fazio

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Abstract
Background Current diagnostic modalities and surgical treatments for ileosigmoid fistulas (ISF) in Crohn's disease (CD) are not well characterized.
Methods ISF patients operated during 2000–2007 in a prospectively collected CD surgery database were included. Disease extent, diagnostic studies, medications, and smoking status were retrospectively reviewed.
Results One hundred four CD patients with ISF (median age 37) underwent ileocolic resection (75 open, 29 laparoscopic). Sigmoid colon was treated with primary repair (26), segmental resection (71), and subtotal colectomy (7). Thirty-eight patients required additional surgery for CD manifestations (ileovesical fistula (11), enterocutaneous fistula (11), and synchronous small bowel disease (22)). Overall sensitivity of studies for ISF detection was 63% (66/104) (colonoscopy 35% (31/89), CT scan 41% (31/76), fluoroscopy 53% (31/58)). Stoma diversion (53 patients, 51%) occurred more with open surgery (81% vs. 63%, $p=0.04$), intraoperative ureteral stents (28% vs. 2%, $p<0.0001$), additional small bowel procedures (42% vs. 18%, $p=0.008$), longer overall length of stay (10 vs. 6 days, $p<0.0001$), preoperative steroid use ≥20 mg prednisone (40% vs. 18%, $p=0.02$), and preoperative albumin ≤3.5 gm/dl (43% vs. 22%, $p=0.02$). Mortality was nil. Overall morbidity was 37% with anastomotic leak 4%. Neither was affected by stoma diversion, laparoscopy use, or sigmoid colon treatment.
Conclusions While most ISF in CD are found preoperatively, some are still incidental surgical findings. Sigmoid resection and primary repair have comparable morbidity if appropriately individualized. Laparoscopic treatment is acceptable in select cases without added morbidity.

Keywords Crohn's disease · Intestinal fistula · Ileal disease · Surgery

Introduction

Fistula development in patients with Crohn's disease (CD) is common and often associated with a more aggressive natural history of disease. Among patients that have an ileocolonic distribution of disease, approximately a third will have an internal or enterocutaneous fistula, with a large minority of these having a component to the sigmoid colon.[1] Overall, fistulas between diseased terminal ileum and the sigmoid colon represent 15% to 30% of patients with internal fistulas[1,2] and approximately 5% of all patients presenting with Crohn's disease.[2,3]

While ileosigmoid fistulas (ISF) in CD are relatively common and surgery is considered to be the mainstay of treatment, historically, their management has been challenging[4,5] with only few recent reports characterizing

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contemporary outcomes.[6,7] The complexity of ISF in CD is in no small part because ISF often occurs in conjunction with more extensive disease including additional small bowel or colonic locations, fistulization to bladder or other bowel segments, or enterocutaneous fistula. Moreover, preoperative diagnostic studies have traditionally been inaccurate, and while the majority of ISF are found preoperatively, it is not uncommon for an ISF to be discovered only at the time of surgery. Expanded uses of laparoscopy in the treatment of ISF have also yet to be formally examined.

In this study, we sought to provide an updated experience of surgical treatment of ISF in CD at a tertiary referral center specializing in inflammatory bowel disease, focusing on the diagnostic work-up and operative management of this condition. In particular, we wished to elucidate the value of diagnostic studies in establishing the preoperative diagnosis of ISF, appropriate use of resection versus primary repair of the sigmoid colon, and outcomes of laparoscopic treatment in a modern cohort.

Materials and Methods

The Cleveland Clinic Department of Colorectal Surgery prospectively maintained database of CD patients was used to identify all patients with operative treatment of an ISF from 2000 through 2007 and a retrospective study of these patients was conducted. This database has Institutional Research Board approval and is HIPAA-complaint in design. Database variables included patient demographics, duration and extent of disease, previous surgical procedures, and preoperative histopathologic diagnosis. Other recorded outcome measures were surgical procedure details, length of hospital stay, postoperative histopathologic diagnosis, and postoperative complications. A retrospective chart review was conducted to verify preoperative diagnostic study results, concurrent medication use, smoking status, and use of colonoscopy preoperatively or intraoperatively.

Computed tomography (CT) scan was performed using traditional CT scan or CT enterography protocols as previously reported at our institution in CD patients.[8] CT scan radiographic reports were reviewed retrospectively. Findings on CT scan in the terminal ileum, cecum, or sigmoid were classified into the following categories: “fistula” (including suspicion of fistula), “stranding or phlegmon”, and “abscess”. Prior to the availability of CT enterography, patients also commonly underwent fluoroscopic evaluation with a small bowel series or contrast enema. These studies were categorized as “positive” or “negative” for the presence of a fistula. For the purposes of this study, the objective findings on colonoscopy of the sigmoid were included in the analysis and not comments stating that there was a “suspicion” for ISF. Colonoscopies were considered normal or had findings in the sigmoid colon which included: “fistula”, “pseudopolyp”, “erythema”, or “stricture”. Colonoscopies with a “fistula” or “pseudopolyp” were considered clinically positive for detection of the ISF for the purposes of analysis.

Overall length of hospital stay included any postoperative readmission or stoma reversal when applicable. Surgical cases initially started as laparoscopic procedures and subsequently converted to open were considered for the purposes of this study as laparoscopic procedures in an intent-to-treat analysis. We also performed a separate analysis treating converted laparoscopic cases as open, as the majority of the case was performed open. Because of the retrospective nature of this study and variations in reporting of the operative and pathologic data, we were unable to consistently identify the size and location of the fistulous opening on the sigmoid colon. Perioperative morbidity and mortality were assessed at 30 days or during same postoperative hospital stay. An ileus was defined as any delay in bowel function for at least 5 days, need for readmission, placement of a nasogastric tube, or if documented in the postoperative period by the surgical team. Medication use was assessed with chart review. Preoperative CD medication use included concurrent use of the medication up to the time of hospitalization or within 30 days of surgery and for Remicade up to 90 days within surgery.

Statistics were obtained using established methods. Statistical significance was accepted for $P<0.05$. Unadjusted bivariate comparisons of continuous variables were performed using the Mann–Whitney rank sum test and comparisons of categorical variables were performed using a χ^2 test. Data are expressed as medians with ranges as appropriate.

Results

Overall, 104 of 1,353 patients with CD who underwent a major abdominal operation over the study period had ISF (55 females, median age 37 (range 18–78) years) (Table 1). With respect to individual surgeon, three of ten surgeons performed both laparoscopic and open approaches with the remainder using an open approach exclusively. The median length of disease of the cohort was 9 (range 0–39) years, with three patients having ISF at the time of their initial clinical presentation of CD. A total of 35 patients (34%) were current smokers and ten (10%) had a history of or current perianal disease. While seven (70%) had resolution of perianal disease at the time of surgery, three (30%) patients had concurrent perianal disease. One patient with a superficial fistula in ano received no treatment at the time

Table 1 Patient Demographics and Crohn's Disease Distribution

Factor	No.
Total	104 (100%)
Female	55 (53%)
Age, median (range) in years	37 (18–78)
Length of CD, median (range) in years	9 (0–39)
Smoking status	
Never	64 (61%)
Current	35 (34%)
Prior	5 (5%)
Albumin ≤3.5 gm/dl	34 (33%)
Current medical treatments	
Infliximab	18 (17%)
Corticosteroids (any)	58 (55%)
Corticosteriods (prednisone ≥20 mg/day)	30 (29%)
Imuran	21 (20%)
Previous laparotomy within 12 months	6 (6%)
Previous or current perianal disease	10 (10%)
Other intra-abdominal fistulous disease	38 (37%)
Ileovesical fistula	11 (11%)
Enterocutaneous fistula	11 (11%)
Other small bowel disease	22 (21%)
Other colonic disease	7 (7%)

of ISF surgery; another with an anorectal stricture underwent dilatation at the time of surgery, and a final patient with a fistula in ano underwent a seton change at the time of surgical treatment of their ISF. Additional synchronous distribution of disease included ileovesical fistula in 11% (11), enterocutaneous fistula in 11% (11), other small bowel disease in 22 (21), and other colonic disease in 7% (seven). Primary presenting clinical symptom or feature was pain, 42 (40%); obstruction, 17 (16%); weight loss, 11 (11%); enterocutaneous fistula, 11 (11%); pneumaturia, nine (9%); abscess, five (5%); bloody stools or diarrhea, six (6%); colonic stricture, two (2%); and fevers, one (1%).

The performances of diagnostic modalities for detecting ISF are summarized in Table 2. Colonoscopy was performed in 89 (86%) patients either as part of the preoperative evaluation, 81 (91%) or as a planned intraoperative component secondary to suspicion of ISF or sigmoid Crohn's colitis, eight (9%). Colonoscopic evaluation of the sigmoid colon was reported as normal in 34 (38%) patients. Findings in the sigmoid colon on colonoscopy included presence of a fistula in ten (11%), erythema in 17 (19%), pseudopolyp in 17 (19%), erythema and pseudopolyp in four (4%), and stricture in seven (8%). CT scan and fluoroscopic contrast studies were able to detect a fistula in 41% (31/76) and 53% (31/58) cases respectively. Of 76 CT scans performed, 36% (27/76) used CT enterography, which was not associated with any statistical difference in ISF detection rates compared to traditional abdominal CT scan protocols (55% (15/27) versus 33% (16/49), $p=0.09$). The combination of all diagnostic studies resulted in preoperative detection of ISF in 66 (63%) patients.

Operative management of the cohort is summarized in Table 3. While most operations used an open approach, 29 (28%) cases started laparoscopically with two patients (7%) requiring conversion to an open procedure both due to complex anatomy and difficulty with completing laparoscopic mobilization for a total of 27 (26%) completed laparoscopic cases. The vast majority of cases (93%, 97 patients) were treated with ileocolic resection combined with primary repair of the sigmoid fistula or sigmoid resection but with preservation of the remaining colon. On the other hand, a small minority (7%, 7 patients) underwent subtotal colectomy in continuity due to more extensive colonic disease. Management of the sigmoid colon was at the discretion of the operating surgeon and included primary repair in 26 patients (25%) and segmental resection in 71 cases (68%). Pathologic examination of the surgical specimen revealed that individuals with histological evidence of CD of their sigmoid colon (36/97, 37%) were more likely to have undergone a segmental sigmoid resection rather than primary repair (45% vs. 16%, $p=0.02$). There were no differences in rates of stoma creation, use of laparoscopic or open surgery, preoperative diagnosis of ISF, rates of small bowel disease requiring surgery, presence of intraoperative phlegmon or abscess, or overall length of stay (LOS) in patients with primary repair versus those with segmental sigmoid resection.

Table 2 Sensitivity of Diagnostic Studies in the Preoperative Detection of Ileosigmoid Fistula

Test	Positive findings (%)
Colonoscopy (fistula)	10/89 (11)
Colonoscopy (fistula or pseudopolyp)	31/89 (35)
Colonoscopy (fistula, pseudopolyp, or erythema)	48/89 (54)
CT scan (fistula seen)	31/76 (41)
CT scan (abscess, phlegmon, or stranding)	59/76 (78)
Fluoroscopic contrast studies	31/58 (53)
Combined tests[a]	66/104 (63)

[a] Colonoscopy (fistula or pseudopolyp) or CT scan (fistula seen) or fluoroscopic contrast studies

Table 3 Operative Management of Patients with Ileosigmoid Fistula and Crohn's Disease

	No.
Approach	
Open	75 (72%)
Laparoscopic attempt	29 (28%)
Laparoscopic completed	27 (26%)
Ileal disease	
Ileocolic resection	97 (93%)
Subtotal colectomy with terminal ileum resection	7 (7%)
Sigmoid colon	
Primary repair/wedge resection	26 (25%)
Segmental resection	71 (68%)
Subtotal colectomy	7 (7%)
Additional small bowel disease	
Resection	15 (14%)
Strictureplasty	5 (5%)
Both resection and strictureplasty	2 (2%)
Protective ileostomy	53 (51%)
Ureteral stents	16 (15%)
Overall length of stay, median (range) in days	8 (2–31)
Primary length of stay, median (range) in days	6 (2–31)

Additional synchronous small bowel disease was managed with resection in 15 patients (14%), strictureplasty in five (5%), or both in two cases (2%). All bladder fistulas were managed with primary bladder repair. No patients required a permanent stoma in this series. Protective stoma was used in 53 (51%) patients and the median overall length of stay was 8 (range 2–31) days. Patients undergoing creation of protective stomas were more likely to have open resection (83% vs. 65%, $p=0.03$), small bowel disease requiring additional surgical intervention (30% vs. 12%, $p=0.03$), placement of intraoperative ureteral stents (28% vs. 2%, $p<0.0001$), longer overall LOS (median 10 vs. 6 days, $p<0.0001$), preoperative steroid use ≥20 mg prednisone (40% vs. 18%, $p=0.02$), and preoperative albumin ≤3.5 gm/dl (43% vs. 22%, $p=0.02$) (Table 4).

While patients with a laparoscopic approach had lower rates of stoma creation (34% vs. 57%, $p=0.04$), there were no differences in use of intraoperative ureteral stents, rates of additional small bowel disease requiring surgical treatment, overall length of stay, treatment of the sigmoid colon, preoperative diagnosis of ISF, or findings of an intraoperative phlegmon or abscess (Table 5). When treating converted laparoscopic procedures as open procedures in a separate analysis, there remained a lower rate of stoma creation (33% vs. 57%, $p=0.03$); additionally, there was a lower rate of small bowel disease requiring resection/strictureplasty (15% vs. 36%, $p=0.03$). Other factors were similar. When performing a subgroup analysis among open and laparoscopic procedures performed by laparoscopic surgeons, there were a total of seven open cases performed by laparoscopic surgeons. Similar to the comparisons made with open procedures overall, laparoscopic procedures had lower rates of stoma creation (100% vs. 34%, $p=0.002$) and additional small bowel disease requiring resection/strictureplasty (57% vs. 17%, $p=0.02$), but were similar with respect to intraoperative ureteral stents use, overall length of stay, preoperative diagnosis of ISF, and findings of intraoperative phlegmon or abscess.

There were no deaths, and overall per-patient morbidity was 37% (Table 6). Surgical site infection rate was 16% (anastomotic leak, four (4%); wound infection, eight (8%); abdominopelvic abscess, eight (8%)). Of the four anastomotic leaks, three were located at the ileocolic site and one was at the sigmoid resection colorectal anastomosis. In addition to elective stoma takedown, a total of six (6%) patients required hospital readmission because of postoperative ileus. Rates of overall morbidity, surgical site infection, and anastomotic leak were not associated with stoma diversion, use of laparoscopic technique, treatment of the sigmoid colon with resection vs. primary closure,

Table 4 Use of Protective Stoma

	Stoma ($n=53$)	No. stoma ($n=51$)	p value
Sigmoid colon resection or subtotal colectomy	81% (43)	69% (35)	NS
Open surgical approach	81% (43)	64% (32)	0.04
Preoperative ISF diagnosis	66% (35)	61% (31)	NS
Small bowel disease with strictureplasty or resection	30% (16)	12% (6)	0.03
Intraoperative phlegmon or abscess	64% (34)	53% (27)	NS
Intraoperative ureteral stents	28% (15)	2% (1)	<0.0001
Overall length of stay[a], median (range) in days	10 (4–29)	6 (2–31)	<0.0001
Preoperative use Remicade (≤90 days)	21% (11)	14% (7)	NS
Preoperative use steroids (≥20 mg prednisone)	40% (21)	18% (9)	0.02
Preoperative albumin <3.5 gm/dl	43% (23)	22% (11)	0.02
Previous laparotomy within 12 months	9% (5)	2% (1)	NS

ISF ileosigmoid fistula, *NS* not significant

[a] Overall length of stay included any postoperative readmission or hospital days associated with stoma takedown

Table 5 Use of Laparoscopy

	Open (n=75)	Laparoscopic (n=29)	p value
Sigmoid colon resection or subtotal colectomy	72% (54)	83% (24)	NS
Covering stoma	57% (43)	34% (10)	0.04
Preoperative ISF diagnosis	64% (47)	62% (18)	NS
Small bowel disease with resection/strictureplasty	35% (26)	17% (5)	NS
Intraoperative phlegmon or abscess	61% (46)	52% (15)	NS
Intraoperative ureteral stents	17% (13)	10% (3)	NS
Overall length of stay[a], median (range) in days	8 (4–29)	7 (2–31)	NS

ISF ileosigmoid fistula, *NS* not significant

[a] Overall length of stay included any postoperative readmission or hospital days associated with stoma takedown

concurrent medication use (steroids, Remicade, or Imuran), or smoking status.

Discussion

We report on a large modern cohort of CD patients with ISF undergoing surgical treatment over an 8-year period at a tertiary referral center specializing in inflammatory bowel disease. We intentionally selected a study period limited to patients treated in the year 2000 or later when the role of laparoscopic treatment of CD is widely accepted and modern diagnostic modalities are routinely available. This study focuses on important unresolved issues in contemporary surgical management, including use of laparoscopy, outcomes following resection or repair of the sigmoid colon, and the efficacy of current diagnostic modalities. Despite the addition of CT enterography as a diagnostic tool, ISF remains an often incidental surgical finding. We observed comparable morbidity of sigmoid resection and primary sigmoid repair. Laparoscopic treatment also appeared to have comparable outcomes to open surgery and was associated with less use of diverting stoma.

Diagnostic modalities have been historically poor for the detection of ISF, with the largest recent series reporting a detection rate of 77%.[6] Another large study by Michelassi et al. which included all types of enteric and colorectal fistulas in CD, preoperative diagnosis of the fistula was achieved in 69% of patients.[9] Despite the availability of multiple complementary studies for detection, only 63% of ISF patients in our cohort had studies providing preoperative knowledge of the ISF. CT enterography has been demonstrated to add diagnostic value in the setting of CD,[8] and MRI enterography has been used with some success compared to small bowel series for CD.[10] In spite of the increasing availability of the state of the art in diagnostic imaging, our results still underline the need for improved diagnostic methods for ISF detection, as well as the importance of intraoperative assessment of the bowel and the importance of a high degree of suspicion for associated disease.

Table 6 Morbidity of Surgical Treatment for ISF in CD

	No.
Mortality	0 (0)
Overall morbidity per patient	38 (37)
Surgical site infection per patient	17 (16)
Anastomotic leak	4 (4)
Wound infection	8 (8)
Abscess	8 (8)
Ileus	22 (20)
Bleeding, requiring perioperative transfusion	7 (7)

The presence of concurrent CD manifestations in the setting of ISF is well documented in previous reports. An early series by Broe and Cameron of ISF in CD reported perianal disease in 6%, enterovesical fistula in 24%, and enterocutaneous fistula in 6%.[2] While the current series of ISF demonstrated enterovesical fistula in 11%, a previous study observed rates of concomitant bladder fistula as high as 30% in patients with ISF.[11] A separate study from the same group in the early 1980s demonstrated additional fistula in 56% of patients, including bladder (17%), enterocutaneous (15%), and enteroenteric (27%).[12] Our overall rate of synchronous disease while still significant might be reduced compared to previous series because of a greater awareness of the complications of Crohn's disease in a contemporary cohort and a more rapid referral for surgery after failure of medical management before extensive fistulization can occur.

Previous series have given conflicting recommendations in the management of the sigmoid colon. In an earlier report from our institution, sigmoid resection was used almost exclusively.[4] A primary criticism of this group of patients was that a substantial number were malnourished and a covering stoma was often created. Several other authors have advocated primary repair of the sigmoid colon and have reported satisfactory results after primary repair of the sigmoid colon.[12,13] In contrast, repair and resection were equally used with comparable morbidity in a large series reported by Young-Fadok et al.,[6] encompassing 90 CD patients with ISF treated over a 20-year period. The majority of patients in our study still required segmental

resection of the sigmoid colon. In general, a sigmoid colon with extensive inflammatory changes also involving the mesocolon would be poorly suited for a primary repair. It is therefore not surprising that in our series patients with sigmoid resection were significantly more likely to have histopathologic evidence of CD of the sigmoid colon. However, when the sigmoid colon is minimally involved and is only the target organ of the fistula originating from the ileocolic CD, a double resection may be unnecessary and the patient can be well served with an ileocolic resection and primary repair of the sigmoid fistula. In patients selected on the basis of the above-mentioned criteria, we encountered no difference in morbidity when comparing resection versus primary repair of the sigmoid colon. Overall, operative decision-making for the sigmoid colon should consider the presence or absence of Crohn's sigmoid colitis, location of the fistula (mesenteric border), size of the fistula defect, and presence of concomitant surrounding inflammation or infection.

With respect to use of protective stomas, some authors previously reported using a loop colostomy to cover the sigmoid colon.[2,12] In contrast, Young-Fadok and colleagues commented that ISF was never directly responsible for stoma creation, which rather depended on the incidence and management of concurrent CD (other fistulas or synchronous small bowel disease) and details of protective stoma use were not explicitly reported. We commonly use protective stomas in the operative management of complicated CD. Creation of protective stomas was associated with other small bowel disease requiring operative treatment, use of intraoperative ureteral stents, longer overall LOS, an open operative approach, malnutrition, and high-dose steroids. Although not statistically significant, we also observed more stoma creation with preoperative use of Remicade and recent laparotomy within the past 12 months. At our institution, when a protective stoma is created, it is typically placed proximal to all areas of resection, strictureplasty, or repair. Our practice is to use a covering stoma in cases of malnutrition, previous failure with operative treatment due to surgical complications or failure to control CD, preoperative use of Remicade or high-dose steroids (>20 mg prednisone), extensive small bowel disease, or extensive fistulization. Similar to the philosophy of Young-Fadok and colleagues, the presence of a fistula to the sigmoid colon is not directly responsible for protective stoma creation. We observed similar rates of morbidity in patients with and without protective stomas.

While a majority of patients had an open procedure, over a quarter of patients underwent a laparoscopic approach. In all but two cases, the procedure was successfully completed laparoscopically with no observed differences in morbidity compared to open surgery, which compares favorably to previous studies in CD that have demonstrated conversion rates from 4–40% often in the setting of concurrent fistulous disease.[14–17] Comparisons between laparoscopic and open surgery are difficult to make based on our data, as there were a number of different operating surgeons not all of which perform laparoscopic surgery. As more surgeons perform laparoscopic procedures in the future, follow-up studies may have less bias with respect to operating surgeon and more meaningful comparisons between open and laparoscopic techniques may be possible. We observed that the rate of sigmoid resection was higher in the laparoscopic group versus the open group. It is unclear from our retrospective study the exact reason that more resections were performed instead of primary repair. Theoretically, with full medialization of the descending and sigmoid colon, primary repair should remain technically feasible even with a laparoscopic approach. In addition, while it was not possible to determine the extent of inflammation from this retrospective analysis consistently, ISF in CD can be associated with a variable degree of inflammatory changes and additional manifestations of CD which all affect the overall complexity of surgical treatment. While only the stoma creation rates and small bowel resection rates were significantly less common in the laparoscopic group, the absolute rates of intraoperative findings of abscess or phlegmon might suggest that more complex patients were generally treated using open technique. However, over 50% of patients treated laparoscopically had phlegmons or abscesses and the absolute rates of sigmoid colon resection were higher in patients treated laparoscopically, thus showing that laparoscopic surgery can still succeed even in a complex condition such as CD-related ISF. Our data therefore suggest that the laparoscopic surgical approach remains feasible in the appropriate patients. The appropriate selection of patients for laparoscopic surgery might allow retention of the recovery benefits associated with laparoscopic surgery at the same time minimizing conversion rates.

While our study provides significant information about current outcomes of CD patients with ISF, it also has several limitations. First, because of the retrospective nature of the study, we were unable to uniformly ascertain the exact factors which contributed to surgical decision-making, particularly with respect to the use of covering stoma and treatment of the sigmoid colon. Furthermore, we do not have any information with respect to patients with ISF and CD that did not require operative treatment. Finally, long-term outcomes after operative repair in our cohort are not included in this study.

Similarly to all operative treatments of CD, treatment of ISF in CD must ultimately be appropriately individualized to the patient and their disease. Resection of ileocolic disease is the standard of care and treatment of the sigmoid colon should be tailored to the presence or absence of

Crohn's sigmoid colitis, fistula location (mesenteric border), fistula defect size, and presence of inflammation or infection. Covering stomas are also appropriate in cases of complicated CD and patients with high risk for anastomotic complications (malnutrition, use of immunosuppressive medications, and intra-abdominal sepsis). In select patients, the laparoscopic approach appears to be satisfactory and technically feasible.

Conclusions

ISF in CD remains a challenging clinical entity to diagnose and manage. ISF often occurs in conjunction with additional distribution of CD and some are still incidental surgical findings. Sigmoid resection and primary sigmoid repair have comparable morbidity if appropriately individualized. Laparoscopic treatment is acceptable in select cases and may allow reduction in diverting stoma rates with similar morbidity.

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ORIGINAL ARTICLE

MicroRNA-143 and -205 Expression in Neosquamous Esophageal Epithelium Following Argon Plasma Ablation of Barrett's Esophagus

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Abstract
Introduction Ablation of Barrett's esophagus using Argon plasma coagulation (APC) is usually followed by the formation of a neosquamous epithelium. Investigating simple columnar or stratified squamous epithelium associated cytokeratin and microRNA (miRNA) expression in neo-squamous epithelium could help determine the identity and stability of the neosquamous epithelium.
Methods Nine patients underwent ablation of Barrett's esophagus with APC. Biopsies were collected from Barrett's esophagus mucosa and proximal normal squamous epithelium before ablation, and from neosquamous and normal squamous epithelium after ablation. Additional esophageal mucosal biopsies from ten nonrefluxing subjects were used as a reference. RNA was extracted and real-time polymerase chain reaction was used to measure the expression of the cytokeratins CK-8 and CK-14 and the microRNAs miR-143 and miR-205.
Results CK-8 and miR-143 expression were significantly higher in Barrett's esophagus mucosa, compared to neosquamous and normal squamous epithelium before and after APC, whereas miRNA-205 and CK-14 expression was significantly lower in Barrett's esophagus mucosa compared to all categories of squamous mucosa. The expression of CK-8, CK-14, miR-205, and miR-143 was similar between neosquamous epithelium compared to normal squamous epithelium in patients with Barrett's esophagus. Only miR-143 expression was significantly higher in neosquamous and normal squamous epithelium before and after APC compared to normal squamous epithelium from control subjects ($p<0.004$).
Conclusions The expression levels of cytokeratins and miRNAs studied in post-ablation neosquamous epithelium and normal squamous epithelium in patients with Barrett's esophagus are similar. In patients with Barrett's esophagus, miR-143 expression is still elevated in both neosquamous mucosa, and the squamous mucosa above the metaplastic segment, suggesting that this mucosa may not be normal; i.e., it is different to that seen in subjects without Barrett's esophagus. miR-143 could promote a Barrett's epithelium gene expression pattern, and this could have a role in development of Barrett's esophagus.

Keywords Barrett's esophagus · Ablation · MicroRNA · Gene expression

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Introduction

Barrett's esophagus develops in some individuals with chronic gastroesophageal reflux disease. It is characterized by the presence of columnar-lined epithelium with intestinal metaplasia in the distal esophagus, and it is associated with an increased risk of developing esophageal adenocarcinoma.[1] Hence, it is current practice for individuals with Barrett's esophagus to undergo endoscopic surveillance, although under some circumstances, ablation of the metaplastic mucosa is undertaken.

We have previously reported clinical outcomes from a randomized trial of argon plasma coagulation (APC) ablation of Barrett's esophagus versus endoscopic surveillance.[2,3] Although ablation induced neosquamous epithelium, the effect on cancer risk remains unknown, although some studies have shown that metaplastic epithelium can recur, and cancer can develop, after apparent complete eradication by APC.[4–7]. Biomarkers might assist clinical decision making for Barrett's esophagus and inform the potential clinical behavior of mucosa after ablative therapy. Abnormal proliferation and p53 staining has been detected in squamous islands after incomplete ablation of Barrett's esophagus.[8,9] Other studies have identified that neosquamous epithelium can still harbor genetic abnormalities, e.g., deletion of p16 gene sequence, and some of these abnormalities are similar to those present in Barrett's esophagus epithelium before ablation.[10,11] These studies have focused on DNA and protein biomarkers associated with neoplastic progression of Barrett's epithelium, rather than gene expression biomarkers that distinguish squamous from columnar cell types. This is potentially limiting, as gene-expression biomarkers of squamous and columnar cell types may be more sensitive than cancer-associated markers for early detection of recurrence of Barrett's epithelium in neosquamous epithelium.

Cytokeratins are potential markers of epithelial differentiation, CK-14 being a basal cell marker in stratified squamous epithelium, and CK-8 a marker of simple columnar epithelium.[12–15] Hence, CK-14 and CK-8 expression in post-ablation neosquamous epithelium could add useful information about the nature of regenerated epithelium after ablation of Barrett's esophagus. Other potential biomarkers are MicroRNAs (miRNA). These are 20–22 nucleotide segments of nonprotein-coding RNA,[16–18] which regulate the expression of many genes, and they can be used to classify some cancers.[19] They have key roles in establishing and maintaining tissue-specific gene expression profiles, and altering the expression of a single miRNA in a cell is sufficient to shift the gene expression profile from one epithelial cell type to another.[20] MiR-205 is highly expressed in esophageal squamous epithelium,, and it is an excellent discriminator between esophageal squamous vs metaplastic epithelium,[21,22] and miR-143 is expressed in columnar mucosa, including Barrett's esophagus.[21,22]

Hence, cytokeratins and miRNAs might be useful markers for investigating the status of neosquamous epithelium after ablation of Barrett's esophagus, and in this study, we investigated regenerated neosquamous epithelium after ablative therapy using the cytokeratins -8, -14, and miRNAs -143 and -205.

Materials and Methods

Nine patients with Barrett's esophagus who underwent ablation of the metaplastic mucosa with APC were included in this study. Barrett's esophagus was defined as columnar epithelium in the esophagus with histologically proven evidence of intestinal metaplasia. All patients were actively treated for gastroesophageal reflux, six by a laparoscopic fundoplication, and three by high-dose proton pump inhibitor therapy. In all patients, reflux symptoms were fully controlled at entry into the study according to the following criteria: (1) no reflux symptoms, and an intact fundoplication at endoscopy or (2) no reflux symptoms, consuming regular PPI medication, and no esophagitis at endoscopy.

All patients underwent baseline endoscopy. Biopsies of the esophageal mucosa were collected (see below) and assessed by conventional histopathological techniques. In all patients, this confirmed intestinal metaplasia within the Barrett's esophagus segment. In addition, changes consistent with low-grade dysplasia (LGD) were also present in two of the patients. The length of the Barrett's esophagus segment ranged from 1 to 10 cm in length.

Following baseline endoscopy, all patients underwent ablation treatment with APC as previously described.[2] Complete ablation of the columnar epithelium was attempted at the first endoscopy in patients with segments of Barrett's esophagus which were less than 3 cm in length. The treatment of long segments of Barrett's esophagus was limited to 50% of the circumference of the esophagus, up to a maximum length of 5 cm in each single treatment session. Treatment was repeated every 4 weeks until either complete (or at least 95%) squamous re-epithelialization had occurred. The number of APC treatments varied from 1 to 5. Complete regression was achieved in three patients, and in six patients, there was greater than 95% regression. Four to 6 weeks after the last treatment, a further endoscopy was performed, and biopsies were taken from the same sites as the previously collected biopsies.

Biopsy Collection

At the initial endoscopy, biopsies were collected from the metaplastic columnar mucosa. Within the Barrett's esophagus segment, biopsies were collected 1 cm above the gastroesoph-

ageal junction, and then proximally every 2 cm for the length of the Barrett's esophagus. At each level, four biopsies were collected (one from each quadrant) and processed for conventional histopathology. An additional three biopsies were collected from each level of Barrett's esophagus for this research study. These biopsies were placed immediately into RNAlater® (Ambion, Austin, TX, USA) for storage using the manufacturer's protocol, and then stored at −20°C until required. An additional three biopsies were taken (and placed into RNAlater®) from the squamous esophageal mucosa, above the Barrett's esophagus segment, 5 cm proximal to the squamo-columnar junction.

One month following APC ablation, further biopsies were collected from the esophagus using the same tissue collection protocol. Biopsies (four fixed in formalin, and three in RNAlater®) were collected from the same esophageal levels that were sampled before the Barrett's esophagus was ablated. Three biopsies were also collected from the normal esophageal mucosa 5 cm above the gastroesophageal junction in an additional ten patients who did not have any known esophageal disease. These patients all met the following criteria: (1) no reflux symptoms, (2) endoscopy was not undertaken for the investigation of reflux, (3) no esophagitis at endoscopy, (4) gastroesophageal junction was closed when viewed from within the esophagus, and (5) gastroesophageal junction was snug around endoscope when viewed by the retroflexed endoscope. The biopsies from the esophagus in these patients were used as controls in this study.

For this study, three biopsies (stored in RNAlater®) from each of the following sites were selected for each patient with Barrett's esophagus:

1. Pre-ablation metaplastic columnar mucosa (with intestinal metaplasia), 1 cm above the gastroesophageal junction (i.e., the biopsied level which was closest to the gastroesophageal junction at which intestinal metaplasia was confirmed to be present).
2. Pre-ablation squamous mucosa, 5 cm above the squamo-columnar junction
3. Post-ablation neosquamous mucosa, 1 cm above the gastroesophageal junction.
4. Post-ablation squamous mucosa, 5 cm above the level of the pre-ablation squamo-columnar junction

The microscopic appearances of the biopsies that were fixed in formalin and then processed using conventional histopathology techniques were used to guide the selection of the appropriate biopsies from those that had been collected in RNAlater®.

Biopsy Processing and RNA Extraction

When required, the RNAlater®-stored biopsies were thawed, and the RNAlater® was removed. A small piece (20% to 30%) of the biopsy tissue was then removed from each biopsy sample, placed in formalin, and assessed using routine histochemical and histopathological methods to ensure that the tissue of origin was correctly identified.

The remainder of the biopsy was used for gene expression analysis. It was transferred to a 1.5 mL snap-top tube containing 500 μL of TRIzol® (Invitrogen Life Technologies, NY, USA). Tissue was homogenized using a plastic pestle attached to a Dremmel® MultiPro™ drill, and total RNA was extracted according to the manufacturer's protocol. The concentration of RNA was determined using a Biophotometer (Eppendorf®, North America, Westbury, USA). RNA quality was determined by electrophoresis through a 1% agarose gel. All RNA samples were confirmed to be undegraded by visualization of distinct 28S and 18S rRNA species. The final RNA solution was stored at −80°C until required for cDNA synthesis.

DNAse treatment of total RNA was performed prior to reverse transcription in order to minimize polymerase chain reaction (PCR) signal arising from carry-over genomic DNA. The Ambion DNAfree™ kit was used. To 1 μg of each RNA sample, i.e. (5 μL of 200 ng/μL RNA), 2 μL of UPW, 1 μL 10× DNase 1 Buffer, 1 μL tRNA (2.5 μg/μL), and 1 μL r-DNA-se I was added. After a quick spin, the samples were incubated for 30 min at 37°C in an Eppendorf® Mastercycler. Two microliters of DNA-se inactivation reagent was added to a total volume of 12 μL in each tube, and the samples were centrifuged at 10,000 rpm for 5 min.

Real Time RT-PCR for Cytokeratin and β-actin

Each reaction received 1 μL dNTP's (10 μM), 1 μL pd (N)6 (250 ng/μL), and 10 μL of RNA. After incubation at 65°C for 5 min, a mastermix consisting of 4 μL 5× First Strand Buffer, 2 μL 0.1 M DTT, 1 μL sterile H_2O, and 1 μL Superscript III reverse transcriptase (200 U/μL) was added. After another incubation, 380 μL of H_2O was added to each sample tube, bringing the final volume of reverse transcription (RT) product to 400 μL. Negative control reactions (the same RT treatment without Superscript III) were included to confirm absence of genomic DNA contamination.

All cytokeratin and β-actin PCR reactions were done on a Rotorgene 6000 machine (Corbett Life Sciences; Sydney, NSW, Australia), using the fluorescence-based real-time detection method. With regard to the cytokeratin and β-actin PCR, each 20 μL reaction consisted of 10 μL 2×QuantiTect™ SYBR®Green mix (Qiagen, Germany), 2 μL forward primer, 2 μL reverse primer, 3 μL water, and 3 μL RT-product. After activation at 95°for 15 min, the PCR cycling conditions (45 cycles) for the cytokeratin -8, -14, and β-actin consisted of a denaturing phase (95° for 20 s), an annealing phase (60°, 54°, and 60°, respectively,

for 20 s) and an extension phase (72° for 20 s). The following primer sequences were used:

CK-8: forward primer 5[1]-AGC GTA CAG AGA TGG AGA AC-3[1], reverse primer 5[1]-TGA GGA AGT TGA TCT CGT CG-3[1]
CK-14: forward primer 5[1]-ACG ATG GCA AGG TGG TGT-3[1], reverse primer 5[1]-GGG ATC TTC CAG TGG GAT CT-3[1]
β-actin: forward primer 5[1]-TTG CCG ACA GGA TGC AGA AG-3[1], reverse primer 5[1]-GCC GAT CCA CAC GGA GTA CT-3[1]

The samples were assayed in triplicate, and β-actin acted as a housekeeping gene for normalizing gene expression levels. Identical positive control samples were included in every run to ensure accurate comparison of results across multiple runs.

Real Time RT-PCR for miR-143, miR-205 and RNU6B

Expression of selected miRNAs was quantified using TaqMan miRNA assays to detect only the mature (active) form of the miRNAs. Five nanograms of total RNA was reverse transcribed into cDNA using gene-specific primers according to the TaqMan miRNA Assay protocol (Applied Biosystems, Foster City, CA, USA). The part numbers of the assays used were 4373143 (hsa-miR-143) and 4373381 (RNU6B), 4373093 (hsa-miR-205). Reverse transcriptase reactions contained 5 ng of RNA sample, 100 nM stem-loop RT primer, 100 mM of dNTPs, 50 U/μL Multiscribe reverse transcriptase, 20 U/μL RNase inhibitor, 1.5 μL 10× RT Buffer (all purchased from Applied Biosystems;) and Nuclease-free water. The 15-μL reactions were incubated in a Thermocycler (Eppendorf Mastercycler, Eppendorf, North Ryde, NSW, Australia) in 0.5 ml tubes for 30 min at 16°C, 30 min at 42°C, 5 min at 85°C and then held at 4°C.

Real-time PCR was performed using a Rotorgene 6000 cycler. The 20 μL PCR reaction included 5 μL RT product, 1 μL of primers, 10 μL 2×QuantiTect™ Probe mix (Qiagen, Germany), and 4 μL of UltraPure H_2O. After activation at 95° for 15 min, the PCR conditions (45 cycles) for miR-143, -205, and RNU6B all consisted of a denaturing phase (95° for 15 s), and a combined annealing and extension phase (60° for 30 s).

Triplicate reactions were performed on all samples. Quantitative real-time RT-PCR analysis was then performed using Q-Gene software.[23] The small nuclear RNA, RNU6B (Applied Biosystems; part number 4373381), was used as a housekeeping gene to normalize miR-143 and -205 expression levels. Identical positive control samples were included in every run to ensure accurate comparison of results across multiple runs.

Statistical Analysis

The steady-state levels of each biomarker for each individual biopsy were determined. For each biomarker, the mean expression level for each tissue type (derived

Table 1 Expression Levels for CK8, CK14, miR-143, and miR-205 for all Tissue Types

	Pre-ablation Barrett's esophagus	Pre-ablation squamous mucosa	Post-ablation neosquamous mucosa	Post-ablation normal squamous mucosa	Control squamous mucosa	*p* Value
CK-8	0.93 (0.57, 1.27)	0.0060 (0.003, 0.011)	0.0060 (0.002, 0.014)	0.0050 (-0.001, 0.021)	0.0040 (0.003, 0.005)	*A*=0.0008* *b*=0.554
CK-14	0.5 (−3.49, 12.60)	2.50 (−4.46, 22.43)	5.96 (−2.63, 34.13)	5.51 (3.18, 8.26)	3.51 (2.09, 4.88)	*A*=0.019** *b*=0.198
miR-143	0.96 (0.53, 1.44)	0.069 (−0.012, 0.41)	0.11 (0.054, 0.28)	0.15 (-0.70, 2.33)	0.023 (0.014, 0.042)	*a*=0.006*** *b*=0.004τ
miR-205	0.003 (−0.28, 1.09)	1.13 (0.67, 3.14)	1.00 (0.73, 1.61)	1.42 (0.80, 3.27)	0.92 (0.80, 1.38)	*a*=0.004ττ *b*=0.449

All figures are median (95% confidence intervals)
a comparison of pre-ablation Barrett's esophagus vs. pre-ablation squamous vs. post-ablation neosquamous vs. post-ablation proximal squamous mucosa using the Friedman test
b comparison of pre-ablation squamous vs. post-ablation neosquamous vs. post-ablation proximal squamous vs. non-refluxing control squamous mucosa using the Kruskall Wallis test
*Posttest—$P<0.05$ for pre-ablation Barrett's esophagus vs. all types of squamous mucosa.
**Posttest—$P<0.05$ for pre-ablation Barrett's esophagus vs. post-ablation neosquamous mucosa
***Posttest—$P<0.05$ for pre-ablation Barrett's esophagus vs. pre-ablation squamous mucosa and pre-ablation Barrett's esophagus vs. post-ablation neosquamous mucosa
τ Posttest—$P<0.05$ for pre-ablation squamous vs. non-refluxing control squamous mucosa, post-ablation squamous vs. non-refluxing control squamous mucosa, and post-ablation neosquamous mucosa vs. pre-ablation squamous vs. non-refluxing control squamous mucosa
ττ Posttest—$P<0.05$ for pre-ablation Barrett's esophagus vs. pre-ablation squamous mucosa, and pre-ablation Barrett's esophagus vs. post-ablation proximal squamous mucosa

from the three biopsies collected for each subject) was then determined, producing a single data point per biomarker for each tissue type in each subject. These data points were then compared across tissue types. The Friedman test was used to determine the significance of differences between paired data sets (pre-ablation metaplastic vs. pre-ablation squamous vs. post-ablation neosquamous vs. post-ablation normal squamous tissues). Dunn's multiple comparison test was used for posttesting to determine the significance of differences between pairs of data sets. The Kruskall–Wallis test was used to determine the significance of differences between unpaired data sets (all categories of squamous tissues versus squamous mucosa from controls). The protocol for this study was approved by the Flinders Clinical Research Ethics Committee.

Results

The levels of expression for CK-8 and CK-14 are summarized in Table 1. CK-8 expression in the pre-ablation Barrett's esophagus mucosa was significantly higher compared to all types of squamous mucosa before and after ablative treatment, as well as the controls. Expression of CK-8 did not differ between the neosquamous tissue and the normal squamous tissues and controls. Expression levels for CK-14 was higher in all types of squamous mucosa compared to Barrett's epithelium and did not differ among any of the squamous mucosa types.

MiR-143 expression was significantly higher in Barrett's esophagus mucosa compared to squamous epithelia of all types (Table 1). The miR-143 levels were similar for all types of squamous epithelium in the patients who underwent ablation therapy. However, miR-143 expression in normal and neosquamous epithelium from patients with Barrett's esophagus who underwent ablative therapy was higher than in normal squamous esophageal epithelium collected from nonrefluxing control subjects (Fig. 1; $p=0.004$).

MiR-205 expression in Barrett's esophagus mucosa was virtually absent and significantly lower than the squamous epithelium groups, including the controls (Table 1). There were no significant differences in levels of miR-205 expression between the normal squamous esophageal epithelium from control subjects vs the normal and neosquamous epithelium from APC patients (Fig. 2).

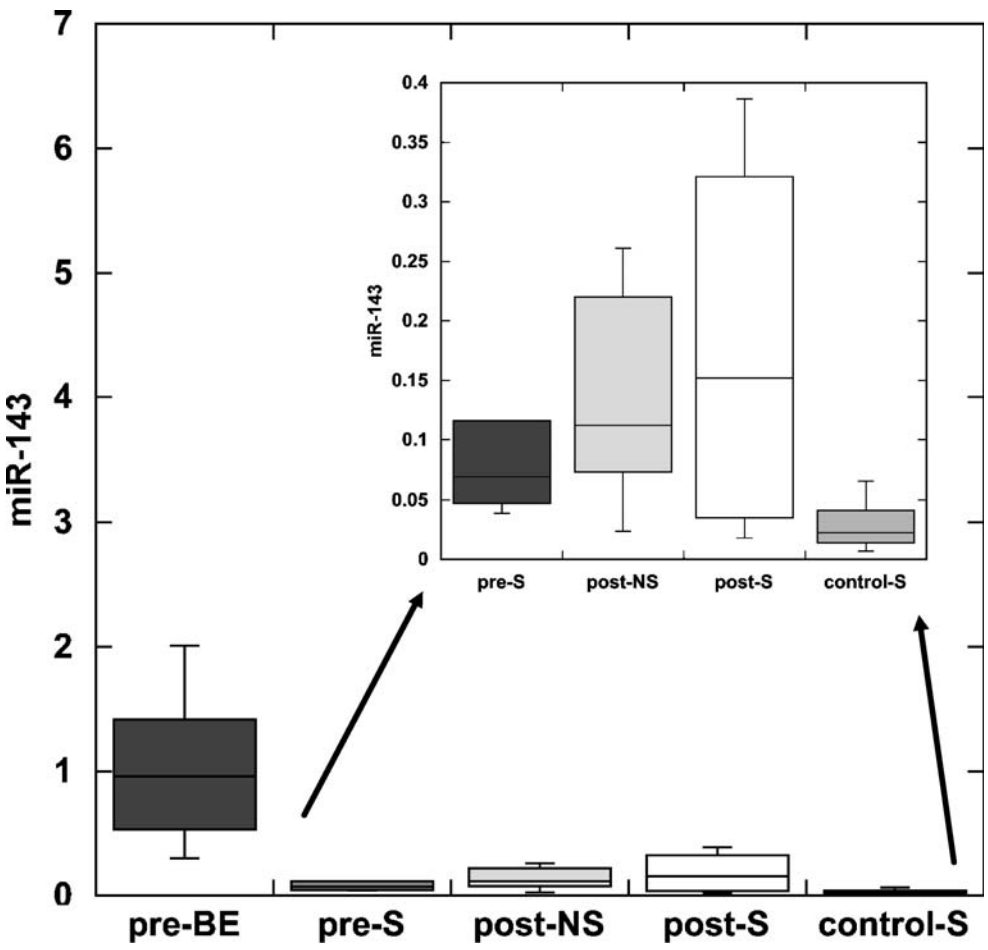

Figure 1 MiR-143 expression for all tissue types—preablation Barrett's esophagus (*pre-BE*) and normal squamous (*pre-S*) mucosa, postablation neosquamous (*post-NS*), and normal squamous (*post-S*) mucosa, and nonrefluxing control squamous (*control-S*) mucosa. *Middle bar in boxes* median, upper, and lower limits of boxes = 25th and 75th percentiles, *"whiskers"* 1.5× interquartile ranges. miR-143 expression in the normal and neosquamous epithelium from patients with Barrett's esophagus who underwent ablative therapy was higher than in normal squamous epithelium from nonrefluxing controls ($p=0.004$).

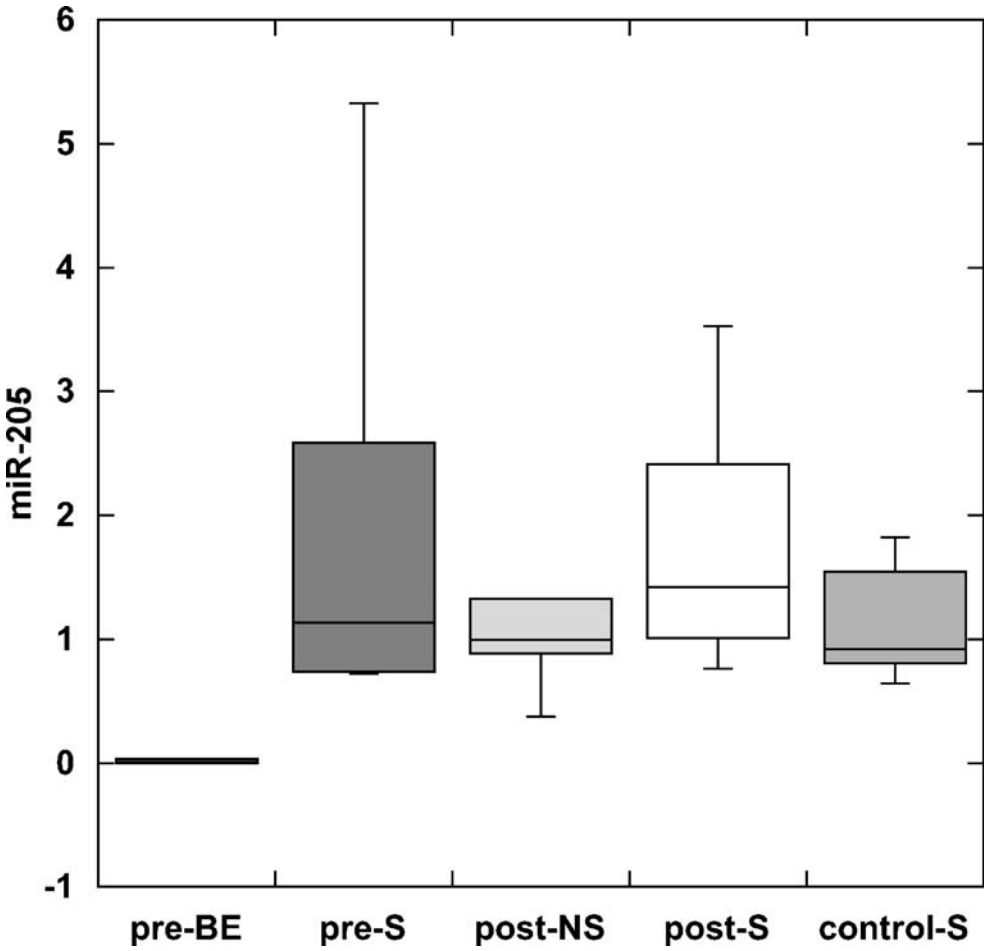

Figure 2 MiR-205 expression for all tissue types—preablation Barrett's esophagus (*pre-BE*) and normal squamous (*pre-S*) mucosa, postablation neosquamous (*post-NS*), and normal squamous (*post-S*) mucosa, and control squamous (*control-S*) mucosa. *Middle bar in boxes* median, upper, and lower limits of boxes = 25th and 75th percentiles, *"whiskers"* 1.5× interquartile ranges.

Discussion

This study evaluated the expression of biomarkers in Barrett's esophagus and neosquamous mucosa after ablation with APC. For each of the evaluated biomarkers, ablation was followed by normalization of expression levels, and these findings were consistent with conversion from a metaplastic columnar mucosa to a squamous epithelium. However, the specific expression of miR-143, while normalized compared to nonablated squamous mucosa in the proximal esophagus in patients with Barrett's esophagus, remained elevated compared to expression levels in normal esophageal mucosa from nonrefluxing patients. Hence, even though the application of ablative therapies to Barrett's esophagus can result in the replacement of the metaplastic epithelium with a new squamous lining, further work is required to demonstrate that the neosquamous epithelium is stable, and currently the long-term outcome following ablation remains unknown.[23–25]

Hence, the clinical question, whether ablation decreases the cancer risk in patients with Barrett's esophagus, remains unanswered. Ideally, clinical questions should be addressed by prospective randomized controlled trials. However, such trials need to recruit a large number of patients, and follow them long term. Investigating the phenotype and genetic profile of regenerated neosquamous esophageal mucosa after ablation could give some indication as to whether ablation is likely to reduce the risk of later malignancy.

A few studies have looked at genetic changes in columnar and squamous epithelium in the esophagus after ablative therapies for Barrett's esophagus. Some report persistent genetic changes in remnant segments of Barrett's esophagus,[25] or describe genetic similarities[11] and differences[27,28] between the neosquamous epithelium and Barrett's esophagus epithelium after ablation. Ours is the first study in which columnar- and squamous-associated cytokeratins and miRNAs have been quantified in Barrett's esophagus, normal squamous epithelium, and neosquamous epithelium before and after ablation. The findings that the levels of CK-8 and 14, and miR 143 and 205 were similar between neosquamous epithelium compared to normal squamous epithelium in patients with Barrett's esophagus suggest that APC results in normalization of the biomarkers we studied in the neosquamous epithelium. This supports the idea that the risk of recurrence of Barrett's esophagus

and subsequent malignant degeneration might be reduced by ablation.

Previous expression profiling studies have shown that CK-14 mRNA is expressed in the esophageal squamous epithelium at levels significantly higher than in Barrett's epithelium,[14, 15] and this is consistent with our study. On the other hand,CK-8 mRNA levels have been shown to be higher in biopsies from Barrett's esophagus epithelium, compared to all categories of squamous epithelium, and again our findings were in agreement with previous reports.[14,15] We observed complete normalization of CK-8 levels in neosquamous epithelium, and this could suggest that the epithelium has no remnant markers of columnar differentiation. Similar to the CK-14 result, this indicates a stable squamous phenotype.

We analyzed the expression of two human miRNAs: miR-143 and miR-205. These markers were chosen because we previously found that they best differentiate columnar GI mucosa and Barrett's esophagus mucosa, from esophageal squamous mucosa.[21,22] In our study, higher miR-205 expression was seen in squamous tissues compared to Barrett's esophagus mucosa, and this matched previous findings.[21,22] Decreased miR-205 expression in Barrett's esophagus epithelium vs squamous epithelium, and a further decrease in esophageal adenocarcinoma have been confirmed elsewhere.[29] Reduced miR-205 expression in Barrett's esophagus mucosa might put this epithelium at increased risk of epithelial to mesenchymal transition, whereas restoration and normalization of miR-205 expression in neosquamous epithelium could indicate that the neoplastic potential of this epithelium is low. However, this hypothesis will need to be investigated in future studies.

MiR-143 is highly expressed in human colonic tissues,[30] and downregulation of miR-143 expression has been shown to occur in colorectal malignancies.[30,31] It is also highly expressed in Barrett's esophagus mucosa compared to esophageal squamous mucosa, and it is down-regulated in esophageal adenocarcinoma.[21,22] In our current study, the finding of normalization of miR-143 expression in neosquamous epithelium to levels which were similar to those in normal squamous epithelium in patients with Barrett's esophagus, both before and after ablation, also suggests that a normal squamous phenotype has been established after ablation with APC.

However, the finding that miR-143 expression in the squamous epithelium above the metaplastic segment, before and after ablative therapy, in Barrett's esophagus patients, as well as neosquamous epithelium after ablation, was higher than the expression levels in biopsies of squamous esophageal mucosa collected from nonrefluxing controls is also important. It suggests that both the neosquamous mucosa, and the apparently "normal" squamous mucosa in patients with Barrett's esophagus, might be different to the squamous esophageal mucosa in patients who do not have Barrett's esophagus. Acid and bile reflux were well controlled by a fundoplication in most of the patients in this study, and this finding is unlikely to have been influenced by an acute reflux effect.

The differences could have either developed at a much earlier time point, when reflux was an active problem, or the upregulated miR-143 in squamous tissues represents a preexisting abnormality in the squamous esophageal mucosa of patients who might be predisposed to develop Barrett's esophagus in the presence of gastroesophageal reflux. As a consequence, miR-143 levels might help us to identify patients who are at greater risk of developing Barrett's esophagus. Alternatively, we cannot exclude an effect on gene expression levels by APC (e.g., miR-143) within the nearby and proximal squamous mucosa, although this is unlikely because the proximal mucosal samples were collected well above the segment of the esophagus which had been treated by APC.

In conclusion, we have shown that the expression of cytokeratins CK-14 and CK-8, as well as miRNA-143 and miR-205 in neosquamous epithelium from patients with Barrett's esophagus who underwent ablative therapy with APC, are similar to normal squamous epithelium in patients with Barrett's esophagus. Our results suggest when APC successfully eradicates Barrett's esophagus, and it is replaced with squamous epithelium, the levels of the biomarkers examined are normalized. However, neosquamous and normal squamous epithelium in Barrett's esophagus patients has significantly increased miR-143 expression compared to squamous epithelium in healthy patients. Further research which focuses on other miRNAs, larger groups of patients, and longer follow-up times could help us to develop a better understanding of the cellular processes involved in the formation of a new squamous mucosa after ablation of Barrett's esophagus and its potential clinical behaviour.

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Conflict of Interest The authors have no conflict of interests to disclose.

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ORIGINAL ARTICLE

Association of Gastroesophageal Reflux and O_2 Desaturation: A Novel Study of Simultaneous 24-h MII–pH and Continuous Pulse Oximetry

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Abstract
Background Proof of the relationship between gastroesophageal reflux disease (GERD) and respiratory symptoms remains a challenge. Our aim was to determine the association between reflux events and O_2 desaturation in GERD patients with primary respiratory symptoms (RS) compared to those with primary esophageal symptoms (ES) using ambulatory monitoring systems.
Methods One thousand eight hundred fifty-one reflux episodes were detected by multichannel intraluminal impedance (MII)–pH testing in 30 patients with symptoms of GERD (20 RS, ten ES.) All patients underwent simultaneous 24-h MII–pH and continuous O_2 saturation monitoring via pulse oximetry. Reflux-associated desaturation events were determined by correlating synchronized 24-h esophageal pH and/or impedance and O_2 desaturation.
Results One thousand one hundred seventeen reflux events occurred in patients with RS and 734 in those with ES. Nearly 60% of these 1,851 reflux events were associated with O_2 desaturation. Markedly more events were associated with O_2 desaturation in patients with RS (74.5%, 832/1,117) than in patients with ES (30.4%, 223/734, $p<0.0001$). The difference in reflux desaturation association was more profound with proximal reflux—80.3% with RS vs. 29.4% with ES ($p<0.0001$).
Conclusions A remarkably high prevalence of O_2 desaturation associated with gastroesophageal reflux was noted in patients with RS. Given further study, simultaneous combined esophageal reflux and O_2 saturation monitoring may prove a useful diagnostic tool in this difficult group of patients.

Keywords GERD · Respiratory symptoms · O_2 desaturation · Pulseox

Introduction

Respiratory symptoms have long been recognized to be associated with gastroesophageal reflux disease (GERD). Indeed, Sir William Osler noted over 100 years ago that asthmatics "learn to take their large daily meal at noon in order to avoid nighttime asthma which occurred if they ate a full supper."[1] It is known that GERD is more often observed in asthmatic patients than in the general population.[2] Cough, wheezing, hoarseness, or recurrent pneumonia are present in as many as 50% of patients with GERD and respiratory complaints are the primary or sole symptoms in 20%.[2,3] Experimental data show that gastroesophageal reflux stimulates physiologic responses in the upper respiratory tract, and direct contact with refluxed material may result in significant pathologic injury including end-stage pulmonary fibrosis. Two pathophysiologic mechanisms are known to occur: microaspiration of gastric contents and vagal reflex responses. In the first mechanism, the reflux of gastric contents may directly overflow into the upper and lower airways causing symptoms and tissue damage. With the second mechanism, reflux of gastric contents can stimulate vagus nerve terminals provoking

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a reflex cough or bronchoconstriction.[4–6] Pathologic changes in the respiratory tract suggesting an association with GERD have been detected in up to 80% of patients with asthma.[7] The association between GERD and respiratory symptoms is further supported by the improvement or resolution of symptoms after surgical or medical treatment of reflux.[3,8,9]

Objectively identifying this association is a major clinical challenge. There is currently no diagnostic method which reliably confirms that respiratory symptoms are secondary to the presence of gastroesophageal reflux. As a result, treatment outcomes are less predictable than with typical esophageal symptoms. Casanova demonstrated that oxygen desaturation coincided with episodes of increased esophageal acidity, as detected by pH monitoring, in 40% of patients with COPD.[10] This fact, combined with studies showing that esophageal acidification causes an increase in airway resistance, led us to hypothesize that oxygen desaturation may occur following episodes of gastroesophageal reflux and that this association may be useful in distinguishing patients with reflux-related respiratory symptoms from those whom reflux may not be causative. The advent of continuous ambulatory O_2 saturation monitoring made it possible to simultaneously assess the association of gastroesophageal reflux with O_2 saturation in patients with and without primary respiratory symptoms using combined simultaneous ambulatory monitoring systems.

Patients and Methods

The study population consisted of 30 patients with symptoms of GERD undergoing foregut diagnostic evaluation between January, 2007 and April, 2008. There were 20 women and ten men with a mean age of 48 years, ranging between 18 and 73 years. Patients having undergone previous upper gastrointestinal (GI) surgery or esophageal dilatation were excluded. All underwent simultaneously timed 24-h multichannel intraluminal impedance (MII)–pH and continuous O_2 saturation monitoring via pulse oximetry as well as esophageal manometry, upper endoscopy, and video barium upper GI examination. The study was approved by our institution's Research Subjects Review Board.

A structured questionnaire to assess foregut symptoms was administered prior to objective testing. The presence and severity of respiratory symptoms including cough, hoarseness, and wheezing, and/or esophageal symptoms including heartburn, regurgitation, or dysphagia were recorded at the initial visit. Based upon the most bothersome symptom reported, patients were classified into two groups: those with primary respiratory and those with primary esophageal symptoms.

Combined Ambulatory MII–pH and O_2 Saturation Monitoring

Simultaneous ambulatory reflux testing using a transnasal MII/pH catheter (Sandhill Scientific, Denver, CO, USA) and pulse oximetry was performed on each subject.[11,12] The MII/pH catheter consisted of six pairs of impedance electrodes and one or two pH sensors. Two catheters were utilized: (a) MII/pH catheter with pH sensor placed 5 cm above the proximal border of the lower esophageal sphincter (LES) and impedance sensors at 3, 5, 7, 9, 15, and 17 cm above the LES and (b) MII/pH catheter with pH sensors placed 5 and 20 cm above the proximal border of the LES and the impedance sensors 3, 5, 7, 9, 15, and 17 cm above the LES. After calibration, the MII/pH probe was passed transnasally and positioned based upon the location of the LES as determined by manometry. Data were acquired and analyzed using BioView analysis software (Sandhill Scientific, Denver, CO, USA).

Oxygen saturation monitoring was performed using the Pulsox-300i (Konica Minolta Sensing, Inc.) and Finger Clip Probe SR-5C (Konica Minolta; Fig. 1). Pulsox-300i measures the oxygen saturation (SpO_2) in arterial blood and pulse rate at a frequency of once per second via the standard photometric noninvasive method as employed in everyday clinical practice. SpO_2 is defined by the following equation:

$$SpO_2 = \frac{C(HbO_2)}{C(HbO_2) + C(Hb)} \times 100(\%\ SpO_2)$$

C (Hb) Concentration of reduced hemoglobin
C (HbO_2) Concentration of oxyhemoglobin

The instrument measures changes in the absorption of red and infrared light passing through tissues to determine the SpO2 of the blood. Measurements range from 0% to 100%

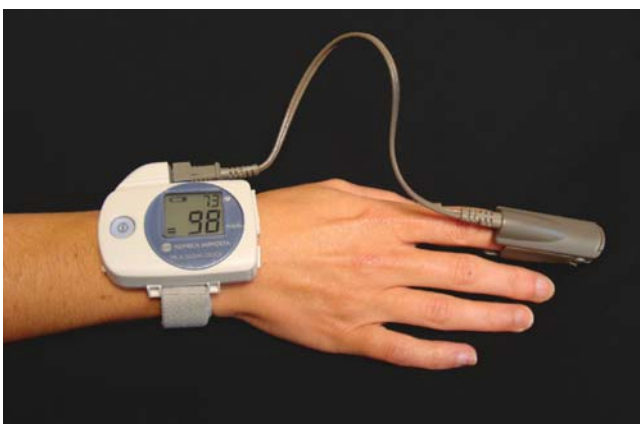

Figure 1 Pulsox-300i with finger probe (Finger Clip Probe SR-5C 0.3 m) used to assess oxygen saturation (Konica Minolta Sensing, Inc.).

for SpO_2 and 30 to 230 bpm for pulse rate. Manufacturer's data reveal that the Pulsox-300i accuracy for SpO_2 is ±2% (70% to 100% range) and for pulse rate is ±2 bpm (30 to 100 bpm range) or ±2% of value (100 to 230 bpm range). Data were acquired and analyzed using Profox Oximetry Software (Profox Associates, Inc., Escondido, CA, USA). The timing of the pulse oximetry was synchronized with the MII–pH study at the onset of the study period. The time drift for the first ten patients was between 15 and 18 s. The Pulsox-300i was secured to the wrist and the probe placed on the index finger in all patients.

Data Definitions

Proximal reflux was defined by the occurrence of pH<4 20 cm above the LES or reflux in the two proximal impedance sensors located 15 and 17 cm above the LES. Reflux events occurring outside the time of continuous oxygen saturation monitoring were not assessed in this study. An abnormal 24-h MII–pH study was defined as a DeMeester score >14.72 or the presence of more than 26 weakly acidic reflux episodes or one alkaline reflux episode (pH>7).[13]

Oxygen desaturation events were defined by one of two observations: (1) SpO_2 <90% or (2) SpO_2 drop of 6% or greater. A reflux–desaturation association was considered present if O_2 desaturation occurred within 30 s prior to or 10 min after a reflux event (Fig. 2).[14–16]

Statistical Analysis

Comparisons between groups were performed using Student's *t* test. Descriptive data for each measured parameter were expressed as mean ± standard error of the mean (SEM). A *p* value of less than 0.05 was considered significant.

Results

Twenty patients had primary respiratory symptoms, including cough in 15 (75%), hoarseness in 12 (60%), and wheezing in

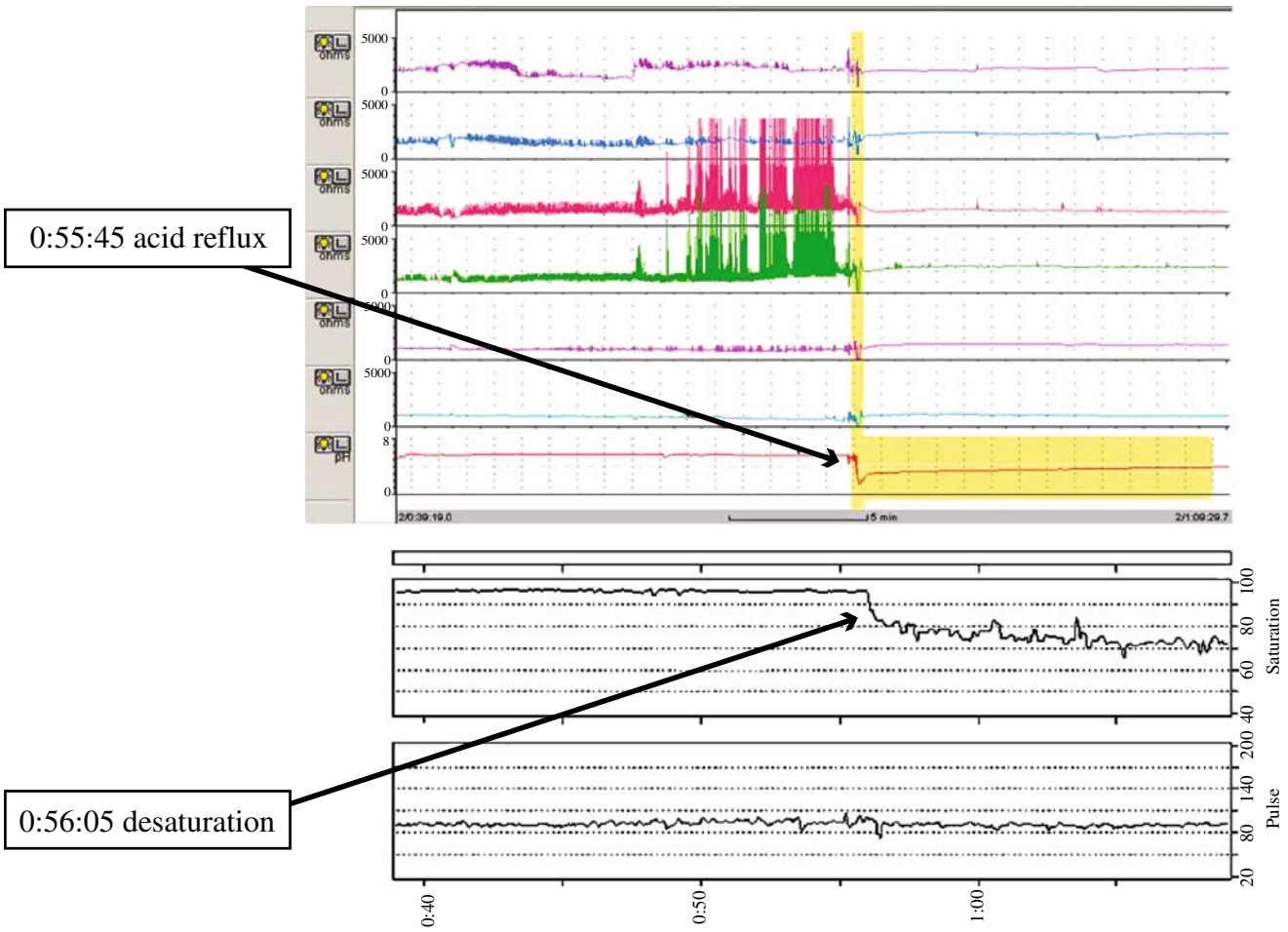

Figure 2 Example of the association between a reflux episode detected by MII–pH study and oxygen desaturation detected by pulse oximetry. The desaturation event was observed 20 s after a reflux episode.

Table 1 Objective Findings in the Two Patient Groups as Detected by Endoscopy, Barium Esophagography, Manometry, and pH/Impedance Evaluation

	Respiratory symptoms (n=20)	Esophageal symptoms (n=10)
Hiatal hernia	15 (75%)	9 (90%)
Erosive esophagitis	6/16 (37.5%)	5/9 (55.5%)
Barrett's esophagus	1/16 (6.2%)	2/9
Defective lower esophageal sphincter	12 (60%)	8 (80%)
Ineffective motility	6 (30%)	1 (10%)
Positive distal esophageal acid exposure	14 (70%)	5 (50%)

For the evaluation of esophagitis and Barrett's esophagus, 16 patients were assessed with endoscopy in the respiratory symptoms group and nine in the esophageal symptoms group

five (25%). Respiratory symptoms were the sole symptoms in two patients (10%). Ten patients with primary esophageal symptoms, including heartburn in all, regurgitation in eight (80%), chest pain in five (50%), dysphagia in three (30%), and epigastric pain in one (10%) were used as a comparison group. Clinical features of the two groups are shown in Table 1.

Abnormal esophageal acid exposure was present in 19 of the 30 patients (14 respiratory, five esophageal symptoms) and was at the upper limit of normal in two (both respiratory group). MII–pH study detected 2,043 reflux episodes of which 1,851 were correlated with continuous O_2 saturation monitoring (Fig. 3a). One hundred ninety-two reflux events were not included in the study because of technical problems with simultaneous O_2 saturation monitoring. The reflux was characterized as acid in 1,541 (average 51 events per patient) and nonacid in 310 (average ten events per patient; Fig. 3b). One thousand one hundred seventeen reflux events occurred in patients with primary respiratory symptoms and 734 in those with primary esophageal symptoms. Nearly 60% of the 1,851 reflux events were associated with O_2 desaturation. Overall, significantly more reflux events of any type were associated with O_2 desaturation in patients with respiratory symptoms (74.5%) than in patients with esophageal symptoms (30.4%, p<0.0001; Fig. 4).

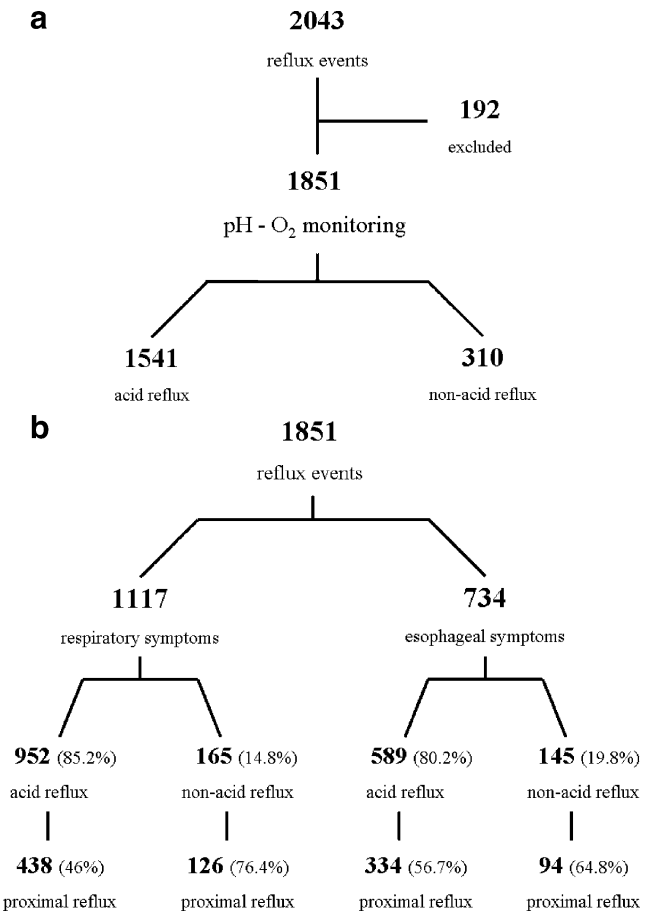

Figure 3 **a** The distribution of reflux into acid reflux events and nonacid reflux events. **b** The distribution of reflux events by patient group.

Primary Respiratory Symptoms Group

In patients with primary respiratory symptoms, 952 (85.2%) of the 1,117 reflux events were acid and 165 (14.8%) were

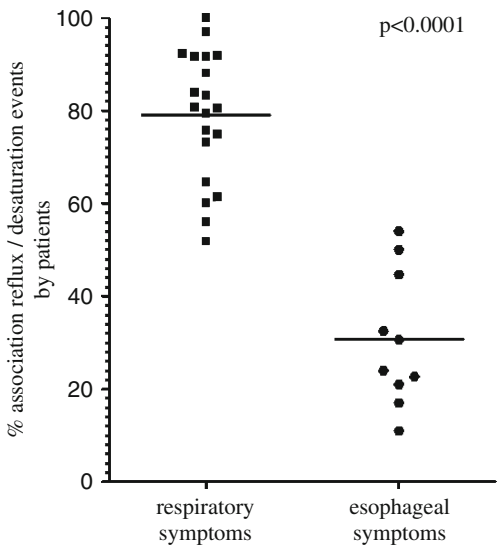

Figure 4 Scatter plot of association between reflux episodes and desaturation events by patient group. The prevalence of reflux-associated desaturations was remarkably different between the two groups (p<0.0001).

Table 2 Reflux and O_2 Desaturation in Patients with Respiratory Symptoms and Those with Esophageal Symptoms

	Respiratory symptoms (n=20 patients)	Esophageal symptoms (n=10 patients)	p value
Mean number of reflux episodes in 24 h	81 (± 10)	80 (± 16)	ns
Mean number of desaturations in 24 h	239 (± 31)	119 (± 34)	$p<0.005$
Time interval (s) from reflux to desaturation (mean)	104 (± 16)	129 (± 11)	$p<0.05$
Time interval (s) from proximal reflux to desaturation	85 (± 19)	121 (± 14)	$p<0.005$* $p<0.05$
Time interval (s) from distal reflux to desaturation	127 (± 7)	139 (± 17)	ns
pO_2 drop of a desaturation episode (mean)	9% (± 0.2)	9% (± 0.2)	ns
pO_2 peak of a desaturation correlated with reflux event (mean)	87.2% (± 0.16)	87.8% (± 0.25)	ns
Mean pO_2 in 24 h[a]	93.92% (± 0.48)	95.36% (± 0.4)	$p<0.05$

Analysis by Student's t test: value (±SEM)
ns not significant
[a] Only the patients that completed the 24-h oxygen saturation monitoring (n=18 for respiratory symptoms group
*$p<0.005$ comparing distal reflux episodes in esophageal symptoms and respiratory symptoms groups and $p<0.05$ comparing distal and proximal reflux episodes in esophageal symptoms group

nonacid. The mean number of reflux episodes in 24 h was 81±10 and the mean number of O_2 desaturations was 239±31. The mean pO_2 in 24 h detected by pulse oximetry was 93.9±0.5% (Table 2). Seventy-four percent (832/1,117) of the distal reflux events were associated with O_2 desaturation episodes (Fig. 5). This correlation was higher (80.3%, 453/564) for proximal reflux events (Fig. 6). Acid reflux was associated with desaturation episodes in 73.6% (701/952) of events, similar to the desaturation noted with nonacid reflux (79.4%, 131/165; Fig. 7). The average time from pH drop to <4 and O_2 desaturation was 127±7 s following a distal esophageal reflux event. This interval was significantly shorter following a proximal reflux event (85±19 s, $p<0.005$). The mean pO_2 drop during a desaturation episode was 9.0±0.2%.

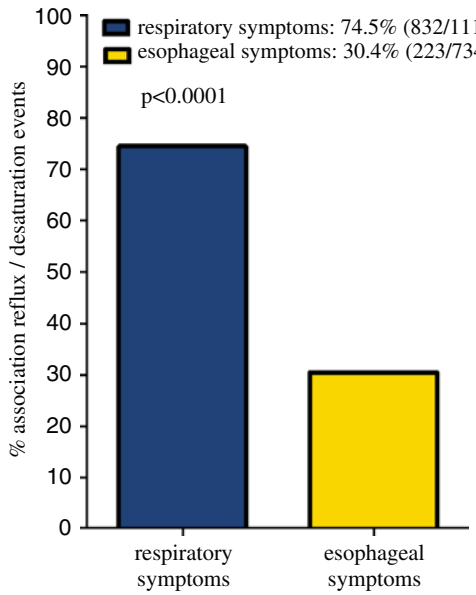

Figure 5 Association between reflux episodes and desaturation events. There is a remarkably high prevalence of oxygen desaturation associated with gastroesophageal reflux in patients with primary respiratory symptoms.

Primary Esophageal Symptoms Group

Ten patients had primary esophageal reflux symptoms. MII–pH monitoring detected a total of 734 reflux episodes in these patients, of which 589 (80.2%) were acid and 145 (19.8%) were nonacid. The mean number of reflux episodes per 24 h (80±16) was similar to the respiratory group, while the mean number of O_2 desaturation events was significantly less (119±34). The mean pO_2 in 24 h detected by pulse oximetry was 95.4±0.4% (Fig. 8). Acid reflux was associated with desaturation episodes in 29% of events (170/589) and nonacid reflux was associated with desatura-

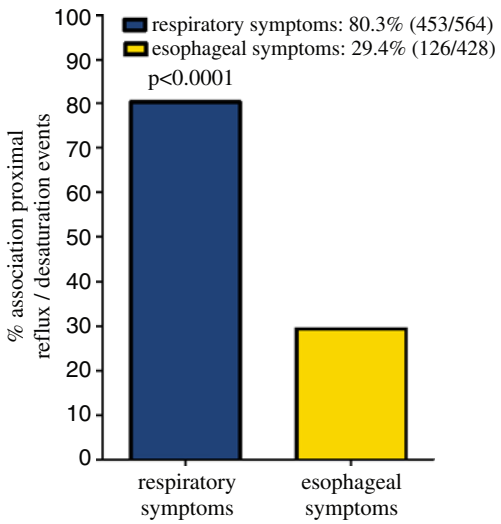

Figure 6 Association between proximal reflux episodes and desaturation events by patient group.

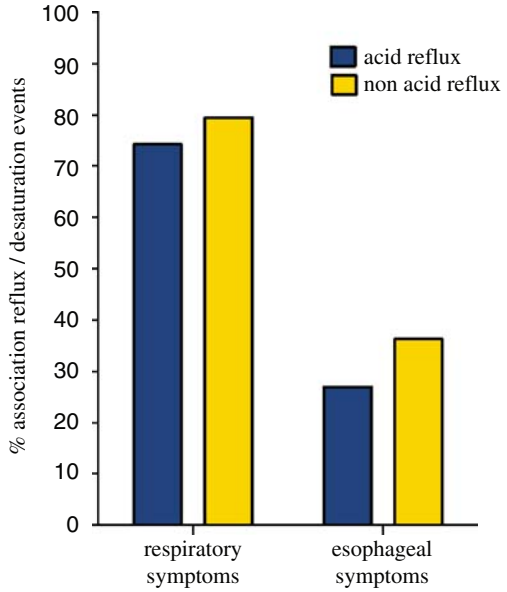

Figure 7 Association between acid and nonacid reflux episodes and desaturation events in patients with and without primary respiratory symptoms. The prevalence was remarkably different between the two groups ($p<0.0001$), though no statistically significant difference was observed between acid and nonacid reflux events within either group.

tion in 36.6% (53/145), both significantly less than in patients with primary respiratory symptoms. The reflux–desaturation association was even more marked when proximal reflux events were compared: 80.3% (453/564) of reflux events were associated with desaturation in patients with respiratory symptoms and 29.4% (126/428) in patients with esophageal symptoms ($p<0.0001$). The mean drop in oxygen saturation associated with reflux episodes was similar in the two groups (9.0±0.2%; Table 2).

Discussion

Our data show a remarkably high prevalence of oxygen desaturation events associated with gastroesophageal reflux in patients with respiratory symptoms. These reflux-associated desaturations are much more prevalent in patients with primary respiratory symptoms than in those with primary typical symptoms. While our data do not prove that reflux is causing the desaturation events, the temporal correlation is intriguing and suggests that reflux may be etiologic.

The association between GERD and respiratory disorders has long been recognized. GERD is a known cause of asthma, cough, recurrent pneumonia, lung abscess, and pulmonary fibrosis leading to end-stage pulmonary failure. In fact, the term "gastroesophageal reflux disease" is an oversimplification in that reflux can occur at multiple levels within the upper aerodigestive tract, not merely across the gastroesophageal junction. Of relevance to the development of pulmonary symptoms is the potential for esophagopharyngeal reflux and pharyngotracheal reflux, potentially exposing the airways and pulmonary parenchyma to duodenal and gastric contents. The term "laryngopharyngeal reflux" has also arisen to denote reflux into the upper airway.

A number of modalities traditionally have been utilized to objectify the presence of GERD. The gold standard test is ambulatory esophageal pH monitoring, though the presence of GERD can also be deduced by the presence of significant erosive esophagitis or Barrett's esophagus on endoscopic assessment or the finding of a hiatal hernia with reflux on barium esophagography. When the patient complains of typical reflux symptoms such as heartburn or regurgitation, such objectification of GERD has proven highly reliable in determining that GERD is causative.

When the patient's primary symptoms are respiratory in nature, such a cause-and-effect relationship to GERD has proven much more elusive. While testing can objectify the presence of GERD, whether GERD is actually contributing to the respiratory complaints may be less than certain. GERD and conditions such as asthma or cough are common and can coexist without being related. In addition, symptoms alone are unreliable in determining such an association and there is no pathologic mucosal abnormality, as detected on histologic assessment of biopsies from the esophagus, larynx, or airways that is pathognomonic for the presence of GERD. Occult GERD can occur in the absence of typical symptoms, and reflux of even small amounts of gastric juice occurring at a remote point in time can induce a lingering cough or precipitate a prolonged asthma

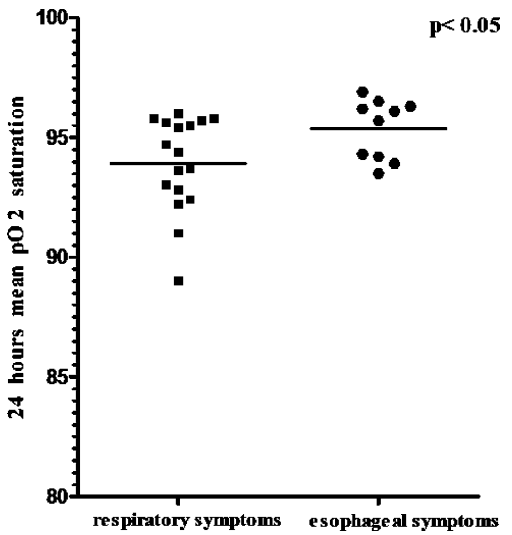

Figure 8 Scatter plot of 24-h mean oxygen saturation in 18 patients with primary respiratory symptoms that had completed 24-h continuous monitoring by MII–pH and pulse oximetry and in ten patients with primary esophageal symptoms.

exacerbation. Repetitive microaspiration episodes can lead to chronic pulmonary parenchymal damage and the insidious onset of "idiopathic" pulmonary fibrosis. The fact that GERD can be a contributor to end-stage lung disease and the development of posttransplant obliterative bronchiolitis or infection has been demonstrated in the lung transplant literature.[17]

Due to the unreliability of commonly utilized testing methods in proving that GERD is etiologic to respiratory symptoms, a common diagnostic paradigm is a therapeutic trial of intensive acid suppressive therapy to assess clinical response. While such a strategy may prove effective in a subset of cases, inherent deficiencies exist in such a protocol. Cough or asthma may improve spontaneously or due to other medical therapies and be unrelated to GERD. On the other hand, nonacid reflux may persist despite intensive acid suppression, leading to persistent complaints even when GERD is causative. Combined MII–pH monitoring has arisen as a tool to detect nonacid reflux. A symptom index can be calculated while on medical therapy and has been shown to predict a response to subsequent antireflux surgery.[18]

Due to the inherent inaccuracies of all of the commonly utilized testing methodologies for GERD in the setting of primary respiratory complaints, the potential for a simple, noninvasive, inexpensive, easily available, and readily applied test holds significant appeal. Ambulatory oxygen saturation monitoring with pulse oximetry is such a diagnostic modality. Application and utilization of the device requires no special training and is readily tolerated by patients with excellent compliance and minimal discomfort.

Our data, while interesting, must be considered preliminary. For ambulatory pulse oximetry to become clinically useful and widely applicable, several issues will need to be resolved. Normal values for oxygen desaturation in age and sex-matched controls in patients with and without pulmonary disease will be important to determine the validity of our observations in patients being evaluated for GERD. Sensitive and specific thresholds will need to be determined for the number or percentage of reflux-associated desaturation events that are predictive of whether GERD is a contributor to pulmonary complaints. Perhaps a "reflux–desaturation" score will be derived that accounts for a number of different factors inherent in such an association. The value of combined reflux and pulse oximetry monitoring will be substantiated only if the findings are reliable in predicting a subsequent response to antireflux therapy, in particular fundoplication. Finally, the correlations between reflux events, both acid and nonacid, and oxygen desaturations currently have to be calculated by hand, a time-consuming and labor-intensive exercise. We are in the process of devising software to automate this process, which could make its application much more practical.

In summary, combined ambulatory MII–pH and pulse oximetry monitoring revealed a high prevalence of oxygen desaturations in temporal proximity to reflux events, particularly in patients complaining primarily of respiratory symptoms. This novel observation adds to our understanding of the pathogenesis of GERD-related respiratory symptoms and, given further study, may lead to the development of a practical and easily applied diagnostic test in this difficult group of patients.

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ORIGINAL ARTICLE

Clinical Remission in Endoscope-Guided Pneumatic Dilation for the Treatment of Esophageal Achalasia: 7-Year Follow-up Results of a Prospective Investigation

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Abstract
Background and Aims Prospective, long-term reports and predictors of outcome of endoscope-guided pneumatic dilation are lacking in the literature. The aim of this prospective 7-year follow-up study is to report the efficacy of endoscope-guided pneumatic dilation and determine the possible confounding factors related to remission.
Methods Between January 1998 and June 2004, 32 patients were enrolled. Each patient was treated with endoscope-guided pneumatic dilation and followed-up at regular intervals for a median of 4.5 years. Remission was determined with the use of a structured interview and a previously described symptom score. Cumulative remission rate was analyzed by using the Kaplan–Meier method with assessment of symptom scores between grades before and after PD at 6 weeks, 6 months, 1 year, and then every year after. Possible confounding factors related to the remissions were analyzed by Cox's proportional hazard model.
Results Complete follow-up until August 2007 was obtained in 100% of all patients. Cumulative remissions were 1 year (86.7%), 2 years (86.7%), 3 years (80.0%), 4 years (76.5%), 5 years (72.9%), 6 years (61.7%), and 7 years (61.7%), respectively. Age is a relevant confounding factor to the remissions showing a worse outcome for those under 45 ($p=0.046$). One esophageal perforation occurred (3.3%).
Conclusions Endoscope-guided PD itself is safe and modestly effective for up to 7 years investigations in current study. Older patients (>45 years) have favorable overall clinical remissions.

Keywords Esophageal achalasia · Endoscope-guided pneumatic dilation · Clinical remissions · Relevant confounding factors

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Introduction

There are many treatment options for esophageal achalasia, including endoscopic intrasphincter botulinum injection,[1,2] fluoroscopy-guided pneumatic dilation (PD),[3] and surgical treatments such as minimally invasive laparoscopic or thoracoscopic cardiomyotomy or the more aggressive cardioplasty or esophageal resection.[4] PD is considered to be the first-line therapy for achalasia especially in the older patients or those who refuses surgery. The principle of the procedure is to weaken the lower esophageal sphincter by generating radial force to tear the muscle fibers.[5,6]

Multiple studies have been published concluding that PD is a safe, effective, and relatively inexpensive option for

achalasia treatment with fluoroscopy.[7,8] However, prospective, long-term reports of endoscopy-guided pneumatic dilation are lacking in the literature.[9] This study aims to report the 7-year follow-up efficacy of PD using Rigiflex balloon dilators to treat primary esophageal achalasia without fluoroscopy, and it analyzes the possible confounding factors related to the clinical remissions.

Methods

Patients

From January 1998 to June 2004, 32 new patients with achalasia who received PD treatment in our unit (19 men; 13 women) were enrolled in our investigation. Patients who had prior treatments such as previous PD, botulinum toxin injection, or Heller operation were excluded. Other exclusions included patients with esophageal obstructions caused by intrinsic and/or extrinsic events as determined by X-ray film and endoscopy and episodes of esophageal or gastric tumors, peptic stricture, and prior surgical fundoplication. The mean age was 47.7±18.1 years (ranging from 18 years to 93 years).

The diagnosis of achalasia was based on clinical symptoms, endoscopic findings, barium esophagograms, and manometric studies. The standard diagnostic manometric findings of achalasia had to fulfill the criteria of aperistalsis of the esophageal body and incomplete low esophageal sphincter (LES) relaxation. All patients had dysphagia of both liquid and solid foods; 25 had food regurgitation (78.2%), 21 had body weight loss (65.7%), nine had chest pains (28.1%), and three had aspiration pneumonia (9.4%). Endoscopic ultrasonography or CT scan was conducted to rule out pseudoachalasia. All patients were followed-up until the final interview in 2007.

Endoscope-Guided PD

After the patients fasted overnight and gave informed consent, PD was carried out under conscious sedation by the authors using a 3-cm-diameter Rigiflex balloon dilator (Microvasive, Watertown, MA, USA). After topical anesthesia was applied to pharynx of each patient, the endoscope was inserted down to the duodenum. A guide wire was placed into the duodenum under endoscopic guidance and then the scope was removed. A 3-cm-diameter Rigiflex balloon dilator, which was marked with a thick-colored marker at the midsection of the balloon, was passed over the guide wire to the stomach. The endoscope was reinserted to serve as a guide to control the position of the balloon in the esophagus. The balloon was withdrawn to the esophagus, until the mark reached the gastroesophageal junction (Fig. 1). Depending on the tolerance of the patient, the balloon was then inflated up to 10–12 psi and maintained for 60 s and fixed during the dilation process. In most of our patients, an "ischemic ring" appeared. The same inflation procedure was repeated once more and held for another 15 to 30 s. The balloon was flattened completely and removed together with the endoscope. Patients ingested gastrografin after the dilation so that we could determine whether esophageal perforation had taken place. At the initial observation or during the follow-up period, if patients developed chest pains, the vital signs would be monitored and chest X-ray films or CT scans would be conducted, depending on the severity of the chest pains.

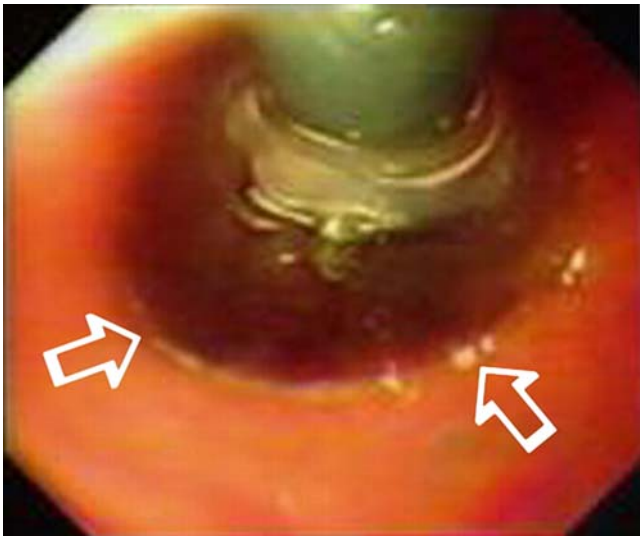

Fig. 1 Endoscopy-guided pneumatic dilation with the balloon fixed at the gastroesophageal junction during the dilation process.

Post-dilation Investigations

Esophagogram

The median gastroesophageal (GE) junction diameter measured in millimeters and median maximal width and height of lumen in centimeters by esophagogram before and 6 weeks after the initial PD were recorded and analyzed in a blinded manner. The degree of esophageal emptying was measured by the percentage reduction of maximal esophageal height × width using barium esophagograms at 5 min before and after PD.

Assessment of Symptom Scores

Structured interviews were performed by the first author using a previously described symptom score (Eckardt scores)[5] at the initial investigation, 6 weeks later, and every 1 year thereafter. Depending on whether dysphagia, regurgitation, and chest pain occurred occasionally, daily, or several times during the day, a symptom score between 0

and 3 was determined. In addition, a symptom score of 0 to 3 was assigned to the degree of weight loss. Thus, a completely asymptomatic patient would have a symptom score of 0, whereas a severely affected patient could have a symptom score of up to 12. Patients were considered to have reached clinical remission if symptoms had totally disappeared or if they had improved by at least two points and did not exceed a total combination score of 3. On the other hand, the patients were considered to be failure if the total combination symptom score still exceed 3 after dilation. Patients who requested further therapy despite having a total combination symptom score of less than 4 were also considered to have treatment failure if it occurred after initial clinical remission.

Manometric Studies

Manometry was carried out by the first author before and after the initial PD using a 4-lumen polyvinyl catheter, with a Dent sleeve operated by means of a pneumohydraulic capillary perfusion system after the patient fasted overnight. LES basal pressure and esophageal peristalsis were recorded with a computerized motility system and analyzed with computer software (Phoenix GI Motility System software by Albyn Medical Group, Dingwall, Scotland).

Statistical Analysis

Responses to the initial PD such as barium esophagographic changes, manometric results, and symptom scores were compared by Wilcoxon signed-rank test. Cumulative remission rate was analyzed by using the Kaplan–Meier method with assessment of symptom scores between grades before and after PD at 6 weeks, 6 months, 1 year, and then every year after. The relevance of clinical remission to age, LES pressure, and the improvement of esophageal emptying on barium esophagogram after initial treatment were also assessed at that time by log-rank test. Cox's proportional hazard model was calculated for the possible relevant confounding factors related to treatment remission. A p value of less than 0.05 was considered a statistically significant difference.

Results

Baseline patient characteristics according to initial treatment were demonstrated in Table 1. Most patients suffered from severe disease with high symptom scores of more than 7 when referred. The mean LES pressure before PD was 35.0±12.5 mm Hg (range, 21–60 mm Hg). The responses to the initial PD according to results of barium esophagograms showed that the median GE junction diameter increased from 2.5 to 8 mm ($p<0.001$), the mean maximal width of lumen decreased from 5.7 to 4.0 cm ($p<0.001$), and the mean maximal height of lumen decreased from 12.5 to 8.0 cm ($p<0.001$). Timed barium esophagograms correlated with symptomatic improvement in up to 71.8% of patients. Seven patients who noted complete relief showed less than 50% improvement in barium column height. Unfortunately, only 19 patients received a second manometry study after the initial PD. The median LES pressure dropped from 35 mm Hg (range, 21–60 mm Hg) to 12 mm Hg (range, 7–40 mm Hg). Median symptom scores dropped significantly from 7 to 1 after the initial PD ($p<0.001$). Average weight gain after initial PD was 4 kg (range, 0–6 kg).

Table 1 Baseline Patient Characteristics According to Initial Treatment

Age, mean (SD), years	47.7 (18.09)
Range, years	18–93
Sex, no. (%)	
Male	19 (59.4)
Female	13 (40.6)
Symptom score, no. (%)	
4	1 (3.1)
7	18 (56.3)
10	13 (40.6)
LES pressure, mean (SD), mm Hg	35.0 (12.47)
Range, mm Hg	21–60

The mean follow-up period was 4.5 years (range, 2.5 to 7 years). We attained cumulative remission rates of 86.7% in the first and second years, 80% in the third year, 76.5% in the fourth year, 72.9% in the fifth year, and 61.7% in the sixth and seventh years (Fig. 2). Twenty patients were available for follow-up at the fifth year, 14 in the sixth year, and three in the seventh year. Eleven patients with treatment failure were observed in our series by the end of the 7-year follow-up period. Four experienced only chest pain and/or very mild dysphagia and needed no further treatment. Seven suffered from recurrence symptoms of dysphagia that affected their quality of life. Two agreed to receive a second PD, which was successful with the use of a 3.5-cm balloon. Four younger patients chose surgery, and one (symptom score, 4) was reluctant to undergo further treatment. Cox's proportional hazard model for possible confounding factors showed that age, sex, symptom scores, and reflux symptoms were not relevant to the clinical remissions when analyzed with univariate analysis (Table 2). However, age is a significant correlation to overall remission rates showing a worse outcome for those under 45 when assessed by log-rank test ($p=0.046$; Fig. 3).

Seven patients (21.9%) had immediate complications after the initial PD. Two had a small amount of tarry stool

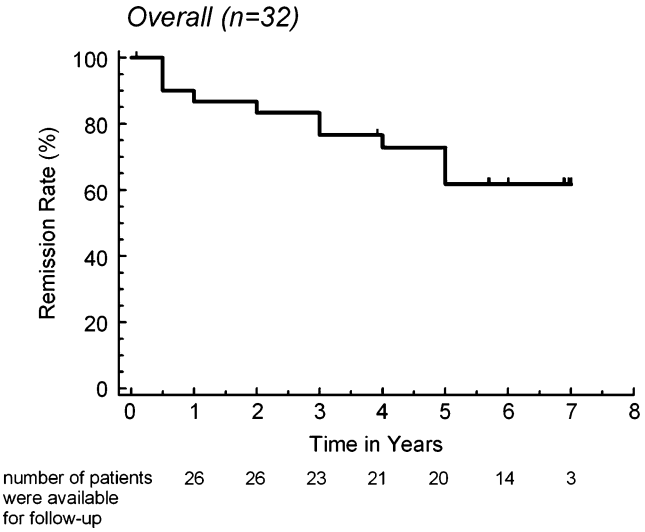

Fig. 2 Overall remission rates of post-pneumatic dilatation in patients with esophageal achalasia.

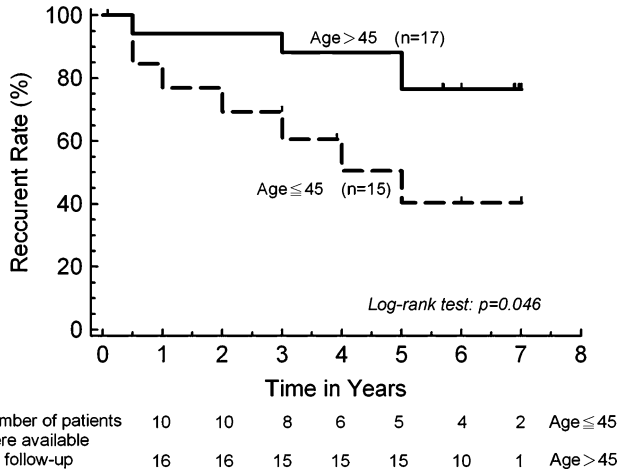

Fig. 3 Overall remission rates of post-pneumatic dilatation in patients with esophageal achalasia and correlation to age.

for 1 day, but they recovered after medical treatment. Both patients had stable vital signs and a drop in hemoglobin level of less than 1.5 g/dL, which was still within normal limits. Therefore, subsequent endoscopy was not performed on these patients. Four patients suffered from reflux esophagitis, with mostly mild symptoms with acid regurgitations. Three of them achieved remission with proton-pump inhibitor therapy once daily for 4 to 8 weeks. One 93-year-old woman had intermittent reflux symptoms since the initial PD, but her condition was well controlled with on-demand proton-pump inhibitors.

Gastrografin was ingested immediately after balloon dilation; no patient had obvious extravasations implying perforation, but one patient developed severe chest pain after PD and CT scan revealed esophageal perforation. She recovered after intensive medical care without surgical intervention. No patients died during our study.

Discussion

Achalasia occurs throughout all ages and affects both sexes and all races equally but has to be distinguished from secondary achalasia.[10] For many decades, many reports were published about long-term efficacy of the use of a 3-to 3.5-cm-diameter Rigiflex balloon to perform PD under the guidance of fluoroscope for patients with achalasia.[5] This procedure may be lost among the current generation of gastroenterologists due to many factors and are based on a misplaced fear of the risk of perforation, decreased immediate morbidity from laparoscopic myotomy compared to an open procedure, and some level of inconvenience to the already overly busy clinician.[3] Moreover, exposure to the X-rays during the procedure under the guidance of fluoroscopy has long been a concern.[11–13] Some of the highest doses to both patients and medical workers arises from interventional radiology procedures.[13] The potential of exposure to high doses of radiation during interventional procedures had been raised and addressed.[14] A safe and convenient PD technique for the treatment of esophageal achalasia was proposed by Lambroza[11] and Levine[12] but the studies were retrospective with only short-term reports. Since then, this technique has been used by many physicians but long-term prospective follow-up reports are lacking.[8,9] In our study, we report a result of a prospective investigation of endoscope-guided PD with a mean follow-up of 4.5 years (range, 2.5 to 7 years).

Our short-term result (86.7%) is close to Lambroza's group[11] (78% in 62 patients) and Levine's group[12] (100% in 27 patients). The overall sustained efficacy of traditional fluoroscope-guided PD has been excellent or good: Symptomatic response was reported to range from 61% to 100%.

Table 2 Cox's Proportional Hazard Model Related to Possible Confounding Factors and Clinical Remission (Univariate Analysis)

Variables	Comparison	HR (95% CI)	*p* value
Age	≤45 vs >45	3.29 (0.95–11.40)	0.05
Sex	Male vs female	0.61 (0.18–2.00)	0.413
Symptom score	Per 1 score increase	0.47 (0.12–1.77)	0.265
Improvement of esophageal emptying on esophageogram	>50% vs ≤50%	3.96 (0.77–20.48)	0.100
Reflux symptoms	Per 1 score increase	0.98 (0.21–4.53)	0.978

However, interpretation of such data is hampered by the fact that most authors used vague criteria.[5] Nevertheless, large-scale, long-term, follow-up investigations by Eckardt reported unfavorable recurrences in their fluoroscopic-guided PD patients. During the prolonged observation period (median, 13.8 years) in a prospective follow-up investigation study conducted by Eckardt and colleagues,[15] only 40% of patients treated with a single instance of PD remained in remission at 5 years. In our study, cumulative remissions were 86.7% in first 2 years and had dropped to 72.9% in the fifth year, but remained at 61.7% in the sixth and seventh years. Eckardt and colleagues[15] observed also that in patients who were still in remission at 5 years, only a few experienced relapse in the next 10 years. Such an observation may explain our study's sixth and seventh year results, but a longer follow-up period is needed. In the literature, about one half of all patients responded to repeat dilation, and the remainder proceeded to surgical management.[6,15] These studies reinforce the variability in success/relapse of this complex disease but underscores the efficacy and safety (perforation rate <1.5%) of even repeated PD.

A notable feature of all treatments for achalasia is the discrepancy between objective and subjective parameters of improvement. Generally, elderly patients and low post-dilated LES pressure are relevant to better remissions in previous studies,[15] although some reports have shown aged patients to have higher LES pressure.[16] In our study, patients older than 45 years have better remissions (Fig. 3). Unfortunately, our study is weakened by the fact that the reluctance of the post-dilated patients in remission status to receive further manometric follow-up studies (merely $n=19$). Therefore, it is hard for us to comment on the post-dilated LES pressure issue. In the literatures, decreases in LES pressure of more than 50% after PD or an absolute end-expiratory LES pressure of less than 10 mm Hg were generally more indicative of clinical success.[15]

The definition of remission is the key to the data interpretation; the outcome assessment in most publications was done using various validated symptom scoring system via a composite score combining all symptoms. This could obscure important findings. Vaezi and colleagues reported that there was a significant association between improvement in patient symptoms and barium height.[17,18] In 72% of their post-PD patients, the degree of symptom and barium height improvement were similar. Our result is similar to the Vaezi's group with the improvement of esophageal emptying after PD as assessed by a significant reduction in both barium height and width ($p<0.001$), and 71.8% of our patients correlated with symptomatic improvement. This may suggest that an additional objective parameter like esophagogram to the subjective symptom scores may be more optimal in assessing clinical remissions.[19,20] However, further investigations that include larger sample size and longer follow-up periods are needed for clarification on this issue.

The number of dilation sessions and the inflation time needed for a successful dilation varies from operator to operator. Some have suggested that a single dilation session is enough but recommend dilation with a bigger dilator based on the patients' symptom scores.[21,22] Others have suggested more progressive methods such as a series of dilations on the same or successive days.[23] Some have suggested a balloon inflation time of 10 s, while others have achieved satisfactory results only after 5 min of continuous inflation. Therefore, no clear consensus exists on balloon diameter and amount and rate of inflation pressure when performing PD. It has been shown that the risk of perforation increases with the increase in the balloon's size. Having been aware that Mikaeli's[24] and Karamanolis's groups[25] claimed that graded pneumatic balloon dilatation with a 30 mm diameter and slower rate of balloon inflation is an effective and safe initial method of therapy for achalasia and the generally smaller body mass index of the Taiwanese population, we chose a smaller (3 cm diameter) balloon and a smaller average inflation pressure of 10–12 psi maintained for 60 s, then repeated it for 15 to 30 s. We attained modest short-term remissions and 7-year cumulative remissions in our study but future recurrences could occur since the follow-up period is not long enough to conclude otherwise. Nevertheless, we showed that such endoscope-guided PDs are safe with only few complications and are attained at a modest mid-term period.

The major adverse event caused by PD is esophageal perforation, with a 2% cumulative rate. It may occur in up to 5% of all reported cases.[26] One of our patients had a perforation after a 3.0-cm balloon PD but completely recovered after intensive medical care. We believe that an inflation pressure not exceeding 12 psi may minimize the risk of perforation. Close observation of clinical symptoms and signs such as severe chest pain and fever suspicious of perforations is mandatory after PD. Studies, including ours, on the technique of Rigiflex balloon dilation of achalasia by positioning the endoscope above the balloon without fluoroscopy have shown results comparable with studies when using fluoroscopy. However, Rai's group[27] introduced a novel technique by the presence of the endoscope across the gastroesophageal junction during the dilation procedure. The potential danger in increase of perforation has been a concern, and some have argued that this technique is likely to interfere with the application of uniform radial force on the spastic sphincter. The effect of dilation toward the side of the endoscope can be compromised and may lead to a decrease in overall efficacy of the procedure and the possibility of generating unequal radial force on the sphincter.[28]

One of the common complications is reflux esophagitis. Our patients with reflux symptoms after PD were mild and transient with acid regurgitations and could be easily controlled with proton-pump inhibitors. In the literature, objective assessment of gastroesophageal reflux after pneumatic dilation has rarely been studied. The symptomatic, endoscopic, or clinical evidence of GERD-related complications is, fortunately, seldom severe.[29]

In conclusion, endoscope-guided PD itself is safe and modestly effective for up to 7 years investigations in current study. Older patients (>45 years) have favorable overall clinical remissions.

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ORIGINAL ARTICLE

The Early Use of PET-CT Alters the Management of Patients with Esophageal Cancer

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Abstract
Introduction The routine use of positron emission tomography–computed tomography (PET-CT) in the staging of patients with esophageal carcinoma remains contentious, with conflicting reports of its benefit. In our unit, PET-CT has been used routinely in the staging of all patients considered for radical therapy (surgery or chemoradiotherapy). Our aim was to determine the frequency with which PET-CT influenced decision making in the management of patients with carcinoma of the esophagus or gastroesophageal junction.
Methods CT, PET-CT, and outcome information were collected on 38 patients considered for radical therapy. Patient proformas, with and without PET-CT findings, were constructed and each independently reviewed in a randomized and blinded fashion by five multidisciplinary team members (three surgeons, two oncologists) and a treatment strategy determined.
Results PET-CT changed the staging for ten patients (26%). This translated into a change in management decision for seven patients (18%). The concordance between individual management plans and treatment intent was 79% for CT (150 of 190 decisions) and it was 92% for PET-CT (175 of 190 decisions). Full concordance between multidisciplinary team members was 66% with CT staging and 74% with the addition of PET-CT.
Conclusion The use of PET-CT early in the staging algorithm for esophageal carcinoma altered the staging for a quarter of patients and the management for a fifth of patients, supporting its inclusion early in the staging algorithm.

Keywords PET-CT · Esophageal cancer · Imaging · Radionuclide scanning

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Introduction

Underpinning the tailored management of patients with esophageal or gastroesophageal junction carcinoma is an accurate assessment of disease extent. Positron emission tomography–computed tomography (PET-CT; co-registered positron emission and computed tomography) has been shown to be accurate in the staging of a number of solid cancers,[1] most notably lymphoma,[2] head and neck cancers,[3] and lung cancer,[4] where it has become incorporated into the staging algorithms. However, the place of PET-CT in the management of patients with esophageal and gastroesophageal junction cancers remains unclear. Previous studies have reported conflicting findings, with PET-CT identifying "occult" metastatic disease in between 2% and 36% of patients.[5,6] There are, however, disparities in the staging algorithms employed by previous authors. Most previous studies used PET imaging as the final staging modality, ^{18}F 2-fluoro-2-deoxy-glucose PET (FDG-PET)

alone rather than PET-CT was employed and attempts were made to stage locoregional disease.

The aim of this study was to determine the frequency with which management decisions would be altered by the use of PET-CT when used early in the staging algorithm to assess for the presence of distant metastases.

Patients and Methods

In Leicester, PET-CT was introduced into our staging algorithm for patients with carcinoma of the esophagus or gastroesophageal junction in November 2006. It was employed as the second imaging test after an initial staging helical CT scan in any patient potentially considered for radical surgical or non-surgical therapy. Patients staged as T1-3 N0-1 on an initial CT scan underwent PET-CT. Patients with evidence of multi-site metastases did not proceed to PET-CT. Those with indeterminate abnormalities on CT scan did proceed to PET-CT. Patients free of distant metastatic disease on CT-PET then underwent endoscopic ultrasound (EUS). Staging laparoscopy was utilized after all noninvasive imaging in those patients with any tumor extension below the diaphragm.

We did not employ PET-CT in the assessment of patients with gastric cancer because previous studies have indicated variable FDG avidity of gastric cancers, such that the primary cancer is only visible in around 50% of patients.[7]

Data were collected on patients undergoing PET-CT over a 13-month period after its introduction until December 2007. Patients were identified from the prospectively maintained computerized Upper Gastrointestinal Cancer Multidisciplinary Team (MDT) database. Proformas detailing patient demographics, tumor type and site, and UICC stage were constructed for each patient. Duplicate proformas were created, one with and one without the PET-CT findings. Each proforma was independently reviewed in a randomized and blinded fashion by five consultant members of the esophagogastric cancer MDT (three surgeons, two oncologists) and their treatment strategy recorded (palliative or potentially curative) in addition to the specific management plan. The management plans of MDT members with and without PET-CT staging were compared to each other and to the actual treatment received.

Imaging

Computed Tomography All patients underwent a helical CT scan of the chest and abdomen with intravenous contrast using 100 ml of iomeron 350 that was injected at 3 ml/s. Images were taken from above the thoracic inlet to the iliac crest following a 25-s delay for the chest and 60-s delay for the liver using a single detector Secura scanner (Philips) with a slice thickness of 5 mm. Oral contrast agents were not used. Lymph nodes were considered metastatic when the long axis of the node was measured to be in excess of 1 cm. CT scans were reviewed by a gastrointestinal radiologist.

Positron Emission Tomography–Computed Tomography Co-registered PET-CT was performed using a GE Discovery ST (General Electric) PET-CT scanner with eight-slice CT scan, producing fused single image scans. Half-body PET acquisition was obtained (from eyes to knees). Patients were fasted for 6 h prior to injection with 370 Mbq of ^{18}F-FDG that was administered to patients lying supine in a quiet and warm environment. Whole-body two-dimensional image acquisition was obtained 60 min after injection of ^{18}F-FDG using a 128×128 matrix. Fused PET-CT images were double reported. The diagnostic CT and previous imaging was available at the time of reporting. The threshold for the diagnosis of metastatic disease on PET-CT was a standardized uptake value in excess of 2.5.

Results

The study population was 38 patients (26 men) of median age 65 years (range 43–85 years). The histological subtype was adenocarcinoma in 28 and squamous cell carcinoma in ten. These 38 patients (35%) were derived from a cohort of 108 patients with carcinoma of the esophagus or gastro-esophageal junction discussed at our MDT meeting during the study period.

Twelve patients had abnormalities at single sites on initial helical CT, suggesting possible metastatic disease (Fig. 1). PET-CT confirmed metastatic disease in six of these 12 patients (50%) and identified unexpected metastatic disease in three of 26 patients (12%) with normal CT scans. In one patient, PET-CT identified a synchronous T4 rectal cancer not evident on the initial CT. Six of the 12 patients with suspicious CT scans were downstaged by PET-CT from M1 to M0. Overall, PET-CT changed the definitive staging of ten patients (26%).

Assuming treatment intention to be determined by a majority decision (60% concordance between clinicians), this would have translated into a change in clinical practice for seven of 38 patients (18%; Table 1). For three patients, the consensus decision would have been to ignore small sub-centimeter lesions on the CT scan and to refer the patient for neoadjuvant chemotherapy, re-imaging, and resection.

Based upon CT findings alone, there was concordance in the treatment intent between the five clinicians for 150 of 190 decisions (79%). This increased to 175 of 190 decisions (92%) with the addition of PET-CT findings.

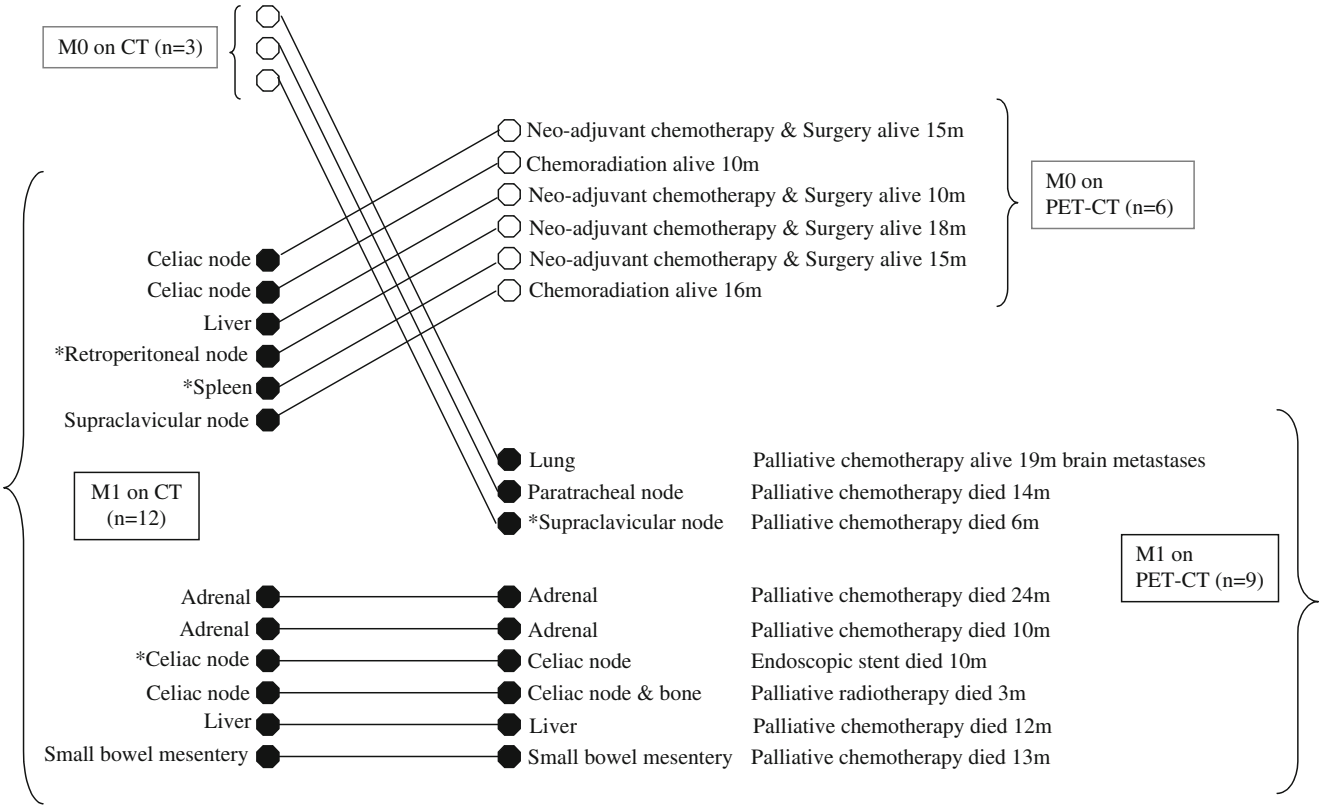

Figure 1 Site of suspicious lesions on CT and PET-CT. Patient outcome is indicated along with survival in months. *Asterisk* denotes patients with squamous carcinoma.

Based upon CT findings alone, complete concordance between all five MDT members was achieved for 25 patients (66%). This increased to 28 patients (74%) with the addition of the PET-CT findings (Table 2).

Table 1 Summary of Each of the Five Clinical Decisions for the 15 Patients Where PET-CT Provided Additional Information

Patient number	Treatment intent change		
	Curative to palliative	No change	Palliative to curative
1	3	2	0
2	4	1	0
3	0	5	0
4	3	2	0
5	3	2	0
6	1	4	0
7	2	3	0
8	0	5	0
9	1	4	0
10	0	3	2
11	0	1	4
12	0	3	2
13	0	2	3
14	0	0	5
15	0	4	1

Figure 2 summarizes patient management. The specificity of PET-CT for the detection of M1 disease was 11/13 (85%).

Discussion

Our principal study findings were that the use of PET-CT early in the staging algorithm of patients with esophageal or gastroesophageal junction carcinoma influenced management in around a quarter of patients. Further, the addition of PET-CT increased agreement between clinicians from 79% to 92%.

The published results of studies using PET and PET-CT in the staging of esophageal cancer are summarized in Table 3. Recent studies have questioned the usefulness of FDG-PET scanning. Van Westereenen et al.[8] evaluated 199 potentially resectable patients with esophageal carcinoma after a staging protocol that included CT, EUS, and

Table 2 Frequency of Concordance Between Five Clinicians for Decision Making for the 38 Patients

	60% concordance	80% concordance	100% concordance
CT	7	6	25
CT and PET-CT	2	8	28

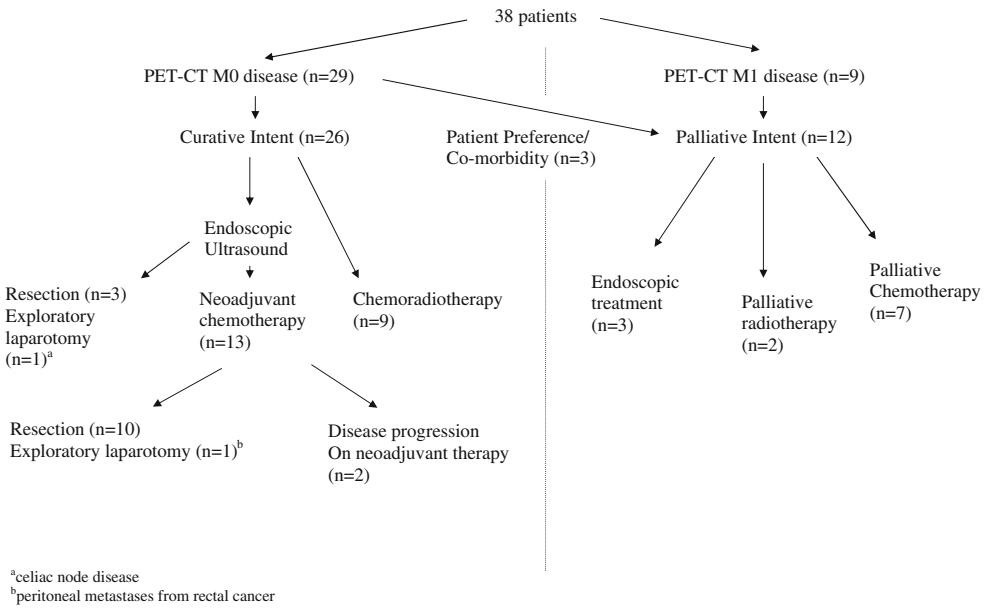

Figure 2 Summary of CT and PET-CT findings and subsequent patient management.

ultrasound of the supraclavicular fossae. Suspicious "hot spots" were demonstrated in 30 patients (15%) on the PET scans. In eight patients, the hot spots indicated metastatic disease (4%), in seven patients (3.5%), synchronous primary tumors were identified, while in 15 patients (7.5%), the scans were assumed to be falsely positive based upon operative or serial scan findings. This study did not employ co-registered PET-CT, with the scans being performed on separate occasions within 2 weeks of each other.

McDonough et al.[6] evaluated co-registered PET-CT in 50 patients with esophageal carcinoma after staging with CT and EUS and found that PET-CT influenced management in only 2% of patients. It is noteworthy that in this study, 44 of the 50 patients (88%) underwent subsequent resection, indicating a referral bias towards patients with relatively early disease.

The majority of published studies have utilized either non-co-registered CT and PET imaging or PET alone (Table 3). These modalities have been superseded by co-

Table 3 Summary of Published Literature on PET Staging of Esophageal Cancer

Author (year)	No. of patients	Pre-PET imaging		PET or PET-CT	Frequency of M1 disease on PET-CT (%)	Frequency of decision change (%)	Sensitivity (%)	Specificity (%)
		EUS	Other					
Block (1997)[12]	58	No	No	PET	29		100	
Luketich (1997)[13]	35	No	No	PET	26		88	93
Kole (1998)[14]	26	No	No	PET	31			
Rankin (1998)[15]	25	No	No	PET	25			
Luketich (1999)[16]	91	No	Bone Scan	PET	30		69	94
Flamen (2000)[17]	74	Yes	No	PET	34		74	90
Lerut (2000)[18]	42	Yes	No	PET	26		77	90
Meltzer (2000)[19]	47	No	No	PET	21		70	90
Wren (2002)[20]	24	No	No	PET	38		67	92
Rasanen (2003)[21]	42	Yes	No	PET	17		47	89
Heeren (2004)[22]	74	Yes	US neck	PET	33		78	91
Sihvo (2004)[23]	55	Yes	No	PET	25		53	89
Bar-Shalom (2005)[9]	32	No	No	Both			100	69
Kato (2005)[24]	149	No	No	PET	16		55	90
Malik (2006)[25]	100	No	No	PET	23			
Katsoulis (2007)[5]	22	No	No	PET	36	23	50	100
Van Westreenen (2007)[8]	199	Yes	US neck	PET	4			
Berrisford (2008)[26]	50	Yes	No	PET-CT	12			
McDonough (2008)[6]	50	Yes	No	PET-CT		2		

registered PET-CT. In a comparative study of PET with PET-CT, Bar-Shalom et al.[9] found that the latter was associated with an improved specificity (81% vs. 59%) and accuracy (90% vs. 83%) compared to the former.

In keeping with published reports, we identified synchronous malignancy in one patient (3%), a rectal carcinoma that was found to be metastatic (peritoneal metastases in the pelvis) at the time of laparotomy. Because of these findings, no esophageal resection was undertaken. The frequency of synchronous tumors has been documented in the range of 1–4% in the literature, with colorectal neoplasia being the most frequently identified.[10,11]

It is apparent from our study and the literature that the influence of PET-CT in the staging algorithm for esophageal cancer is dependent upon its position in the staging algorithm in relation to other tests.[8] Indeed, for our patients, endoscopic or cervical ultrasound would likely have detected distant nodal disease for four of the nine with M1 disease. We consider that it does not matter which order the imaging investigations are performed in, but that it would seem sensible to exhaust noninvasive tests first.

We are aware of the limitations of this study, notably the paucity of information on the sensitivity of PET-CT. However, we considered that there was good evidence validating the technique of PET-CT, making it unethical to subject patients to unnecessary biopsy to confirm M1 disease. Indirect confirmation that the PET-CT abnormalities were metastatic in nature was derived from the survival information for the nine patients with M1 disease. According to most recent follow-up, eight of these nine patients have died (Fig. 1).

In summary, we found that PET-CT altered the stage of ten of 38 patients (26%) with esophageal or gastroesophageal junction carcinoma. When this information was reviewed by five esophagogastric interest consultants in a blinded fashion, it would have translated into a change in management decision for seven of 38 (18%) patients. PET-CT has a useful role as the second imaging modality in patients being considered for radical therapy.

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ORIGINAL ARTICLE

Results of Completion Gastrectomies in 44 Patients with Postsurgical Gastric Atony

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Abstract
Introduction Postsurgical gastric atony occurs infrequently after gastric surgery. However, the symptoms are disabling and refractory to medical management. The only effective treatment is completion gastrectomy. A few studies have examined in detail the long-term results of this radical procedure.
Methods From 1988 through 2007, 44 patients (84% female, 16% male) underwent near-total or total completion gastrectomies for refractory postsurgical gastric atony. The average age was 52 (range 32–72). Gastric atony was documented using radionuclide solid food emptying studies. Charts were reviewed retrospectively to identify preoperative symptoms and long-term postoperative function, and the patients were contacted by phone to evaluate their current level of function.
Results Of the original 44 patients, 66% (n=29) were evaluated postoperatively at a mean of 5.6+4.5 years (range 0.5–15.0 years). Fourteen patients (32%) had died, and seven (16%) were lost to follow-up. Most common presenting symptoms were abdominal pain (98%), vomiting (98%), nausea (77%), diet limitation (75%), heartburn (64%), and weight loss (59%, average=19% of BW). Postoperative complications occurred in 36% (n=16), most commonly bowel obstruction (11%), anastomotic stricture (9%), and anastomotic leak (7%), and there was one perioperative death. At last follow-up, there were significant improvements in abdominal pain (97% to 59%, $p<0.001$), vomiting (97% to 31%, $p<0.001$), nausea (86% to 45%, $p<0.001$), and diet limited to liquids or nothing at all (57% to 7%, $p<0.001$). Some symptoms were more common postoperatively, including early satiety (24% to 89%, $p<0.001$), and postprandial fullness (10% to 72%, $p<0.001$). Average BMI at the time of surgery and at last follow-up were 23 and 21, respectively. Osteoporosis was diagnosed pre- and postoperatively in 17% and 67% of patients, respectively ($p<0.001$). Seventy-eight percent of patients stated that they were in better health after surgery, while 17% were neutral, and 6% stated that they were worse off. Mean satisfaction with surgery was 4.7 (1–5 Likert scale).
Conclusion Completion gastrectomies in this patient population resulted in significant improvements in abdominal pain, vomiting, nausea, and severe diet limitations. Most patients, however, have significant ongoing gastrointestinal complaints, and the incidence of osteoporosis is high. Patient satisfaction is high; about 78% of patients believed their health status is improved. We believe these data support the selective use of completion gastrectomies in patients with severe postsurgical gastroparesis.

Keywords Gastroparesis · Gastric atony · Completion gastrectomy

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Introduction

Postgastrectomy syndromes occur commonly after gastric procedures for peptic ulcer or cancer. These syndromes can be divided into two categories: postcibal and nutritional. The nutritional consequences of gastric surgery include malabsorption of calories, iron, and nutrients. Weight loss is common due to fear of eating caused by postcibal symptoms and loss of appetite. The postcibal syndromes

are largely due to motility disorders such as rapid gastric emptying or delayed gastric emptying.[1] Postsurgical gastric atony (PSGA) or gastroparesis is an uncommon but devastating consequence of gastric surgery, characterized by nausea, vomiting, abdominal pain, early satiety, bloating, and weight loss. In severe cases, patients with PSGA require frequent hospitalizations and become dependent on parenteral nutrition.[2]

Acute gastroparesis occurs in as many as 50% of patients undergoing gastric resection or other procedures involving the stomach.[3] It usually resolves within a few days without intervention. Chronic gastric atony or gastroparesis typically develops years later and is not always preceded by acute gastroparesis. Chronic PSGA is thought to be related to vagal nerve injury as well as the anatomic changes resulting from surgery.[2,4] Although patients who develop gastroparesis following truncal vagotomy and drainage may have rapid initial emptying of liquids due to impaired fundic relaxation with loss of reservoir function, they will not empty solids normally due to an absence of the normal lag phase for solids.[4,5,6]

The incidence of severe PSGA is probably less than 5% in patients after most operations for peptic ulcer.[3,7] The incidence is much higher after secondary procedures for postgastrectomy syndromes, such as Roux-en-Y diversion procedures in patients thought to have bile-reflux gastritis.[7,8,9,10] Medical therapy for PSGA consists of dietary restrictions and prokinetic medications such as metoclopramide, erythromycin, and domperidone.[2,11] However, these medications have significant side effect profiles and usually have little effect on the symptoms. Many patients become addicted to narcotic analgesics which further impair gastric emptying.[2]

Most reports describing the results of surgery for intractable PSGA are small with incomplete symptom evaluation and short follow-up. One large series concluded that only 43% of patients had good results after gastrectomy for PSGA.[12] On the other hand, several smaller series and one other large series reported successful reduction of symptoms in as many as 80% of patients.[6,13–20] The goal of this study was to analyze our series of patients who have undergone completion gastrectomies for documented PSGA, by comparing preoperative symptoms to long-term postoperative symptoms and health status, and to evaluate patient satisfaction with the procedure.

Materials and Methods

Study Participants

A search of the medical records by CPT code for all patients who underwent total or near-total gastrectomies for documented postsurgical gastroparesis by the primary gastric surgeon at our institution was performed. Inclusion criteria were all patients that had total or near-total gastrectomies for documented gastric atony after previous gastric surgery. Exclusion criteria were any patients under the age of 18 and any patients that chose to opt out of the study. Between 1988 and 2007, a total of 44 patients underwent total or near-total gastrectomy by a single surgeon at our institution for documented postsurgical gastric atony. No patients were excluded based on age, and none chose to opt out of the study. Gastroparesis was documented in all 44 patients by symptomology and confirmed with radionuclide solid food emptying studies. Only one patient (2%) was unable to tolerate the solid food emptying study, and while they did have a normal liquid emptying study, their symptoms, combined with the fact that they were unable to tolerate the solid food study, were considered sufficient documentation of gastroparesis. Gastric outlet obstruction was ruled out by endoscopic evaluation of the stomach. Symptoms of gastroparesis were considered to be nausea, vomiting, abdominal pain, diet limitation, weight loss, bloating, early satiety, and postprandial fullness. Data was extracted on all of these patients from the medical record, including demographics, symptoms, functional status, health status, previous operations, diagnostic studies, operation performed, postoperative course, morbidity and mortality, and short- and long-term follow-up.

Follow-up

Long-term follow-up was performed by searching the medical record and contacting the patients. The Social Security Death Index was consulted to identify deceased patients, and all other patients were contacted by mail at their last known address to advise them that the study was in progress, and that they would be contacted with a survey about their current health status. Contact was attempted with all living patients using their last known phone number, and when reached, a phone survey was conducted regarding their current symptoms, health status, diet and weight status, and patient satisfaction. All phone interviews were conducted by individuals without prior contact with the patients. In the event that a living patient could not be reached by phone, a paper copy of the same survey was mailed to their last known address with instructions to fill out and return. Patient satisfaction was evaluated both by directly asking patients if they felt better now with respect to their gastroparesis symptoms than they did prior to their operation and by asking them to rate their satisfaction on a 1–5 Likert scale (1 = not satisfied, 2 = somewhat dissatisfied, 3 = neutral, 4 = somewhat satisfied, 5 = very satisfied). Twenty-nine patients (66%) were evaluated postoperatively at a mean (+SD) of 5.6+4.5 years (range 0.5–15.0 years). Fourteen patients (32%) were deceased, and seven (16%) were lost to follow-up.

Demographics

Thirty-seven (84%) patients were female and seven (16%) were male, with an average age of 52 (range 32–72). Average BMI prior to operation was 23 kg/m^2 (range 15 to 34). Average weight loss was 19% of their total body weight between the onset of symptoms and their completion gastrectomy. Sixty-three percent of patients had a history of chronic narcotic use for pain related to their gastroparesis symptoms. Presenting symptoms are listed in Table 1, with the most common presenting symptoms being abdominal pain (98%), vomiting (98%), nausea (77%), and any diet limitation (75%).

We noticed that the pain reported in these patients was consistent in character and location, particularly those who had had prior antrectomies. Pain typically occurred minutes after eating a meal and was consistently centered at or just above the left costal margin about 4 cm to the left of the midline. Patients consistently cup the fingers of the left hand with the fingers hooking the left costal margin when asked to localize their pain.

Fifty-six percent of patients reported a diet limited to liquids or nothing at all, and 11% reported being unable to tolerate any oral nutrients [i.e., total parenteral nutrition (TPN) or jejunostomy tube dependent]. Other symptoms upon initial presentation were heartburn (64%), diarrhea (34%), bloating (25%), early satiety (23%), and postprandial fullness (11%). Preoperatively, anemia was reported in 58% of patients, osteoporosis in 19%, and diabetes in 12%. The initial operations are shown in Table 2. Our patients had undergone an average of 2.5 previous gastric operations; 61% had had two or more previous gastric operations. Two patients (5%) previously had a gastric electrical stimulator placed. The indications for the original operations were peptic ulcer disease (75%), morbid obesity (11%), GERD (9%), and bile reflux (5%). Most patients, 35 out of 44, had vagotomies performed at their index operations. In the remaining nine patients with complications of bariatric surgery or anti-reflux surgery, it was our opinion that vagal damage was a contributing factor in their gastric atony. Congo red testing was used to confirm abnormal vagal innervation in these patients. Early in our experience, we performed preoperative vagotomy testing (sham feeding and/or Congo red testing) in all patients. In a previous report,[21] we concluded that vagotomy testing affected operative planning or intraoperative decision making in many patients, since complete vagotomy is an essential component of any Roux-en-Y gastrojejunostomy. Of patients tested, about 20% had evidence of persistent vagal innervation or incomplete vagotomy. More recently, in patients undergoing total or near-total (less than 20 cc remnant) gastrectomies, we have not routinely performed vagotomy testing

Operation

Of the 44 patients, 19 (43%) underwent total completion gastrectomies with esophageal transection and Roux-en-Y esophagojejunostomy reconstruction. Esophagojejunostomy was performed using an end-esophagus to side-jejunum anvil stapler technique. Twenty-five (57%) patients underwent near-total completion gastrectomies with a small cuff of stomach tissue left in place (range, small rim of tissue to 25 cc pouch). The anastomosis in these patients was either a two-layer, hand-sewn end to side anastomosis, or alternatively, a stapled end to side anastomosis. Sixty-seven percent of patients had feeding jejunostomies placed at the time of operation.

Data Analysis

All data presented are reported as the mean (+SD) except where noted. The frequency of preoperative versus postop-

Table 1 Presenting Symptoms of Patients

		Symptoms before and after surgery in patients with follow-up		
Symptom	Percent of all patients (%)	Preoperative (%)	Postoperative (%)	*p* Value
Abdominal pain	98	97	59	<0.001
Vomiting	98	97	31	<0.001
Nausea	77	86	45	<0.001
Diet limitation	75	71	46	0.06
Heartburn	64	62	35	0.06
Weight loss	59			
Diet limited to liquids or nothing	56	57	7	<0.001
Diarrhea	34	34	41	0.59
Bloating	25	21	39	0.18
Early satiety	23	24	89	<0.001
Postprandial fullness	11	10	72	<0.001

Table 2 Initial Operation of Patients with PSGA

Operation	Percent of patients (%)
Vagotomy/antrectomy/Billroth I	36
Vagotomy/antrectomy/Billroth II	25
Vagotomy/pyloroplasty	11
Nissen fundoplication	9
Vagotomy/antrectomy/Roux-en-Y	7
Vagotomy/gastrojejunostomy	2
Vertical banded gastroplasty	2
Pancreatico-biliary bypass/partial gastrectomy	2
Unknown	5

erative symptoms and health status data was evaluated for statistical significance using Fisher's exact test. A p value of <0.05 was considered to be statistically significant.

Results

Outcomes

Detailed long-term (> 6 months) follow-up was available in 29 (66%) of the 44 patients at a mean of 5.6+4.5 years (range 0.5–15.0 years). Long-term follow-up was unavailable in 15 patients, none of whom were listed in the Social Security Death Index. Symptoms of gastroparesis at follow-up were compared to preoperative presentation in the same patients (paired t test). The records were specifically searched to quantify the frequency of the typical left upper quadrant pain descriptor. The location of the pain, when specifically mentioned in the medical record, was classic in 83% of patients.

Table 1 shows symptoms that were improved at follow-up after completion gastrectomies. Patients had improvement in abdominal pain (97% to 59%, $p<0.001$), vomiting (97% to 31%, $p<0.001$), nausea (86% to 45%, $p<0.001$), and diet limited to liquids or nothing at all (57% to 7%, $p<0.001$). Symptoms including any limitation in diet (71% to 46%, $p=0.06$) and heartburn (62% to 35%, $p=0.06$) trended toward improvement at postoperative follow-up. As shown in Table 1, symptoms at presentation were similar in all patients and in those available for long-term follow-up.

Table 1 shows symptoms that were worsened at follow-up. Significant increases were seen in the percent of patients reporting early satiety (24% to 89%, $p<0.001$) and postprandial fullness (10% to 72%, $p<0.001$). Increased frequencies of bloating (21% to 39%, $p=0.18$) and diarrhea (34% to 41%, $p=0.59$) were not statistically significant.

Table 3 shows the effect of operation on several health measures. Average BMI decreased from 23.4+4.5, preoperatively, to 20.7+4.3 at follow-up. Incidence of osteoporosis was significantly increased postoperatively (17% to 67%, $p<0.001$). Incidence of anemia (59% to 67%, $p=0.58$) and diabetes (10% to 11%, $p=1$) were unchanged. Although patients reported less pain, the frequency of chronic narcotic use was 59% and 62% pre- and postoperatively, respectively.

Patient satisfaction was measured in two ways. Patients were asked whether they were better off with respect to their gastroparesis symptoms at follow-up; 78% reported that they were in better health. Seventeen percent reported that their health status was unchanged, and 6% reported that they were worse. When asked to rate their satisfaction with their surgery on a 1–5 Likert Scale (1 not satisfied, 2 somewhat dissatisfied, 3 neutral, 4 somewhat satisfied, 5 very satisfied), the average response was 4.7+0.6 (1=0%, 2=0% , 3=6%, 4=18%, and 5=76%).

Morbidity and Mortality

There was one in-hospital, postoperative death. This patient had a near-total resection and developed a leak at the gastrojejunostomy leading to sepsis and respiratory failure, and care was withdrawn approximately 3 weeks postoperatively. One or more complications occurred in 16 of 44 patients (36%). Small bowel obstruction was the most common complication, occurring in five patients (11%). Three of the five small bowel obstructions occurred at the site of the feeding jejunostomy. Thus, three out of 26 or 12% of patients having jejunostomies placed had known bowel obstructions related to their feeding catheters. Anastomotic strictures occurred in four patients (9%), all of which had undergone a total gastrectomy with esophagojejunostomy. All

Table 3 Health Measures Compared Pre- and Postoperatively

	Preoperative	Postoperative	p Value
Average BMI	23	21	
Osteoporosis	17%	67%	<0.001
Anemia	59%	67%	0.58
Diabetes	10%	11%	1
Chronic narcotic use	59%	62%	0.81

were treated successfully with endoscopic dilation. Anastomotic leak occurred in three patients (7%), two of which had undergone near-total gastrectomy and one of which had undergone total gastrectomy. Other reported complications included wound infection (7%), intra-abdominal abscess (5%), pancreatic fistula (2%), jejuno-cutaneous fistula (2%), and bile reflux (2%). There have been no known marginal ulcers. At follow-up, 14 patients (32%) were found to be deceased at an average age of 57+10.1 years (range 35 to 74 years of age) and at an average of 3.8+2.7 years postoperatively (range, 0.1 to 9.0 years). Causes of death were pneumonia in three patients, multiple organ failure, and cerebral vascular accident, all unrelated to the surgical procedure. The cause of death was unable to be determined from our records in eight of the 14 patients (57%) who were deceased at the time of the study.

Feeding Jejunostomy

Feeding jejunostomy data was available in 39 of the 44 patients. Of these, 26 (67%) had feeding jejunostomies placed during the initial operation. Twenty-three (88%) patients remained on at least supplemental alimentation through their feeding jejunostomies after discharge for a minimum of 2 weeks postoperatively. One or more complications directly related to feeding jejunostomy placement occurred in four of the 26 patients (15%). The median duration of use of the feeding jejunostomy was 27 days (range 5–1,475 days), and one patient (4%) was still on supplemental feeding through their jejunostomy tube at long-term follow-up (1,475 days postoperatively).

Discussion

The present study represents the third largest reported series describing the results of completion gastrectomies in patients with postsurgical gastric atony. These patients tend to be women (85%) and had, on average, 2.5 previous gastric operations. This female to male ratio is the same as that seen in patients with idiopathic gastroparesis and is consistent with the hypothesis that many of these patients had impaired gastric emptying prior to their original gastric operation. In addition, a significant number had ill-advised Roux-en-Y diversions for bile reflux. We believe that the primary pathologic state in most patients with the bile reflux syndrome after gastric operations is impaired emptying and/or clearance of bile, not pathologic reflux. This distinction is critical, since the most commonly performed remedial procedure in these patients, a Roux-en-Y diversion, will exchange one syndrome (bile reflux gastritis) for a worse syndrome (the Roux syndrome). In our opinion, the majority of patients with bile-reflux gastritis who need operations should have total or near-total gastrectomies as their definitive operation.

Completion gastrectomy was successful in approximately 78% of patients, with significant reductions in incidence of abdominal pain, nausea, vomiting, and severe limitations in diet. While several studies have suggested similar success rates,[6,13–20] Forstner-Barthell and co-workers from the Mayo Clinic reported a success rate of only 43% based upon classification of patients by Visick grade.[12] In the Visick grading system, patients are classified according to the frequency and severity of symptoms. Thus, in the Mayo Clinic series, only 43% of patients were in the favorable Visick grades I–II. Most patients continue to have significant gastrointestinal symptoms after total gastrectomies, thus resulting in frequent Visick III–IV classification. In our opinion, this ignores the clinically and statistically significant improvement in most symptoms. That is, we believe that patients with significant improvements in almost all symptoms and improved health status after surgery should be classified as successes. For example, prior to surgery, 57% of our patients reported that their diet was limited to liquids or nothing at all. At postoperative follow-up, only 7% were limited to liquids or less, a reduction by 88% of patients whose diets were limited in this severe manner. We also found that 39% of patients had complete resolution of their abdominal pain, 68% had complete resolution of their vomiting, and 48% had complete resolution of their nausea. Many of our patients reported modest weight loss after surgery, with an average reduction in BMI of only 2.7 kg/m^2. Other gastrointestinal symptoms were still common: 59% of patients still had some abdominal pain (most still used narcotics), 45% still had occasional nausea, 31% still had occasional vomiting, and 46% still had some type of diet limitation. The explanation for the lack of weight gain in many of our patients despite subjective improvement in their symptoms is unclear. Experience in patients with total gastrectomies for gastric cancer (10–20% loss in body weight) suggests that anorexia after gastrectomy is a very important contributor to weight loss. We now realize that pre- and postoperative consultation with dieticians with special interests in postgastrectomy syndromes is an essential part of care.

We noticed that the pain reported in these patients was consistent in character and location, particularly those who had had prior antrectomies. Pain typically occurred minutes after eating a meal and was consistently centered at or just above the left costal margin about 4 cm to the left of the midline. Patients consistently cup the fingers of the left hand with the fingers hooking the left costal margin when asked to localize their pain. PSGA is the only known condition that presents in this manner with chronic postprandial pain centered at or just above the left costal margin about 4 cm to the left of the midline. This sign was seen in 83% of the patients in our study.

Osteoporosis, a well-known complication of total gastrectomy, was common in our patient population. Absorption of calcium has been shown to be normal in most patients after gastric resections.[22] Malabsorption of fats and fat-soluble vitamins due to a decrease in pancreatic enzyme secretion and poor mixing likely contributes to osteoporosis. Previous studies of postgastrectomy patients have documented abnormal bone biopsies, elevated serum alkaline phosphatase, and parathyroid hormone levels, and decreased serum 25-hydroxy vitamin D levels.[1] These patients are prone to pathologic fractures. Standard of care in these patients involves supplementation of vitamin B12, folate, iron, calcium, and vitamin D. Although there are no studies that have demonstrated convincingly that supplementation in this manner will decrease the likelihood of developing bone disease, we recommend that postgastrectomy patients be monitored closely postoperatively for development of osteoporosis. Many of our patients did not supplement their diets as prescribed.

Feeding jejunostomies were placed in a majority of our patients, and in the last several years have been placed in all of our completion gastrectomy patients. A majority of patients were discharged on at least partial tube feedings with the median duration of use of the feeding jejunostomy being 27 days. Although jejunostomy tubes resulted in small bowel obstructions in about 10% of patients (a frequency similar to that in the trauma literature), we believe the benefits are greater than the risk. Others have utilized tube duodenostomies for temporary alimentation in this patient population. We recommend that all patients undergoing this procedure for PSGA have feeding catheters placed at the time of operation.

A Roux-en-Y gastrojejunostomy is an ulcerogenic operation. Thus, if any stomach is retained, the remnant must be very small (i.e., less than 20 cc pouch). If more stomach is retained, the risk for marginal ulceration is significant, and preoperative vagotomy testing and repeat vagotomy should be strongly considered. Furthermore, we believe the risk for recurrent symptoms of poor emptying is likely if the remnant is larger than 20–30 cc. The size of the gastric remnant must be very small. We have begun to use the near-total gastric resections with Roux-en-Y gastrojejunostomy reconstructions in these patients whenever possible. We feel as though this operation is safer than a total gastrectomy, as esophagojejunostomy with a small cuff of stomach provides a safer anastomotic conduit. Reported leak rates in the literature are between 2% and 9% for esophagojejunostomy after total gastrectomy,[23–25] versus the standard leak rate of less than one percent reported in recent bariatric literature after a standard Roux-en-Y gastric bypass.[26,27] Furthermore, all four of our patients who had postoperative anastomotic strictures requiring dilatation had undergone a total resection with esophagojejunostomy. In some patients, leaving even a small gastric remnant is impossible, due to the nature of the previous operations, adhesions, and distortion at the gastroesophageal junction. Thus, total gastrectomy with esophagojejunostomy may be necessary. However, we recommend performing near-total resection with gastrojejunostomy in most patients.

The number of patients for whom long-term follow-up was not available, mainly due to the number of deceased patients, is a limitation of this study. Most of these deaths were not directly related to their gastric operation or their gastrointestinal complaints, but rather to more chronic medical conditions. However, a lack of proper nutrition may lead to an increase in chronic medical conditions and may have been an underlying cause of death in some of these patients.[28,29] The number of deaths in our study raises the concern that the poor nutritional status of this patient population, both *before* and *after* surgery, may adversely affect longevity.

In summary, we found that patients undergoing completion gastrectomies for refractory, documented PSGA have statistically significant reductions in abdominal pain, nausea, vomiting, and severe diet limitations. However, most patients still have significant gastrointestinal complaints, and further weight loss is common. The incidence of osteoporosis is increased and must be monitored closely. Feeding jejunostomies should be placed and used in all patients. Patients are satisfied with the results of their operation. A majority (78%) of our patients stated that they felt better as a result of their surgery, and the overall satisfaction rating was high.

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ORIGINAL ARTICLE

Risk Factors of Survival and Surgical Treatment for Advanced Gastric Cancer with Large Tumor Size

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Abstract
Background The purpose of this study was to clarify the clinical significance of tumor size in advanced gastric cancer and to evaluate the risk factors of survival in advanced gastric cancer with large tumor size.
Methods The cut-off point for tumor size, 90th percentile value of tumor size in advanced gastric cancer, was determined to be 10 cm. We retrospectively studied the clinicopathological features and prognosis of 406 patients with advanced gastric tumors measuring 10 cm or more.
Results Large tumors had a propensity for the following: Borrmann type IV, adjacent organ invasion, lymph node and distant metastasis, and stage IV classification. Tumor size was an independent risk factor for lymph node metastasis and survival in advanced gastric cancer. In patients with large advanced gastric cancer, Borrmann type IV, adjacent organ invasion, and N2–3 nodal involvement were independent factors associated with a poorer prognosis. The 5-year survival rate in large gastric cancer patients without any risk factors (65.5%) was similar with those in small gastric cancer patients (59.3%, P=0.123).
Conclusion Tumor size was a simple predictor for lymph node metastasis and survival in advanced gastric cancer. Radical surgery should be recommended for large advanced gastric cancer patients without risk factors, while large gastric cancer with risk factors may not be a surgically treatable disease.

Keywords Advanced gastric cancer · Tumor size · Surgical treatment

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Introduction

The prognosis of advanced gastric cancer is still unfavorable, even after radical surgery.[1] It is important to determine the prognosis and perform appropriate therapeutic modalities for patients with advanced gastric cancer. Some potential clinicopathological factors, such as age, tumor size, macroscopic type, depth of invasion, nodal status, distant metastasis, and pathologic type, have been evaluated to identify the factors affecting survival in patients with gastric cancer.[2–4] Many studies have demonstrated that the depth of tumor invasion and status of lymph nodes metastasis are the most important prognostic factors in gastric cancer. Tumor size is another valuable clinicopathological feature because it can be measured easily before or during operation. However, the prognostic value of tumor size in patients with gastric cancer remains controversial. Some studies showed that tumor size served as a simple predictor of long-term survival after resection of advanced

gastric cancer.[5–6] Conversely, other studies reported that tumor size was not an independent prognostic factor in patients with gastric cancer.[2–4] The purpose of this study was to clarify the clinical significance of tumor size in advanced gastric cancer and to evaluate the risk factors of survival in advanced gastric cancer with large tumor size.

Patients and Methods

From January 1987 to December 2001, a total of 5,955 patients with gastric cancer underwent gastrectomy in the Department of Surgery, College of Medicine, Yonsei University in Korea. According to the Japanese Classification of Gastric Cancer,[7] 1,975 patients were histologically proven to suffer from early gastric cancer and the remaining 3,980 patients who had advanced gastric cancer were enrolled in this study.

Tumor size was measured according to the Japanese Classification of Gastric Cancer. The dissected stomach specimen was fixed on a flat board, and the maximum tumor diameter was determined. The distribution of patient number linked with tumor size was shown in Fig. 1. Tumor size ranged from 0.5 to 25 cm (mean 5.7 cm, median 5.0 cm). The 90th percentile value for tumor size was 10 cm. Furthermore, we performed a survival analysis using Cox proportional hazards model based on tumor size, depth of invasion (T2–4), and lymph node metastasis (N0–3). The cut-off value for tumor size was defined as the test size with which the highest Wald chi-square value was obtained in this study. That highest chi-square value was 13.999 ($P<0.001$, hazard ratio=1.538, 95%CI=1.263–1.722) for a test tumor size at 10 cm. Based on this result and the 90th percentile value, we set the cut-off point for tumor size at 10 cm. Using this value, patients were divided into two groups: the small size group (tumor size <10 cm, $n=3,574$) and the large size group (tumor size ≥10 cm, $n=406$).

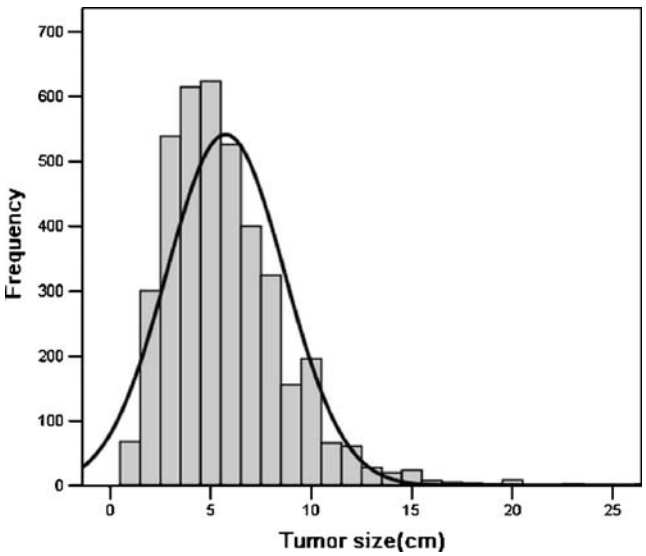

Figure 1 The distribution of patient number linked with tumor size. Tumor size ranged from 0.5 to 25 cm (mean 5.7 cm, median 5.0 cm).

The clinicopathological features, such as gender, age, Borrmann types, depth of invasion, status of lymph node metastasis, hepatic metastasis, peritoneal dissemination, TNM stage,[8] pathological classification, and surgical type, were collected from the database and compared between the two groups.

Statistical Analysis

Statistical analysis was performed with the Statistical Package for Social Science (SPSS) version 13.0 for Windows (SPSS, Chicago, IL, USA). Data were analyzed statistically using Student's t test and chi-square test. Survival rate was analyzed using the Kaplan–Meier method, and the difference between the curves was assessed using the log-rank test. Multivariate analysis was performed using the logistic regression model for analysis of lymph node metastasis and the Cox proportional hazards model for survival analysis (backward Wald). A P value of <0.05 was considered statistically significant.

Results

Clinicopathological Characteristics

Compared to the small tumors, large tumors were frequently observed in female patients ($P=0.006$) and had a larger proportion of the following characteristics: Borrmann IV macroscopic type, adjacent organ invasion, N2–3 lymph node metastasis, hepatic metastasis, peritoneal dissemination, stage IV classification, and undifferentiated histology ($P<0.001$; Table 1). Patients with large tumors received more total gastrectomies (70.9% vs 32.4%) and combined resections (59.1% vs 26.2%) than patients with small tumors.

The mean number of total retrieved lymph nodes in patients with large tumors was more than that in patients with small ones. The patients with large tumors had more lymph node metastasis than those with small tumors (85.5% vs 69.8%, $P<0.001$). Using univariate analysis, a large tumor size, Borrmann types III and IV, serosal invasion, mean number of total retrieved lymph nodes more than 40, and undifferentiated histological type were significantly associated with lymph node metastasis. Multivariate logistic regression analysis showed that tumor size, macroscopic types, depth of invasion, mean number of total retrieved lymph nodes, and undifferentiated histology were independent risk factors of lymph node metastasis in advanced gastric cancer (Table 2).

Table 1 Clinicopathological Findings in Patients with Advanced Gastric Cancer

Variables	Tumor size		*P* value
	<10 cm (*n*=3,574)	≥10 cm (*n*=406)	
Age (mean, years)	55.7±11.7	54.7±13.1	0.119
Gender			0.006
Male	2,440 (68.3)	250 (61.6)	
Female	1,134 (31.7)	156 (38.4)	
Borrmann type			<0.001
Type I	201 (5.6)	31 (7.6)	
Type II	823 (23.0)	40 (9.9)	
Type III	2,169 (60.7)	150 (36.9)	
Type IV	330 (9.2)	182 (44.8)	
Unknown	51 (1.4)	3 (0.7)	
Depth of invasion			<0.001
T2	1,026 (28.7)	26 (6.4)	
T3	2,211 (61.9)	239 (58.9)	
T4	337 (9.4)	141 (34.7)	
Total retrieved LN number	41.5±16.3	44.8±19.2	<0.001
Lymph node metastasis			<0.001
N0	1,081 (30.2)	59 (14.5)	
N1	1,295 (36.2)	108 (26.6)	
N2	692 (19.4)	94 (23.2)	
N3	506 (14.2)	145 (35.7)	
Hepatic metastasis			<0.001
Negative	3,520 (98.5)	384 (94.6)	
Positive	54 (1.5)	22 (5.4)	
Peritoneal dissemination			<0.001
Negative	3,403 (95.2)	331 (81.5)	
Positive	171 (4.8)	75 (18.5)	
Stage			<0.001
I	496 (13.8)	9 (0.2)	
II	928 (26.0)	43 (10.6)	
III	1,380 (38.6)	123 (30.3)	
IV	770 (21.5)	231 (56.9)	
Pathologic classification			<0.001
Differentiated	1,286 (36.0)	95 (23.4)	
Undifferentiated	2,288 (64.0)	311 (76.6)	

Survival Analysis

The cumulative survival rate was significantly lower in patients with large tumors than in those with small tumors ($P<0.001$). The cumulative 5- and 10-year survival rates were 32.5% and 26.0%, respectively, for patients with large tumors and 58.3% and 47.2%, respectively, for those with small tumors.

Using multivariate analysis of survival, we found that tumor size (risk ratio=1.455, $P<0.001$), as well as age, serosal invasion, lymph node metastasis, hepatic metastasis, and peritoneal dissemination, was an independent prognostic factor in patients with advanced gastric cancer (Table 3). Furthermore, we performed Cox regression analysis in all 406 patients with large tumors and found that Borrmann type IV, adjacent organ invasion (T4), and N2–3 lymph node metastasis were independent risk factors for such patients (Table 4). The overall 5-year survival rate in large gastric cancer patients without risk factors (65.5%) and in patients with small gastric cancer (59.3%) were significantly higher than those in large gastric cancer patients with any risk factors (24.0%, $P<0.001$). No statistical difference in survival rate was found between large gastric cancer patients without risk factors and patients with small gastric cancer ($P=0.123$; Fig. 2).

Table 2 Multivariate Analysis of the Risk Factors for Lymph Node Metastasis in Advanced Gastric Cancer

Variables	Risk ratio	95%CI	*P* value
Size (cm)			
<10	1		
≥10	1.631	1.210–2.195	0.001
Borrmann type			
Types I, II	1		
Types III, IV	1.321	1.138–1.540	<0.001
Total number of retrieved LN			
≤40	1		
>40	1.201	1.087–1.503	0.002
Depth of invasion			
T2	1		
T3	2.684	2.292–3.143	<0.001
T4	5.299	3.889–7.220	<0.001
Histology			
Differentiated	1		
Undifferentiated	1.169	1.009–1.347	0.041

Table 3 Multivariate Analysis of Prognostic Factors in Advanced Gastric Cancer Patients Using the Cox Proportional Hazards Model

Variables	Risk ratio	95%CI	*P* value
Age (years)			
≥55 vs <55	1.208	1.103–1.322	<0.001
Gender			
Female vs male	0.948	0.860–1.044	0.278
Tumor size(cm)			
≥10 vs <10	1.455	1.276–1.659	<0.001
Serosal invasion			
Present vs absent	1.986	1.748–2.257	<0.001
Total number of retrieved LN			
≥40 vs <40	1.082	0.946–1.326	0.132
Lymph node metastasis			
Positive vs negative	2.265	2.004–2.559	<0.001
Hepatic metastasis			
Positive vs negative	2.440	1.885–5.175	<0.001
Peritoneal dissemination			
Positive vs negative	3.364	2.900–3.9014	<0.001
Histology			
Undifferentiated vs differentiated	1.059	0.960–1.168	0.253

Table 4 Multivariate Analysis of the Risk Factors for Survival in Advanced Gastric Cancer with Tumor Measuring 10 cm or More

Variables	Risk ratio	95%CI	*P* value
Borrmann type			
Types I and II	1		
Type III	1.209	0.824–1.774	0.332
Type IV	1.694	1.152–2.490	0.007
Depth of invasion			
T2	1		
T3	1.244	0.683–2.269	0.475
T4	2.404	1.309–4.416	0.005
Lymph node metastasis			
N0	1		
N1	1.163	0.747–1.811	0.505
N2	2.004	1.297–3.095	0.002
N3	2.650	1.726–4.069	<0.001

Discussion

Previous studies demonstrated that tumor size was significantly associated with lymph node metastasis and was an important indicator for using minimally invasive surgery in early gastric cancer.[9] Two centimeters is the most common cut-off value for tumor size in early gastric cancer; however, there is no such universally accepted value for tumor size in advanced gastric cancer. In some studies, patients were divided into three groups by tumor size smaller than 4 cm, 4–10 cm, and larger than 10 cm.[5] In another study, patients were grouped by tumors measuring up to 26 mm, between 26 and 50 mm, and over 50 mm.[6] Moreover, some investigators define tumors measuring 10 cm or more in diameter as large,[10] but no evidence supported the aforementioned tumor size scales. In the present study, the cut-off point for tumor size was determined by multivariate analysis of survival, and the result coincided with the 90th percentile tumor size value for total advanced gastric cancer. Thus, we set an appropriate cut-off point for tumor size at 10 cm.

In this study, large tumors were characterized by aggressive clinicopathological features, including Borrmann IV macroscopic type, adjacent organ invasion (T4), and higher lymph node and distant metastasis rates, leading to a larger proportion of total gastrectomies and combined resections. Consequently, patients with large tumors had a larger proportion of stage IV tumors, resulting in a significantly worse prognosis than those with small tumors. Another interesting finding of this study was that there was a large proportion of undifferentiated pathological types and female predomination in patients with large tumors. Adachi et al. reported that patients with gastric cancer of poorly differentiated pathological type were distinguished by their female predomination, infiltrative gross type, serosal invasion, lymph node metastasis, peritoneal dissemination, and advanced stage.[11] Although the pathological type was not an independent factor for survival under multivariate analysis, undifferentiated histological type predomination may play some role in the malignant behavior of larger tumors.

Lymph node metastasis is one of the most important prognostic factors after surgery for gastric cancer.[12–14] Shen et al. reported that tumor size was an independent risk factor (odds ratio=1.9) correlated with lymph node metastasis in gastric cancer.[15] In this study, patients with large tumors not only had higher lymph node metastasis rates (85.5%) but also had a larger proportion of N2 and N3 (58.9%) involvement than those with small tumors. Furthermore, univariate and multivariate analyses revealed that tumor size was an independent risk factor of lymph node metastasis. Therefore, tumor size is a simple indicator of advanced lymph node metastasis in patients with advanced gastric cancer.

Although several previous studies have described some prognostic factors in gastric cancer,[5,6,16–18] the prognostic significance of tumor size was inconsistent in their studies. In our studies focused on advanced gastric cancer, we found that the prognosis of patients with large tumors was significantly worse than that of patients with small tumors. Cox regression multivariate analysis verified that tumor size is one of the independent prognostic factors in advanced gastric cancer. Thus, tumor size can serve as a simple and valuable predictor for prognosis in advanced gastric cancer.

Furthermore, in 406 patients with large advanced gastric cancer, multivariate survival analysis showed that Borrmann type IV, adjacent organ invasion, and N2–3 lymph node metastasis were significantly associated with poorer prognosis. Although patients with large advanced gastric cancer had worse prognosis than those with small

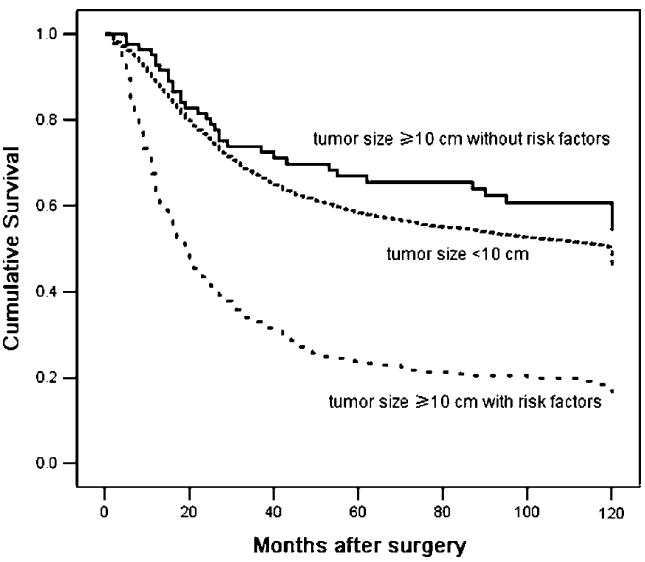

Figure 2 Survival curves for large gastric cancer patients without risk factors (Borrmann IV, adjacent organ invasion, and N2–3 lymph node metastasis), with any risk factors, and patients with small gastric cancer.

tumors, large gastric cancer patients without any risk factors had similar long-term survival with patients with small gastric cancer. The interesting result in this series suggests that gastrectomy with extended lymphadenectomy can be radical treatment for the large gastric cancer patients without findings of risk factors preoperatively or intraoperatively. In our center, almost all patients with advanced gastric cancer were treated with adjuvant chemotherapy after surgery. Because the regimen of chemotherapy varied during the long period in this study, we did not evaluate survival benefit related to adjuvant chemotherapy. In future, the survival benefit of chemotherapy for advanced gastric cancer with large tumor size should be evaluated by prospective clinical trials.

Due to the very poor prognosis after surgery in large gastric cancer patients with any risk factors, such cases may not be a surgically treatable disease. In addition, operative factors, such as operation time and blood loss, can influence the frequency of postoperative complications when patients with large gastric cancer are treated by radical gastrectomy.[19] For advanced gastric cancer, neoadjuvant therapy may offer the potential advantages of reducing tumor size, downstaging, and allowing a R0 resection.[20] However, the benefit of this treatment strategy for patients with large gastric cancer is unclear, so a prospective randomized clinical trial is also necessary.

Conclusion

Advanced gastric cancer with large tumor size was characterized by aggressive clinicopathological features, and tumor size was a simple and valuable predictor for lymph node metastasis and survival rate in advanced gastric cancer patients. In patients with large advanced gastric cancer, Borrmann type IV, adjacent organ invasion, and N2–3 lymph node metastasis were independent prognostic factors. Radical surgery should be recommended for large advanced gastric cancer patients without these risk factors. Large gastric cancer with risk factors may not be a surgically treatable disease.

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ORIGINAL ARTICLE

Gallstone Formation after Gastric Cancer Surgery

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Abstract
Background Gallstone formation is one of the most common complications after gastric cancer surgery, but the mechanism and etiology for such formation are unclear because of a lack of collective clinical investigation.
Method We evaluated the influence of various surgical factors on the incidence of gallstone formation after gastrectomy. Gallstone formation was confirmed by ultrasound examinations that were routinely carried out after surgery on a periodic basis.
Results Gallstone formation occurred in 173 of 672 (25.7%) patients who had undergone gastrectomy with lymph-node dissection for gastric cancer. The types of gastrectomy and reconstruction had no significant effect on the incidence, but the extent of lymph-node dissection was a significant factor ($p<0.001$: D1+α vs. D2+α; $p<0.01$: D2 vs. D2+α). Gallstones were usually formed within 2 years after gastrectomy, but in most cases, gallstone formation was asymptomatic.
Conclusion The extent of lymph-node dissection was a significant factor in gallstone formation after gastrectomy; therefore, prophylactic cholecystectomy should be considered in cases of extensive lymph-node dissection.

Keywords Gallstone · Gastrectomy · Lymph-node dissection · Reconstruction

Introduction

The incidence of gallstone formation has been documented as one of the most common complications after gastrectomy.[1–3] The reported reasons for this postoperative disease have included gallbladder physiological change[4] as well as lithogenic change in bile juice.[5] Such changes may be caused by the various surgical procedures involved in vagotomy,[6,7] gastric resection[8], and intestinal reconstruction.[9,10] Gastric surgery for malignancy now includes a number of options regarding methods for gastric resection, reconstruction, and lymph-node dissection.

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The most important surgical outcome for malignant disease is a good patient prognosis, but we should not neglect the quality of a patient's postoperative condition. Gallstones may lead to severe cholecystitis[1,3] requiring further surgical treatment; therefore, the incidence of gallstone formation after gastrectomy needs to be clinically reevaluated including the propriety of performing prophylactic cholecystectomy.

Material and Methods

A total of 1,503 patients underwent gastric resection for gastric carcinoma from January 1991 to December 1995 at the National Cancer Center Hospital in Tokyo, Japan, with 893 patients followed more than 5 years. Among those 893 patients, 55 had undergone local resection of the stomach, 29 had previous gallstone surgery, and 137 underwent cholecystectomy at the time of gastrectomy. The remaining 672 patients were analyzed in this study.

All 672 cases involved either total gastrectomy, distal gastrectomy, proxymal gastrectomy, or pylorus-preserving

gastrectomy (PPG) associated with systematic lymph-node dissection. The standard lymph-node dissection was D2, which included total removal of perigastric lymph nodes together with those lymph nodes located along the hepatic, left gastric, splenic, and celiac arteries. A total of 478 patients (71%) underwent D2 dissection, 99 patients (15%) underwent restricted D2 dissection that we referred to as D1+α, and 95 patients (14%) underwent extended lymph-node dissection, including the para-aortic area referred to as D2+α. Every patient underwent vagotomy associated with gastrectomy and lymph-node dissection. Intestinal reconstruction was performed using the Roux-en Y method or jejunal interposition for total gastrectomy and Billroth I or II anastomosis or Roux-en Y reconstruction for distal gastrectomy.

All 672 patients routinely received follow-up ultrasound examinations on a periodic basis. Such examinations were first performed within 6 months after gastric surgery and subsequently repeated every 6 months. The primary objective of such examinations was the detection of metastatic disease, but gallbladder information was recorded in every examination. A gallstone was identified as a mobile, highly echoic body with an acoustic shadow located in the gallbladder.

Using a database compiled in the Gastric Surgery Division, we analyzed the incidence of gallstone formation after gastrectomy, the influence of various surgical factors on such formation, the interval between surgery and detection of a gallstone, and the progress of any detected gallstone. Statistical analysis was performed using the chi-square test.

Results

Gallstone formation was observed in 173 of the 672 patients (25.7%) included in this study. In 33 patients, gallstone formation was found in the first ultrasound performed within 6 months after gastrectomy. In 79 patients, it was found in second ultrasound within 1 year after surgery. Therefore, in 112 patients, gallstone formation was detected within 1 year after surgery (Fig. 1).

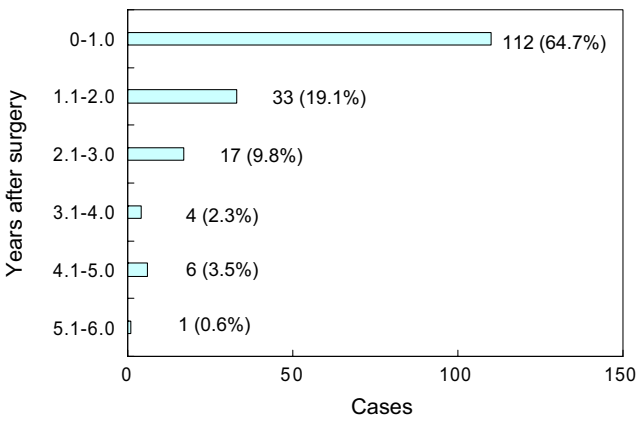

Figure 1 Interval between surgery and detection of gallstone formation. Many gallstones were formed within 1 year after surgery.

Table 1 Frequency of Gallstone Formation by the Type of Gastrectomy

	Stone (+)	Total	Ratio (%)
Total gastrectomy	51	173	29.5
Distal gastrectomy	117	474	24.7
Proxymal gastrectomy	5	14	35.7
PPG	0	11	0

Not significant: total gastrectomy vs. distal gastrectomy

PPG pylorus-preserving gastrectomy

Among the 173 patients who had undergone total gastrectomy, 51 patients (29.5%) had gallstones. Likewise, 117 of 474 patients (24.7%) who had undergone distal gastrectomy and five of 14 patients (35.7%) who had undergone proxymal gastrectomy also developed gallstones. None of the 11 PPG patients, however, experienced any gallstone formation. There were no significant statistical differences between the frequency of gallstone formation and any of the various types of gastrectomy (Table 1).

With regards to the 111 patients who had undergone total gastrectomy with Roux-en Y reconstruction, 35 of them (31.5%) had gallstones, while 16 of 62 patients (25.8%) who had undergone total gastrectomy with jejunal interposition also developed gallstones. As for the 392 patients who had undergone distal gastrectomy with Billroth I anastomosis, 94 of them (24.0%) had gallstones. In addition, four of 12 patients (33.3%) with Billroth II anastomosis and 18 of 67 patients (26.9%) with Roux-en Y reconstruction also experienced the formation of gallstones. Once again, there were no significant statistical differences in the frequency of gallstone formation based on the various types of intestinal reconstruction (Table 2).

Of the 478 patients who had undergone gastrectomy with standard D2 lymph-node dissection, 116 of them (24.3%) developed gallstones, and 17 of 99 patients (17.2%) with restricted D1+α lymph-node dissection and 40 of 95 patients (42.1%) with extended D2+α lymph-node dissection also had gallstones. This time, however, significant statistical differences in the frequency of gallstone formation according to the extent of lymph-node dissection existed between both D1+α and D2+α ($p<0.001$) and D2 and D2+α ($p<0.01$; Table 3).

In terms of the 173 cases of actual gallstone formation, only 12 patients (6.9%) with gallstone symptoms underwent surgery. In contrast, 161 patients (93.1%) did not suffer any gallstone symptoms. In 23 of those asymptomatic cases (14.3%), there was an increase in size and/or

Table 2 Frequency of Gallstone Formation by Type of Reconstruction

Total gastrectomy			
Roux-en Y	35	111	31.5%
Interposition	16	62	25.8%
Distal gastrectomy			
Billroth I	94	392	24.0%
Billroth II	4	12	33.3%
Roux-en Y	18	67	26.9%

Not significant: Roux-en Y VS, interposition for total gastrectomy, Billroth I vs. Roux-en Y for distal gastrectomy

number of gallstones; there were no changes in 124 of the cases (77.0%). In six other cases (3.7%), there was a decrease in the number and/or size of gallstones, and follow-up ultrasound examinations revealed that gallstones had completely disappeared in the remaining eight cases (5.0%; Table 4).

Discussion

Gallstone formation is a relatively common complication after gastrectomy and, in fact, occurred in 25.7% (173/672) of the cases analyzed in our study, which was within the frequency range of 10% to 47% cited in previous reports.[1–3,10] The prevalence of gallstone formation after gastrectomy is quite obviously higher than for the general population without gastrectomy.[11] The remarkable progress achieved in surgical techniques and early detection of gastric cancer have made the prognosis of gastric cancer patients so much better now that postoperative quality of life should be an increasingly important consideration, but prevention of this complication continues to be difficult.

Vagotomy associated with gastrectomy is considered to be the principle reason for gallstone formation after gastric surgery. In particular, damage to the hepatic branch of the vagal nerve induces a reduction in the contractive function of the gallbladder, which may lead to a stagnation of bile juice. The effect of vagotomy could not be assessed in this study, however, because every patient underwent vagotomy associated with gastrectomy and lymph-node dissection.

Table 3 Frequency of Gallstone Formation by the Extent of Lymph-node Dissection

	Stone (+)	Total	Ratio (%)
D1+α	17	99	17.2
D2	116	478	24.4
D2+α	40	95	40.8

$p<0.001$, D1+α vs. D2+α; $p<0.01$, D2 vs. D2+α

Gallstone formation is thought to take place soon after gastrectomy. In previous reports, gallstone formation occurred within 2 years of gastrectomy.[1,2] In this particular study, 64.3% of all such cases were detected within 1 year and 83.6% within 2 years following gastric cancer surgery, which may be related to recovery of the contractive ability of the gallbladder approximately one year after surgery.[8]

The prevalence of gallstone formation was not affected by whether the method of gastrectomy used was total gastrectomy or distal gastrectomy. Total gastrectomy has previously been associated with a high risk of gallstone formation,[1] although no statistical difference in gallstone formation was detected between total gastrectomy and distal gastrectomy in our study, which corresponded to the results of another earlier report.[2] PPG is regarded as being beneficial in reducing the incidence of gallstone formation,[12] but the number of PPG cases in this study (11) was too small to make a valid statistical analysis. PPG has become so popular in Japan following the period covered by this study, however, that we are now preparing a follow-up report that will include many more PPG cases.

The type of reconstruction performed after gastrectomy was unrelated to the frequency of gallstone formation. There was no significant statistical difference in the prevalence of gallstone formation between patients with Roux-en Y reconstruction and jejunal interposition in total gastrectomy cases. Similarly, there were no significant statistical differences in patients undergoing Billroth I anastomosis, Billroth II anastomosis, and Roux-enY reconstruction for distal gastrectomy. There have also been other reports indicating the type of reconstruction did not affect gallstone formation,[2,4] which can be interpreted to mean that gallstone formation is unrelated to whether or not food passes thorough the duodenum.

Extended lymph-node dissection is a risk factor for gallstone formation after gastrectomy. D2 lymph-node dissection is the standard surgical procedure for gastric cancer in Japan, so we divided our study's cases into three groups: D1+α (restricted), D2 (standard), and D2+α (extended). The incidence of gallstone formation was significantly higher for those patients in whom extended

Table 4 Progress of Detected Gallstone

	Case	Ratio (%)
Symptomatic		
Surgery	10	5.8
Asymptomatic		
Increase in number/size	23	13.4
No change	124	73.6
Decrease in number/size	6	3.5
Disappeared	8	4.7

lymph-node dissection was performed compared to patients who underwent standard or restricted lymph-node dissection. Extended lymph-node dissections included the dissection of the para-aortic lymph nodes, the lymph nodes around the hepatoduodenal ligament, and the lower mediastinal lymph nodes for cardiac cancer. Lymph-node dissection around the hepatoduodenal ligament is reported to increase the risk of gallstone formation due to total removal of the nerve system controlling gallbladder function,[2] so we always perform combined cholecystectomy whenever we dissect such lymph nodes. It was impossible, therefore, to evaluate the effect of that particular type of extended dissection on gallstone formation in this study. Overall, though, extended lymph-node dissection increased the prevalence of gallstone formation.

Is prophylactic cholecystectomy necessary? Gallstone formation without any symptoms is often observed, but not treated by cholecystectomy. However, we always performed cholecystectomy simultaneously with gastric cancer surgery for existing gallstones even asymptomatic ones because of our concern with postoperative acute cholecystitis resulting from bile juice stagnation and infection. In contrast, many gallstones formed after gastrectomy do not cause severe symptoms requiring further surgery, as shown by the results of this study in which only 12 of 173 patients (6.9%) with gallstone formation underwent an operation for gallstones subsequent to gastric cancer surgery. Accordingly, prophylactic cholecystectomy is unnecessary for the large majority of patients who undergo gastric case surgery, but in cases of extended lymph-node dissection, such additional surgical treatment seem necessary, given the high frequency of gallstone formation following gastrectomy.

Conclusion

There is a frequent incidence of gallstone formation after gastric cancer surgery. Based on the results of this study in which the extent of lymph-node dissection was shown to be a significant factor in gallstone formation after gastrectomy, prophylactic cholecystectomy should be considered in such cases of extensive lymph-node dissection.

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ORIGINAL ARTICLE

Local Treatment for Recurrent Colorectal Hepatic Metastases after Partial Hepatectomy

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Abstract
Objective The objective of the study was to identify patients who may benefit from local treatment in recurrent colorectal liver metastases.
Materials and methods A total of 51 consecutive patients were treated for hepatic recurrence(s) after an initial partial hepatic resection. Surgery was considered as the primary treatment option for eligible patients. Patients with a small liver remnant after major hepatectomy were treated with radiofrequency ablation (RFA) or stereotactic body radiation therapy (SRx). SRx was given as an outpatient, emerging local treatment option for patients with intra-hepatic recurrences not eligible for surgery or RFA. Partial liver resection was performed in 36 patients (70%), RFA in ten patients (20%), and SRx in five patients (10%).
Results Median hospital stay was 7 (range, 3–62) days with a morbidity of 16% without in-hospital death. None of the patients received adjuvant chemotherapy. There was no difference in recurrence or survival between the three treatment modalities. Overall 5-year survival was 35% with an estimated median survival of 37 months. Patients with a disease-free interval between first hepatectomy and hepatic recurrence less than 6 months did not survive 3 years.
Conclusions Resection, RFA, and SRx can be performed safely in patients with recurrent colorectal liver metastases and offer a survival that seems comparable to primary liver resections of colorectal liver metastases.

Keywords Colorectal liver metastases · Recurrent hepatic metastases · Hepatic resection · Radiofrequency ablation · Stereotactic body radiation

Introduction

Colorectal cancer is one of the most common malignancies and a leading cause of death. Liver metastases develop in 50–60% of patients,[1,2] and surgical resection currently represents the best treatment for long-term survival and even cure in patients with colorectal liver metastases. Despite the curative intent, more than 60% will suffer from recurrence after liver resection, the liver being the most common location.[3] Since liver resection has become safer through improvements in surgical techniques and per-operative management, repeat hepatic resection is being more frequently performed in patients with hepatic recurrences. Several studies on repeat hepatic resection have been reported in the last decade.[4–9] Recent technologic advances have also made local ablative treatments for liver tumors accessible.[10] Patients with small central recurrences after a prior major liver resection and patients who are poor candidates for surgery are often treated by radiofrequency ablation (RFA). Stereotactic body radiation therapy (SRx) is another emerging local treatment option for patients with intrahepatic malignancies not eligible for surgery or RFA.[11]

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Unfortunately, most patients who develop a recurrence after colorectal liver surgery cannot undergo secondary procedures. Systemic chemotherapy (CTx) is used in these patients with increasing median survival rates with current multimodality treatments.[12,13] Approximately 5% to 10% of patients who develop hepatic recurrence after liver resection are amenable to a second resection or local ablative treatment. Most reports are based on small populations or on combined populations from several centers. In this article, we report our experience in a single center with local treatment for recurrent liver disease. The purpose of this study was to evaluate prognostic factors for overall, disease-free survival and to identify patients who might benefit most from secondary local treatment.

Patients and Methods

Between March 1988 and October 2007, 520 partial liver resections were performed in our center because of colorectal liver metastases. Fifty-one patients were treated for hepatic recurrences after a first partial hepatic resection for colorectal liver metastases.

Criteria for repeat liver treatment were similar to those for first hepatectomy: the presence of technically removable metastases (preserving at least two segments of the liver parenchyma), and the possibility of an oncological radical procedure. Surgery was considered as the primary treatment option for eligible patients. Nowadays, surgery provides the best outcome for the treatment of colorectal liver metastases. To date, no randomized trial has been performed between resection versus local ablation. Therefore, in colorectal metastases, surgery is still the gold standard.[14,15] For patients with a small liver remnant after major hepatectomy, RFA or SRx were alternatives if the metastases were <3 cm.[10,11] RFA was first treatment option, but in case of ill location of the metastases (nearby main vessel and/or bile ducts), SRx was the alternative.

Patients with extrahepatic disease that was resectable were also included in this study.

RFA was performed with a 200-W RF generator and the cluster RF electrode was introduced into the hepatic malignancies during laparotomy or by imaging guidance percutaneously.[10] SRx was mostly given in three fractions of 15 Gy, and the prescription isodose was 65%.[11]

Data analyzed included demographics, pathological tumor–node–metastases stage of the primary tumor, maximum size and number of metastases on computed tomography (CT), plasma carcinoembryonic antigen (CEA) level, type of liver surgery, overall duration of hospital stay, complications, radicality, site, and treatment of recurrence.

Overall survival and disease-free survival (DFS) were measured from the start of treatment of hepatic recurrence. The nomenclature and extent of hepatic resection were recorded according to the terminology defined by Couinaud.[16] We defined a positive surgical margin as the presence of exposed tumor along the line of transaction.

After partial hepatectomy, patients routinely underwent a physical examination and determination of CEA level and abdominal/chest CT or ultrasonography every 4 months for the first year, every 6 months the second year, and once a year thereafter. Endoscopic surveillance was performed after 1 year and thereafter depending on the findings.

The nonparametric log-rank test was used to identify prognostic variables associated with survival after the second liver resection, with significance at $p = 0.05$.

Results

First Partial Liver Resection

Clinical data of the first partial hepatectomy are depicted for all 51 patients in Table 1. At the time of the first hepatectomy, one patient had extrahepatic disease of the lung and underwent a pulmonary lobectomy. In another patient a peritoneal metastasis was detected during laparotomy and resected simultaneously with the liver metastases. The

Table 1 Clinical Data on the First and Second Local Treatment

	First hepatectomy $N=51$	Second local treatment $N=51$
Neoadjuvant CTx		
Yes	26	11
No	25	40
No. of tumors[a]	2 (1–8)	1 (1–5)
Size of tumor (cm)[a]	3 (1–10)	2.5 (1–7)
Preoperative CEA-level (μg/L)[a]	17 (1–5315)	10 (1–126)
Tumor distribution		
Unilobar	30	44
Bilobar	21	7
Liver surgery		
Extended hemihepatectomy	2	–
Hemihepatectomy	16	6
Extra-anatomic	33	30
RFA	–	10
SRx	–	5
Morbidity (%)	12 (24%)	8 (16%)
Mortality (%)	0	0
Hospital stay (days)	8	7
Positive surgical margin (%)	7 (14%)	2 (4%)

[a] Median

resection margin at permanent section was microscopically not free of tumor in seven patients. There was no in-hospital death, 12 patients had per-operative complications without surgical re-intervention, and median hospital stay was 8 (range 4–72) days.

Intrahepatic Recurrences

Clinical data of the 51 patients who underwent treatment for recurrent metastases are depicted in Table 1. The median interval between first hepatectomy and recurrent hepatic metastases was 11 (range, 3–78) months. Partial liver resection was performed in 36 patients (70%), RFA in ten patients (20%, two open and eight percutaneous procedures) and SRx in five patients (10%). One patient showed peritoneal disease, and the omentum was resected. One patient showed ingrowth of the diaphragm, and a partial resection of the diaphragm was performed. Two patients received additional SRx for solitary lung metastases and one patient for a solitary costal metastasis. There was no in-hospital death. Eight patients had per-operative complications without surgical intervention, and median hospital stay for patients who underwent resection or open RFA was 7 (range, 3–65) days. None of the patients were treated with adjuvant CTx.

Follow-Up

Median follow-up from secondary treatment for recurrences were 22 (3–115) months. Thirty-two patients (63%) developed a secondary recurrence. Five patients underwent palliative systemic CTx for pulmonary metastases. One patient developed a local recurrence in the pelvis and underwent resection. Of the 26 patients with intra-hepatic recurrence, 14 patients were treated with palliative CTx or analgesic treatment and 12 patients with repeat local treatment. Disease-free survival after treatment of hepatic recurrence was 47% at 1 year, and estimated median DFS was 11 months.

Survival

Overall 3-year and 5-year survival rates were 55% and 35%, respectively, with an estimated median survival of 37 months. The results of univariate analysis of overall 3-year survival after treatment of recurrent hepatic metastases are depicted in Table 2. Patients with an interval of more than 6 months between first hepatectomy and second local treatment and patients with metastases detected synchronously with the primary tumor have a significantly better survival ($p = 0.01$ and $p = 0.006$, respectively). After a median follow-up of 22 months, 18 patients died, and 33

Table 2 Univariate Analysis of Prognostic Factors for Survival after Repeat Treatment for Recurrence of Intrahepatic Disease

Prognostic factor	*N* (%)	Survival 3 years (%)	Significance (*p*)
Age			
≤60	25	54	
>60	26	56	0.57
Gender			
Male	34 (67)	64	
Female	17 (33)	19	0.05
Site of primary tumor			
Colon	31 (61)	56	
Rectum	20 (39)	54	0.71
First metastases			
Synchronous	32	68	
Metachronous	19	26	0.006
pT primary tumor			
T0-2	6	100	
T3-4	45	50	0.09
pN primary tumor			
Negative	26	50	
Positive	25	59	0.50
Interval (months) of first hepatectomy to date of recurrence			
≤6	6	0	
>6	45	62	0.01
Second metastases			
No. of tumors			
1	30	54	
>1	21	72	0.86
Size of tumor (cm)			
≤5	47	58	
>5	4	33	0.85
Neoadjuvant CTx			
Yes	11	64	
No	40	53	0.68
CEA			
≤50	43	54	
>50	4	100	0.66
Distribution of metastases			
Unilobar	44	57	
Bilobar	7	38	0.47
Extrahepatic disease			
Absent	46	59	
Present	5	0	0.32
Type of treatment			
Resection	36	53	
RFA/SRx	15	59	0.71
Positive lymph nodes			
No	49	36	
Yes	2	36	0.62
Margin of hepatectomy			
R0	34	42	
R1	2	0	0.72

patients are alive of whom 24 patients are alive without disease.

Discussion

Without treatment, patients with colorectal liver metastases have a life expectancy of less than 1 year.[17] With the increasingly efficient chemotherapy regimens, median survivals currently reach 16–22 months.[12,18] In our study group, median overall survival was 37 months after local treatment of the intra-hepatic recurrences. Our study reports overall 3-year and 5-year survival rates of 55% and 35% after local treatment of recurrent colorectal liver metastases, which is comparable to the outcome in our series of first hepatectomies that we published previously.[19] Low morbidity (16%) and no in-hospital death showed that repeat local treatment for colorectal hepatic metastases can be performed safely. These results are comparable with those of other studies (Table 3).[4–9]

Improvements in surgical techniques and per-operative management increase the number of repeat hepatic resection in patients with isolated hepatic recurrence.[20] A reduction of blood loss, which is associated with preoperative morbidity and mortality, was obtained over the past decade with a corresponding decrease of transfusion requirements. This was related to an increase in parenchymal-sparing resection, performing of resections with a low central venous pressure, and with the advent of portal pedicle ligation maneuvers.[21] The extent of liver resection depends on the size, location, distribution, and the relation of the major afferent and efferent vasculatures and bile ducts to liver metastases. More wedge resections can be performed because several recent studies have indicated that a margin less than 1 cm is not a contraindication to resection of colorectal liver metastases.[22–25] Moreover, a margin of 1 mm seems to be appropriate, despite the fact that the pathological report will define the procedure as a microscopic irradical resection.[24] Current techniques with ultrasonic dissectors aspirate a part of the liver parenchyma interposed between the specimen and the normal liver, making assessment of the true margin difficult.

The rate of wedge resection in our study was higher in repeat hepatectomies than in the initial hepatectomies because the extent of resection at repeat hepatectomy depended on the amount of remnant liver after first hepatectomy. It seems that the extent of hepatic resection does not influence the outcome of secondly resected patients, providing that all metastatic tissue is removed, which is in agreement with the results of Zorzi et al.[26] A deeper knowledge of the segmental anatomy of the liver[16] and the routine use of intraoperative ultrasonography has eliminated the need of "blind" extensive resection, therefore limiting the amount of resected parenchyma.

The present study shows that 3-year survival rate is significantly better for those patients with an interval of more than 6 months between first hepatectomy and hepatic recurrence. Patients who had an interval shorter than 6 months did not survive longer than 3 years (median estimated survival 27 months). This is in agreement with the results of Bhattacharjya et al. who suggest that tumors recurring early following liver resection are less likely to be amenable to re-resection because of adverse tumor characteristics and a higher potential for spread of disease.[27] They concluded in their study that aggressive follow-up during the first 6 months was not advisable because none of the patients could benefit from local treatment. Together with our results, it may be concluded that patients with intrahepatic recurrences within 6 months after partial hepatectomy should be offered systemic CTx because the median survival of patients who were treated with modern systemic chemotherapy also may exceed 20 months.[28]

The other significant factor was synchronicity of the metastases of the primary tumor. Patients with synchronous metastases showed a significantly ($p=0.006$) improved survival after intra-hepatic recurrences that could be treated by local treatment than patients with metachronous disease.

Table 3 Literature Review of Large Series (>50 pts) of Repeat Local Treatment in Patients with Recurrent Colorectal Liver Metastases in the Last 10 Years

Authors	Year	No. of centers	No. of patients	Mortality (%)	Morbidity (%)	Median survival (months)	Survival	
							3 years	5 years
Adam[4]	1997	1	64	0	19	46	60	41
Sugarbaker[7]	1999	20	170	NR	19	34	45	32
Yamamoto[9]	1999	1	70	0	11	31	48	31
Petrowsky[5]	2002	2	126	1.6	28	37	51	31
Thelen[8]	2006	1	94	3.1	23	NR	55	38
Shaw[6]	2006	1	66	0	18	56	68	44
Present series	2008	1	51	0	16	37	55	35

A clear explanation cannot be given besides the fact that the number of patients is small.

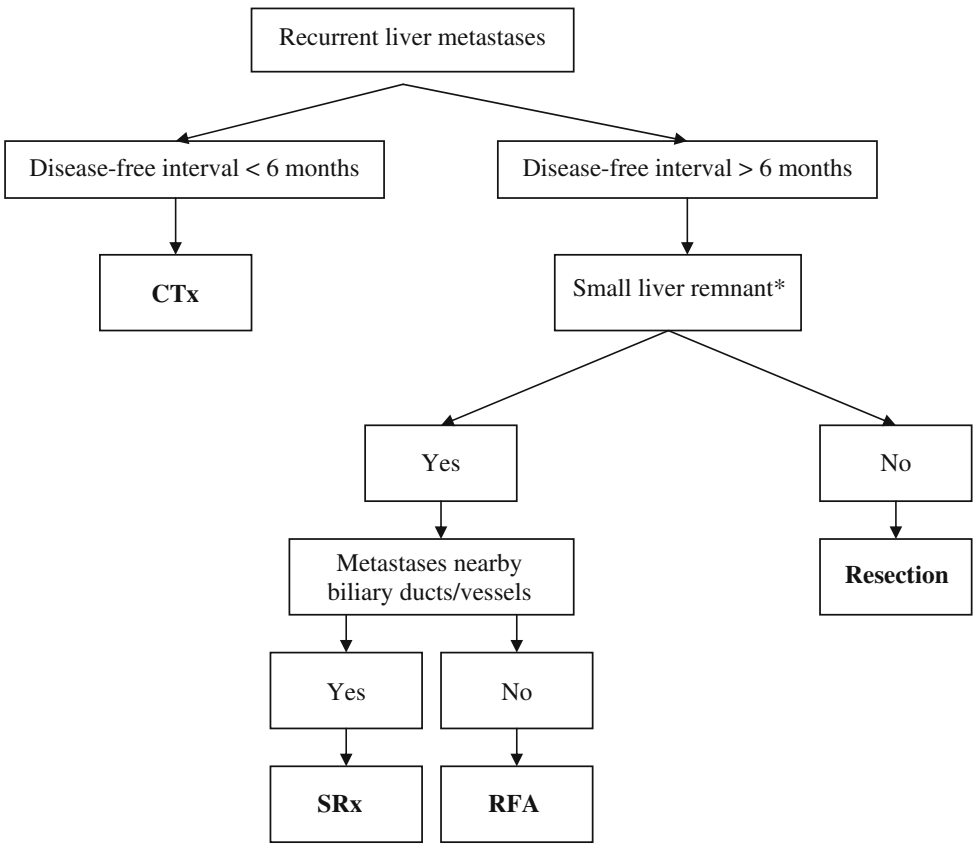
Despite favorable results of repeat hepatic resection for patients with recurrent colorectal liver metastases, there remains controversy regarding the optimal treatment for such patients. The advent of minimally invasive therapies such as RFA or SRx may offer less procedure-associated morbidity and mortality. A concern is the variable rate of local recurrence that can follow such targeted therapies. Lesions treated with RFA have local recurrence rates of 4% to 55%.[10,29]Crude local control rates of 78–100% are reported in tumor-based analysis after SRx.[30] RFA has achieved an important role for patients unfit for surgery with small (<3 cm) liver metastases. Some authors even stated that the time has come to perform a randomized trial between resection and other local ablative methods.[31] In our center, resection is still the gold standard.[15] The treatment failure rate after radiofrequency ablation even in small tumors is higher than local recurrence rates after definitive resection. Again, the results of the local ablative treatments are promising, and therefore, local ablation therapies may be applied in patients not suitable for surgery because of ill location of the tumor and/or the physical state of the patients.

In the current study, no difference was found in recurrence or survival in patients treated with resection, RFA, or SRx. In our practice, patients with small central located intra-hepatic recurrences after a prior major liver resection are often treated by RFA. RFA could be performed percutaneously, avoiding the complications associated with partial hepatectomy. RFA and SRx may be used in conjunction with operative resection to increase resectability. Furthermore, these alternatives to surgery may increase the population considered for treatment of hepatic recurrences in case of patients unfit for operation. A possible algorithm for different treatment modalities of recurrent liver metastases is proposed in Fig. 1.

Conclusion

These repeat local treatments can be performed safely, without greater risk than first liver resections, and offer a survival rate as good as first liver resections. Resection should be the preferred approach, but RFA and SRx are good alternatives with a beneficial outcome. Patients with intra-hepatic recurrences within 6 months after first partial hepatectomy should be offered systemic chemotherapy.

Figure 1 Algorithm.



* <2 segments

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ORIGINAL ARTICLE

A Series of Laparoscopic Liver Resections with or without HALS in Patients with Hepatic Tumors

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Abstract
Background Differences were compared between laparoscopic surgery with and without hand-assisted laparoscopic technique (HALS) in order to assess whether HALS is a safe and feasible alternative to laparotomy and to determine what factors contributed to successful laparoscopic liver surgery.
Method From a total of 416 liver resections, 45 patients with 46 hepatic tumors were chosen for laparoscopic liver resection with or without a hand-assisted technique. For each patient, her/his surgical duration, intraoperative blood loss, tumor size and location, hospital stay after surgery, mortality, and morbidity were recorded for analysis.
Results The 45 surgical laparoscopic liver resections included 19 left lateral lobectomies, three hemihepatectomies, three segmentectomies, and 21 partial hepatectomies. A HALS was used more frequently in the right posterior group (14/16) than in the anterior group (6/29). There was no notable difference between these two groups in terms of tumor size, mean surgical time, blood loss during surgical procedure, hospital stay after surgery, and occurrence of complication.
Conclusion Surgical results between HALS and non-HALS usage were similar except for higher blood loss with HALS, higher use of HALS when liver cirrhosis was present, and less likelihood of using HALS when there was a superficial location of the tumor or lesion.

Keywords Laparoscopy · Hepatectomy · HALS

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Introduction

Laparoscopic liver resection has proved to be a safe and alternative procedure to open surgery under proper patient selection, but it has not been widely accepted as an alternative procedure by most surgeons due to technical difficulties in hemostasis during liver resection, risk of gas embolism,[1,2] inadequate tumor clearance, and possible spreading during manipulation.[3–5] With such concerns, many surgeons therefore recommended that resections should be limited to small lesions and only for those located in the superficial area.[6–8] However, with improvements in technology and experiences, inclusion criteria for resection have expanded and the results have been encouraging, with low mortality and low morbidity, although the sizes of these studies are small.[9–15]

Hand-assisted laparoscopic technique (HALS) has been reported in the literature for esophagectomy, gastrectomy, hepatectomy, pancreatectomy, splenectomy, bariatric surgery, colectomy, nephrectomy, hysterectomy, and aortobifemoral

bypass.[16] Recent studies have compared HALS to total laparoscopic surgery to assess which is the best type of laparoscopic approach. In a study where HALS was used selectively for 25 patients with solid liver tumors, liver resection reproduced low morbidity and mortality rates and effectiveness of 3-year survival that had been obtained with open surgery.[17] Hand-assisted laparoscopic liver resection can be safely performed and is advantageous over traditional liver resection if no more than two segments of the liver need to be resected. The best candidates for resection have a tumor located at the inferior edges of the liver, or have a tumor confined only to the left lateral segment, because of technical issues pertaining to tumor access and ease of retraction of these areas for parenchymal transection.[18] In a patient who had hepatocellular carcinoma with cirrhosis, HALS was used for a left-lateral segmentectomy and had safety advantages over a full laparoscopic method, with no major complications resulting.[19]

When used for patients with colorectal disease, HALS was shown to be safe and effective when compared to standard laparoscopic surgery, with the benefit of a minimally invasive procedure that allows for the relatively easy performance of a complex operation.[20] When used for colectomy, HALS reduced the operative time and generated the acceptable morbidity rates and recovery benefits associated with minimally invasive surgery and thus may be preferable to extensive colorectal procedures such as total proctocolectomy and total abdominal colectomy.[21]

Our aim and objective is to compare the differences between laparoscopic surgery with and without HALS to solidify our hypothesis that under appropriate patient selection, laparoscopic surgery with HALS is a safe and feasible alternative to laparotomy. We also wanted to determine what factors (inclusion criteria for patient selection) contribute to successful laparoscopic liver surgery. We have performed laparoscopic liver resection and used the HALS technique since October 2001.[16] Herein, we present results from 5 years of experience by a single surgical team with laparoscopic liver resection for patients with liver tumors.

Material and Methods

From October 2001 to September 2006, 45 patients were evaluated as candidates for laparoscopic liver resection. Informed consent from patients was obtained upon admission. In the meantime, there were 416 cases of liver resection performed by this surgical team at the En-Chu-Kong Hospital and at the Taipei Medical University Hospital. Patients were selected as candidates based on their liver function and tumor characteristics. Patient inclusion criteria were (1) liver function is child's A or B status and the indocyanine green test at 15 min is below 20%, (2) tumor does not involve or is not adjacent to the hilar area hepatic vein and/or inferior vena cava, (3) the tumor is not located in the caudate lobe, (4) the tumor size does not exceed 6 cm in diameter, which is not considered as a contraindication since the 35th case. A right hemihepatectomy was still excluded for laparoscopic liver resection in this series of studies. The criteria found in the literature for laparoscopic liver resection are a small tumor size and the location of the tumor. The size of the tumor for our patient cohort is less stringent. We propose that tumor size is not a crucial criterion, because with increased experience, any limitations caused by this can be overcome by skilled surgical technique. The tumor locations and terminologies of liver resection were defined according to Couinaud's classification: left lateral lobectomy (segments II and III), left hepatectomy (segments II, III, IV), and segmentectomy and partial hepatectomy (nonanatomic resection or within one segment).

Operative Procedure

Patient and Surgeon Positioning

After a series of modifications during surgical procedures, we selected the lithotomy position with the table tilting 30° upward. If tumors were in the right posterior portion, the right side trunk was supported by a bag to become a left semidecubitus position.

In the case of a tumor found in the right side of the liver, the surgeon would stand on the left side of the patient. The assistant would be on the right side of patient and the camera-holding assistant would position himself between the patient's legs (Fig. 1a). In the case of a tumor found in the left side of the liver, the surgeon would stand between the patient's legs. The assistant then gets on the patient's left side and the camera-holding assistant would be on the patient's right side (Fig. 1b).

HALS Technique

In our series, the HALS technique was introduced during an operation under two situations: (1) if the tumor or intended resected specimen was too large and would have increased the risk of the tumor rupturing from instruments during manipulation and (2) if it was too difficult to expose the tumor by laparoscopic instruments or if it was in the right posterior portion of liver (Fig. 2). The position of the hand-assisted device was placed according to the location of the tumor. In the case of right-side tumor, the device was placed in the right subcostal area, replacing the subxyphoid port. In the case of left-side tumor, the device was placed along the left subcostal area, replacing the left subcostal

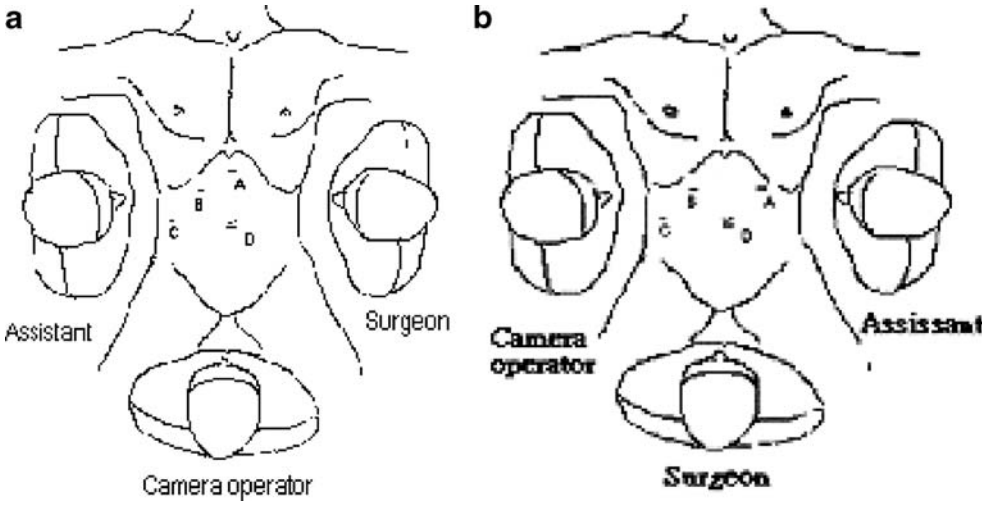

Figure 1 **a** The standing positions of surgeons and port site placements for tumor resection of the right lobe. **b** The standing positions of surgeons and port site placements for tumor resection in the left lobe. *A*, *B*, *C* 10–12 mm port, *D* 10 mm port.

port. The hand-assisted laparoscopic device we applied initially was HandPort system (Smith & Nephew, MA USA), which we later changed to LapDisc (Ethicon, USA) since 2004.

Tumor Localization

After the liver lobe that contains the tumor has been mobilized so that it moves freely, the liver is inspected and the tumor is assessed by intraoperative laparoscopic sonography (Fig. 3). The tumor localization is crucial for liver parenchymal dissection. The steps of this procedure should include the identification of the tumor that will be resected, the recognition of the precise correlation between the tumor's anatomy with adjacent vessels and bile duct, the detection of any new lesions, and the determination of the distance between the parenchymal transection and the tumor margin. For a malignant tumor, the parenchymal transection was planned at least 1 cm away from the tumor margin, and a line was electrocautery-marked under laparoscopic sonographic guidance.

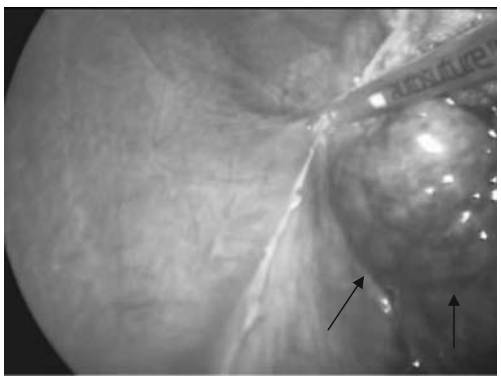

Figure 2 In the partial hepatectomy of the posterior portion of the right lobe, the right coronary and triangular ligaments were divided to mobilize the intended resected liver. The *black arrows* indicate the tumor location.

Vascular Control

In the case of a left lateral lobectomy or hemihepatectomy, the hepatic artery, left portal vein, and left bile duct were isolated in the hilar area and divided by using an endovascular stapler before parenchymal transection. The left hepatic vein was identified by using laparoscopic sonography during parenchymal transection. Finally, the left hepatic vein was divided by using endovascular staplers or after the application of endoclips to clamp the vascular stump. In the case of a partial hepatectomy, instead of the vascular inflow control technique, repeated laparoscopic sonographies were applied in our series to confirm the major vessels hidden in the dissected parenchyma. Some authors have advocated the application of the portal triad inflow control, by tying or clamping at porta hepatis,[8,9] as an intermittent Pringle maneuver. This technique was not applied in our series.

Hemostasis During Parenchymal Transection

In our series, the parenchymal transection was carried out by using the ultrasonic dissector Ultrashear along a previously marked line. Small vessels were coagulated and divided during parenchymal dissection. Vessels or bile ducts that were larger than 3 mm in diameter were clipped with endoclips for hemostasis. Endovascular staplers were used for massive liver parenchymal transection to achieve vascular control of major vessels hidden in the parenchyma, so that the transection could proceed more rapidly and effectively. After a parenchymal transection was completed, the resected surface was coagulated with electrocautery only and the vascular stump was secured by endoclips if

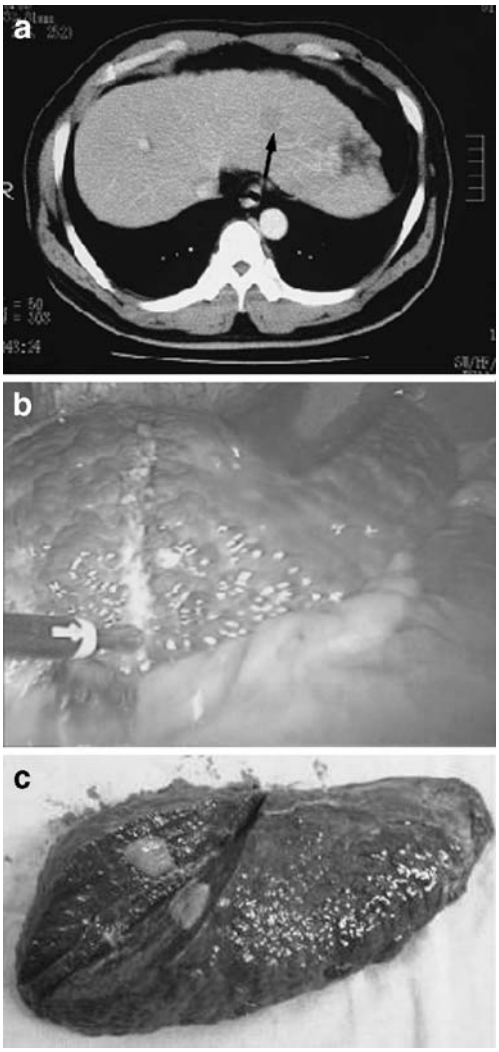

Figure 3 **a** The *black arrow* indicates the tumor location in the left lateral segment in a preoperative computed tomography. **b** Laparoscopic sonography was used after full mobilization of the intended resected liver to localize the tumor, regional vessels, and define the surgical margin. **c** Specimen from the left lateral lobectomy with a 2.0 cm in diameter and 2.5 cm surgical margin.

oozing was present. We did not use any fibrin glue or sealant on the resected surface to control bleeding or prevent bile leakage.

Removal of Specimens

Once the resected parenchyma was divided completely, it was placed in a plastic bag to avoid having the tumor contaminate adjacent organs or seed itself on the peritoneum. The bag containing the intact resected specimen was extracted through the enlarged peri-umbilical port which was protected by a plastic shield. If a hand-assisted device was applied during surgery, the bag was extracted directly through the device. The surgical field was irrigated using normal saline and the transected liver bed was checked again for any bleeding or bile leakage. After fluid was aspirated, a drain was placed near the transected liver bed. The port wounds were then closed in layers after deflation of the pneumoperitoneum.

Postoperative Care

Oral intake with liquids was started on the next day after surgery and progressed to solid food within 24 h. Patients were discharged depending on the time of drainage removal. All of the patients had follow-up contact for 12 months after the operation; patients with malignant tumors received regular check-ups for recurrence every 3 months.

Statistical Analysis

In our evaluation, the following variables were considered: surgical duration, blood loss, transfusion rate, tumor and specimen size, perioperative mortality and morbidity, and hospital stay. We also grouped patients under the categories of HALS, liver cirrhosis, hepatocellular carcinoma (HCC), and anterior and posterior liver surgery. We then compared the variables between these groups to better understand the effects of these factors.

Surgical duration was calculated as the time from the first port skin incision until the last wound was sutured. The blood loss was estimated by the fluid amount aspirated from the abdominal cavity during surgery. Tumor and specimen size were defined by the largest dimension which was reported in the pathological analysis after formalin fixation. Hospital stay was defined by the number of days in the hospital after surgery. Perioperative morbidity and mortality were defined by any complications occurring within 30 days after operation. All data were collected and entered into a computer database.

Continuous data were expressed as the mean ± standard deviation or median (range), and categorical data were expressed as frequencies and percentage. Patients' characteristics were compared using the *t* test, the Wilcoxon rank-sum test, the chi-square test, or Fisher's exact test depending on their distribution. Logistic regressions with stepwise selection were used to explore how surgical outcome and certain conditions affected the surgical procedure. Data were analyzed using SAS 9.0 (SAS Institute Inc., Cary, NC, USA) and a P value<0.05 was considered statistically significant.

Results

From October 2001 to February 2006, 46 laparoscopic hepatectomies were performed in 45 patients; one of them

received two partial hepatectomies in the left lobe. Table 1 shows patients' characteristics, clinical characteristics, pathology, location of tumors and the procedure of resection used, and the surgical results of 45 patients. There were 17 females and 28 males. The mean age was 58.5 years, ranging from 35 to 80 years old. Five cases had previous upper abdominal histories including two cases of laparoscopic cholecystectomy, two cases of subtotal gastrectomy, and one case of pancreatic pseudocyst after an internal drainage procedure. One patient had previously received a right hemihepatectomy due to hepatocellular carcinoma. There were 21 patients with liver cirrhosis, and of these, 11 were child A status and ten were child B status in the preoperative liver function evaluation. In terms of American Society of Anesthesiologists (ASA) classification, there were 22 cases in class I, 11 cases in class II, and two cases in class III. Twenty cases out of 44 completed their hepatectomy procedures by using the HALS technique. The pathology of lesions, tumor location and surgical procedure, and the types of laparoscopic liver

Table 1 Patients' Characteristics, Clinical Characteristics, Pathology, Location of Tumors and the Procedure of Resection, and the Surgical Results of 45 Patients

Variable	Summary statistics	Note
Age	58.45±11.85	
Male	28 (62.22)	
Upper abdominal surgery	5 (11.11)	
Previous hepatectomy	1 (2.22)	
ASA I/II/III	22 (48.89)/11 (24.44)/2 (4.44)	
Hand assisted technique	20 (44.44)	
Malignant tumor	33 (73.33)	27 HCC
		1 Cholangiocarcinoma
		3 Colon cancer metastasis
		2 Breast cancer metastasis
Benign tumor	12 (26.09)	5 Hemangioma
		4 Focal nodular hyperplasia
		1 Cyst with bleeding
		2 Intrahepatic stone
Liver cirrhosis	21 (46.66)	2 Hemangioma
		19 HCC
Child status A/B for liver cirrhosis	11 (26.19)/10 (22.22)	
Location		
Segment II or/and III	25 (55.56)	19 left lateral lobectomy
		4 partial hepatectomy
		1 left hemihepatectomy
Segment IV	3 (6.67)	3 partial hepatectomy
Segment V	1 (2.22)	1 segmentectomy
Segment VI	11 (24.44)	2 segmentectomy
		9 partial hepatectomy
Segment VII	4 (8.89)	4 partial hepatectomy
Segment VIII	1 (2.22)	1 partial hepatectomy
Surgical duration (min)	120.00 (95.00, 177.50)	
Blood loss (ml)	200.00 (100.00, 400.00)	
Tumor size (cm)	2.50 (2.00, 4.00)	
Specimen (cm)	10.00 (7.00, 15.00)	
Hospital stay (days)	5.00 (5.00, 6.50)	
Conversion	3 (6.66)	
Transfusion	5 (11.11)	
Complications	5 (11.11)	2 Intraoperative bleeding
		1 Diaphragm injury
		1 Bile leakage
		1 Postoperative bleeding

Data presented as mean ± standard deviation, *n* (%) or median (interquartile range)

resection in combination with tumor location are summarized as well. The median surgical duration was 120 min (40 to 240 min) and the median blood loss during the operation was 200 ml (0 to 1,500 ml). The median size of a resected specimen was 10.48 cm (3.4 to 19.0 cm) and the median tumor size was 3.4 cm (1.0 to 11.0 cm). Conversion to laparotomy occurred in three patients (6.7%) due to occurring intraoperative complications.

Surgical Mortality and Morbidity

There was no mortality during or after the surgeries. Five (11.1%) operative-related complications occurred out of the group of 45 patients, and four of these five patients were HCC with cirrhosis patients. Three intraoperative complications have been described in the previous sections and all these cases were converted to laparotomy. The other two postoperative complications included one bile leakage and one hemorrhage. The bile leakage complication occurred on the fifth postoperative day, and the patient was later discharged on the seventh postoperative day with drainage. The other patient was diagnosed with postoperative bleeding, which was controlled by fresh frozen plasma and platelet transfusion.

Follow-up in the Patients with Malignant Tumors

Ten of the 27 HCC patients developed tumor recurrence (at 3, 6, 6, 7, 12, 14, 18, 23, 27, 56 months) after the operation and seven patients eventually died due to tumor recurrence or distant metastasis. Two patients with colon cancer developed a recurrence at 6 and 15 months after the operation. None of these recurrent tumors could be attributed to the laparoscopic procedure nor did they occur at the resected liver margin. There was no case of port site metastasis in patients who received laparoscopic hepatectomy for malignant diseases.

HALS vs. Non-HALS

A comparison of demographic data, surgical results, and certain conditions including liver cirrhosis, hepatocellular carcinoma, and location (right posterior/superficial) was made between the usage of the HALS technique and non-HALS (see Table 2). We can see that HALS was used less frequently in the left superficial group ($P<0.001$). As for the surgical results, the percentage of patients with liver cirrhosis and the amount of blood loss during the operation were higher in the HALS group ($P=0.028$ and $P=0.033$, respectively). The percentage of HCC and superficial location is higher in the non-HALS group ($P=0.018$ and $P=0.001$). There were no other surgical outcomes measured.

Effects of HCC, Liver Cirrhosis, and Position of the Tumor on HALS

Results using logistic regressions on how surgical outcome and certain conditions affected the surgical procedure are shown in Table 3. The univariate result is similar to Table 2—large specimens are 0.25 times less likely to require HALS ($P=0.031$), amount of blood loss is 5.33 times higher in HALS than in non-HALS ($P=0.012$), patients with liver cirrhosis are 3.95 times more likely to have HALS ($P=0.031$), patients with HCC are 5.09 times more likely to require HALS ($P=0.018$), and a superficial location is 0.96 times less likely to require HALS ($P<0.001$). The stepwise multivariate logistic regression result shows that location is the only factor associated with HALS.

Surgical results of hepatocellular carcinoma, liver cirrhosis, and location (right posterior/superficial) are presented in Table 4. Patients with HCC experienced greater blood loss during the operation and a longer length of hospital stay ($P=0.050$ and $P=0.012$, respectively). Patients with liver cirrhosis had a longer time for both the surgery and length of hospital stay, and the percentage of complication was

Table 2 Data and Surgical Results of the HALS and Non-HALS groups

	Non-HALS group ($n=25$)	HALS group ($n=20$)	P value
Age[a]	56.58±12.06	60.70±11.49	0.256
Male[b]	14 (56.00)	14 (70.00)	0.336
Tumor size (cm)[c]	2.70 (1.90, 4.70)	2.50 (2.00, 4.00)	0.869
Specimen (cm)[c]	13.50 (7.00, 15.25)	8.00 (6.00, 11.25)	0.055
Blood loss (ml)[c]	150.00 (100.00, 300.00)	300.00 (175.00, 400.00)	0.033*
Surgical time (min)[c]	120.00 (90.00, 150.00)	150.00 (117.50, 180.00)	0.165
Hospital stay (day)[c]	5.00(5.00,6.00)	6.00 (5.00, 7.00)	0.107
Complication[d]	2 (8.00)	3 (15.00)	0.642
Liver cirrhosis[b]	8 (32.00)	13 (65.00)	0.028*
HCC[d]	11 (44.00)	16 (80.0)	0.018*
Superficial[d]	23 (92.00)	6 (30.00)	<0.001*

Data presented as mean ± standard deviation, number (%) or median (range)

*$P<0.05$

[a] t test

[b] Chi-square test

[c] Wilcoxon rank-sum test

[d] Fisher's exact test

Table 3 Logistic Regressions on How Surgical Outcome and Certain Conditions Affect the Surgical Procedure (HALS vs. Non-HALS)

	Univariate		Stepwise multivariate	
	OR (95%CI)	*P*	OR (95%CI)	*P*
Tumor size >2.5 cm	0.82 (0.25–2.68)	0.736	–	–
Specimen >10 cm	0.25 (0.07–0.88)	0.031*	–	–
Blood loss >200 ml	5.33 (1.45–19.58)	0.012*	–	–
Surgical time >120 min	2.77 (0.77–9.97)	0.119	–	–
Hospital stay >5 days	2.84 (0.51–15.96)	0.235	–	–
Complication	2.03 (0.31–13.51)	0.464	–	–
Liver cirrhosis	3.95 (1.14–13.71)	0.031*	–	–
HCC	5.09 (1.32–19.65)	0.018*	–	–
Superficial location	0.04 (0.01–0.21)	<0.001*	0.04 (0.01–0.21)	<0.001*

Continuous data were categorized into two groups by their median for easier interpretation

*$P<0.05$

higher in the cirrhotic group ($P=0.012$, $P=0.001$, and $P=0.017$, respectively). As for tumor location, the specimen size was larger in the superficial group as compared to the right posterior group ($P<0.001$). The multivariate logistic regression results in Table 3 and location results in Table 4 suggest that HALS can be applied safely to remove small cancers located on the right posterior side of the liver without increasing the risk of other surgical outcomes.

Discussion

Laparoscopic liver resection is a specialized and difficult surgical technique because the liver is at a unique anatomical location and with abundant vascularity, which presents technical difficulties with the narrow laparoscopic visual field and bleeding control. However, laparoscopic liver resection may offer many advantages including less blood loss during the surgical procedure,[17,20] quicker recovery,[22] shorter postoperative hospital stay,[8,20,21,23] less adverse functional impact to the liver,[10,24] and fewer complications in cirrhotic patients.[25] Although laparoscopy was initially used for hepatic resection when small, peripheral, benign lesions were present, experienced teams are now performing laparoscopic resections for benign and malignant hepatic masses with relatively low morbidity.[26] In a study that compared laparoscopy to open cases, there were equivalent perioperative complications between the two approaches, and overall, laparoscopic results are comparable with the open approach in cancer patients.[22] Laparoscopic resection is rapidly becoming the new standard of care for a solitary malignant liver tumor located in the left lateral segment.[26] The surgical results in this series were compatible with those found in reports previously published, including the surgical time, blood loss, hospital stay after operation, and complication rate.

The criteria of patient selection for laparoscopic liver resection vary depending on the laparoscopic technique that is applied and surgical experience. The percentage of laparoscopic liver resection application ranged from 12% to 46.5% in the reported series,[6–8,13] with the usage of this technique being 10.8% in this study. In one series, 31 HALS operations were performed over a period of 7 years with the following selection criteria: lesions must involve two hepatic segments or fewer and must be located either (a) at the inferior edge of the liver (segments 5 and 6) or (b) confined to the left lateral segment (segments 2 and 3).[15] In a study describing 21 HALS liver resections, the authors created several caveats for surgery: HALS should not be performed if (a) there are central lesions or (b) if there are large bulky tumors that reduce the amount of working space for laparoscopy.[27]

Increasing experiences with the laparoscopic technique of liver resection allowed us to expand the criteria for patient inclusion. Many of the surgical results between the HALS and non-HALS group were similar, with the exception of blood loss, presence of liver cirrhosis of HCC, and superficial location of the tumor or lesion. Those with cirrhosis or HCC would benefit from HALS, even though the risk of blood loss is greater. These factors would be taken into account by adjustment of the surgical technique. The tumor size was no longer considered as a limiting factor, since the 15th case was a huge hepatocellular carcinoma 9 cm in diameter located in the left lobe, which we were able to safely remove. We started to perform left hemihepatectomies at the 35th case. We took this case of a left intrahepatic stone after we had more experiences with the technique in the hilar vascular dissection. After our collective experience with performing this procedure, our patient inclusion criteria for performing HALS for liver resection is (a) unlimited tumor size, (b) specimen size <10 cm, (c) liver cirrhosis, (d) HCC, and (e) superficial location of the lesion or tumor.

Many studies have proved the feasibility and safety of laparoscopic liver resection.[7,9,11–14] In reviewing recent articles including 534 patients (Table 5), only three patients

Table 4 Surgical Results of Certain Conditions

	Hepatocellular carcinoma			Liver cirrhosis			Location		
	Non-HCC group	HCC group	*P*	Non-cirrhotic group	Cirrhotic group	*P*	Right posterior group	Superficial group	*P*
N	18	27		24	21		16	29	
Tumor size (cm)[a]	2.50 (2.00–3.60)	2.50 (2.00–4.00)	0.701	2.80 (2.00–4.20)	2.50 (2.00–4.00)	0.455	2.50 (2.00–3.15)	2.70 (2.00–4.70)	0.370
Specimen (cm)[a]	7.25 (5.00–14.00)	11.50 (8.00–15.00)	0.089	8.50 (6.00–14.50)	11.50 (7.00–15.00)	0.327	6.50 (5.00–8.50)	14.00 (9.00–15.00)	<0.001*
Blood loss (ml)[a]	150.00 (100.00–250.00)	300.00 (100.00–500.00)	0.050*	150.00 (100.00–300.00)	300.00 (150.00–500.00)	0.051	275.00 (100.00–400.00)	150.00 (100.00–400.00)	0.558
Surgical time (min)[a]	120.00 (90.00–150.00)	140.00 (110.00–180.00)	0.170	120.00 (90.00–150.00)	150.00 (120.00–180.00)	0.012*	120.00 (95.00–167.50)	135.00 (100.00–180.00)	0.575
Hospital stay (day)[a]	5.00 (4.00–6.00)	6.00 (5.00–7.00)	0.012*	5.00 (4.00–6.00)	6.00 (5.00–7.00)	0.001*	6.00 (5.00–7.00)	5.00 (5.00–6.00)	0.237
Complication[b]	0 (0.00)	5 (18.52)	0.073	0 (0.00)	5 (23.81)	0.017*	2 (12.50)	3 (10.34)	1.000

Data presented as median (interquartile range) or number (%)

* $P<0.05$

[a] Wilcoxon rank-sum test

[b] Fisher's exact test

Table 5 Summary of Conversion Rate, Morbidity, and Mortality in the Recently Reviewed Literature

	Patient number	Conversion	Morbidity	Mortality
Kaneko (7)	52	1 (2%)		
Morino (8)	30	2 (6.6%)	2 (6.6%)	0
Cherqui (9)	30	3 (6%)	6 (20%)	0
Mala (11)	53	3 (6%)	8 (15%)	0
Buell (12)	100	0	23 (23%)	0
Vibert (13)	89	12 (13%)	Major 19 (21%) Minor 13 (13%)	1 (1.1%)
Drager (14)	70	7 (10%)	11 (15.7%)	1 (1.4%)
Belli (22)	23	1 (4.3%)	3 (13%)	1
Cherqui (23)	27 HCC	7 (27%)	1 (3.6%)	0
Hompes (24)	45	3 (6.6%)	2 (4.4%)	0
This series	45	3 (6.6%)	5 (11%)	0

died perioperatively. The total perioperative morbidity after surgery ranged from 2% to 23% and most of them were related to each patient's underlying diseases according to surgical definitions. In this series, the perioperative complication rate was 11.1% (5/45) and all patients recovered uneventfully. Also, there was no perioperative mortality or reexploration for any complication after surgery. Our results confirmed that laparoscopic liver resection could be performed safely under proper patient selection.

The conversion rate is also related with the criteria of patient selection for laparoscopic liver resection. Kaneko[6] suggested that the indications for laparoscopic hepatectomy should include tumors located in the lower or lateral segments of the liver and nodular tumors sized smaller than 4 cm in diameter, or pedunculated-type tumors smaller than 6 cm. Patients who required anatomic resection, such as right hemihepatectomy, were not candidates for laparoscopic liver surgery in Kaneko's studies. The conversion rate was 3.3% (1/30) in his series. The indications of Vibert and his colleagues[13] were extended, and only procedures with the requirement of vascular or biliary reconstruction were excluded. There was no upper limit on tumor size. The conversion rate was higher, up to 13% (12/89). So the degree of restriction in patient selection also demonstrated a critical role in determining the feasibility and conversion rate of laparoscopic liver resection. The conversion to open liver resection occurred in three patients (6.6%) in the present study, which was comparable with a recent large series reporting a conversion rate of 0% to 13%. Our results confirmed that laparoscopic liver resection is feasible under proper selection.

Besides the previously mentioned indications, a successful laparoscopic liver resection without complication is also related to several factors including liver cirrhosis, extension

of hepatectomy selected, tumor location, instruments, and surgical experience. Many pioneers[7–9] did not recommend the laparoscopic technique for tumors in the right posterior and upper portion of the liver because of difficulties in exposure, inadequate resection margin for malignant tumors, and risks of bleeding and gas embolism due to the connection with the vena cava and major hepatic veins. However, we introduced the HALS technique to successfully perform hepatectomy in the right posterior liver without increasing the risk of bleeding, gas embolism, and conversion rate. Although some authors have criticized the disadvantages of a decreased operation field when using the hand-assisted laparoscopic technique,[14] other reports[18,19,28,29] and our previous report[16] have demonstrated the advantages of this technique, including good tactile sensation, facilitation of liver mobilization and exposure, parenchymal bleeding control, and precise endovascular stapler loading during parenchymal transection. It also improved the diagnostic and staging accuracy for malignancy, especially in the case of cirrhotic patients.[30]

The majority of our patients received a laparoscopic left lateral lobectomy and nonanatomic hepatectomy. Three laparoscopic left hemihepatectomies were carried out in the last ten cases after our team had gained more experience in the hilar vascular dissection. We did not perform any laparoscopic right hemihepatectomy, although it had been proved feasible and safe in some series.[13–15,31] The reasons that we did not perform right hemihepatectomy were (1) there is a higher possibility of massive bleeding occurring when performing a right side liver mobilization in a cirrhotic case, (2) we do not have enough experience in the isolation of the junction of the right hepatic vein and inferior vena cava with the laparoscopic technique, and (3) for tumor integrity, a large wound of over 10 cm is needed for the retrieval of the resected specimen and such a wound would lose the advantages of minimal invasive surgery.

As in the open hepatectomy, uncontrolled bleeding is still the main complication requiring further investigation in many studies.[11,13–14,27] In this series, five cirrhotic cases required a blood transfusion during the operation, and one of them continued to receive a transfusion with packed red blood cells and fresh frozen plasma to correct the coagulopathy after the operation. Two of these five bleeding cases were converted to laparotomy. Liver cirrhosis caused prominent portal vein collaterals and easy bleeding during mobilization, exposure of the liver, or parenchymal transection. Our results also demonstrated that the cirrhotic group was at risk for a greater blood loss, longer surgical time, longer hospital stay, and higher complication rate during laparoscopic liver surgery. Tumor location, on the other hand, was not a causative factor for bleeding or a deciding factor for conversion to open surgery in this study.

While hepatectomy is the standard therapeutic choice for liver malignancy, the application of laparoscopic surgery remains controversial, owing to the problems of oncological inadequacy and tumor spreading during manipulation. Some authors have emphasized that there is an inadequate resection margin for malignancy with the laparoscopic technique,[5] but there is no difference in the resection margin between laparoscopic and open techniques in the recent literature.[8,9,23] The mean resection margin in our series was 1.8±1.4 cm for liver primary malignancy and 1.4±1.6 cm for liver metastasis, which are both compatible with those of other series.[10,27] According to other recent reports, there was no port site metastasis or intra-abdominal tumor seeding.[8,9,27,32,33] In our patients, there were ten recurrences in the primary malignancy group and two recurrences in the metastatic tumor group, but no patient had experienced port site metastasis or any laparoscopic-related intra-abdominal tumor seeding. Laparoscopic surgery offered the benefits of less wound pain, reduced peritoneal adhesion, and earlier returns to daily activities due to less abdominal wall destruction. In fact, many articles have demonstrated several advantages of using laparoscopic liver resection for HCC with liver cirrhosis, including a decreased amount of ascites, fewer complications, and better quality of life after surgery.[10,32–34] As long as precise localization of the tumor and resection margin is obtained by laparoscopic sonography before resection of the liver and dissection, manipulation, and retrieval of the specimen do not compromise the principle of tumor integrity, we believe that an increasing risk of tumor metastasis or an inadequate resection margin will not occur with this technique. However, long-term follow-ups and more patients with malignant liver tumors are required to better assess the functionality and reliability of laparoscopic liver resection in the treatment of malignant liver tumors.

Conclusion

The percentage of patients with liver cirrhosis and the amount of blood loss during surgery were higher in the HALS group, with less likelihood of using HALS when there was a left superficial location of the tumor or lesion. The percentage of hepatocellular carcinoma and number of superficial tumors was higher in the non-HALS group, although patients with hepatocellular carcinoma were more likely to require HALS. Specimen size was larger in the superficial group as compared to the right posterior group, but large specimens were less likely to require HALS.

This study indicates that HALS can be safely used for the resection of solid hepatic tumors following proper patient selection. When we used HALS to remove tumors in the right posterior liver, there was no increase in the risk

of bleeding or gas embolism. Patients with hepatocellular carcinoma had greater blood loss during surgery and a longer length of hospital stay. Liver cirrhosis is related to greater blood loss during hepatectomy and higher percentage of complication, and longer surgical times and hospital stays are required for such patients. The immediate benefits of HALS hepatectomy are clear, but the long-term outcome and the efficacy of laparoscopic liver resection for treatment of malignant tumors requires further study.

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ORIGINAL ARTICLE

Detrimental Effect of Postoperative Complications on Oncologic Efficacy of R0 Pancreatectomy in Ductal Adenocarcinoma of the Pancreas

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Abstract
Background Margin-negative resection of pancreatic cancers has proven to be the most effective treatment to date. Although there are frequent surgery-related complications following pancreatectomy, the oncologic effect of these complications following pancreatectomy for pancreatic cancer has not been studied.
Materials and Methods Retrospective observation of medical records of resected pancreatic ductal adenocarcinoma performed from January 1990 to June 2006 was used in this study. Potentially curative surgical resections of pancreatic ductal adenocarcinoma were performed on 103 patients. Survival was analyzed according to various clinicopathologic variables.
Results Negative surgical margins (p=0.0075) and absence of postoperative major complications related to surgery (p=0.0116) were all significantly favorable prognostic factors in both univariate and multivariate analysis. Margin-negative pancreatectomy without major complications showed the most favorable oncologic outcomes in resected pancreatic cancer (median survival, 35.6 months; 95% confidential interval, 25.8–45.4 months), while major morbidities diminished survival benefit of R0 resection [R0-Cx(+), Exp(β)=1.925, p=0.034, and R1, Exp(β)=3.129, p=0.001].
Conclusion Surgery-related major complication diminished the oncologic efficacy of R0 pancreatectomy. Margin-negative resection without major complication can enhance postoperative oncologic outcomes in ductal adenocarcinoma of the pancreas.

Keywords Pancreatic cancer · Complication · R0 · Pancreatectomy · Survival

Introduction

Pancreatic ductal adenocarcinoma is believed to be one of the most lethal gastrointestinal malignancies in the world; its incidence rate is almost equal to its cancer-related mortality. In the USA, about 32,180 pancreatic cancer patients were anticipated in 2005, with an expected 31,000 deaths.[1] In Korea, pancreatic cancer is the eighth most common cancer in men and the tenth in women, trailing cancers of the stomach, lung, liver, breast, colon, and cervix. At our institution, the frequency of pancreatectomy for pancreatic ductal adenocarcinoma has increased over the last decade (Fig. 1).

Despite advances in surgical techniques, in perioperative management, and in the understanding of the carcinogenesis of pancreatic cancer, the 5-year survival rate for all patients with pancreatic cancer remains extremely poor. Currently, margin-negative pancreatectomy is considered the most effective mono-therapy for pancreatic cancer.[2–4] Therefore, almost all analyses of resected pancreatic cancer focus on the role of curative resection of the pancreas.[5–11]

Although the incidence of postoperative mortality and morbidity has been reduced following pancreatectomy, the

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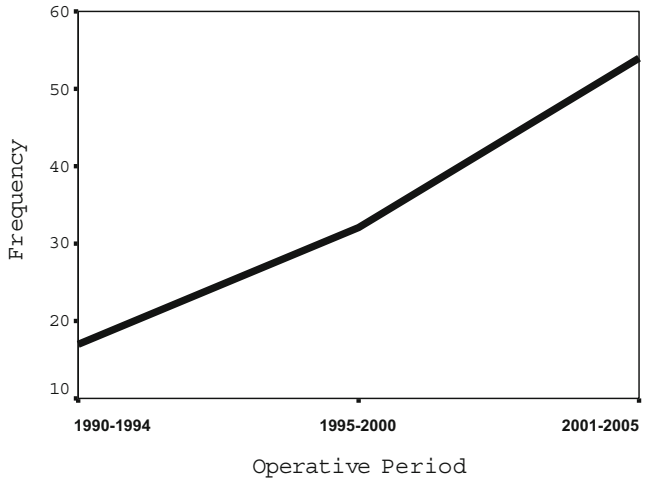

Figure 1 Cases of pancreatectomy for ductal adenocarcinoma of the pancreas at the Yonsei University Health System, Seoul, Korea

postoperative complication rate still remains high, with overall complication rates of up to 60%.[12] There are several reports suggesting a relationship between postoperative complications and unfavorable oncologic outcomes. Khuri et al.[13] evaluated the effect of these complications on survival in major surgery in a prospective multi-center study and concluded that postoperative complication is more important in determining survival after major surgery. Impaired survival outcomes in patients with postoperative complications following resection of head and neck,[14] esophageal,[15] liver,[16] colorectal[17] cancers has been also noted. Pancreatic surgery is also at high risk for significant morbidity, and yet, there are few studies that have dealt with the potential impact of surgical complications of the oncologic outcomes of resected pancreatic cancer.[18–20]

In this retrospective analysis, we have tried to delineate the relationship between major complications after pancreatectomy for pancreatic ductal adenocarcinoma and survival outcome. The surgeon's role in improving survival of pancreatic cancer may not be limited only to margin negative pancreatectomy.

Materials and Methods

From January 1990 to June 2006, grossly curative surgical resections of pancreatic ductal adenocarcinoma were performed on 103 patients in our department at Yonsei University Health System, Seoul, Korea. We retrospectively reviewed all 103 medical records that contained data on survival outcome as well as on patient and tumor characteristics. Four hepatobiliary surgeons were initially involved in the pancreatectomies. Pancreaticoduodenectomy or distal pancreatectomy with splenectomy, including the main pancreatic tumor and associated regional lymph nodes (LNs) with retroperitoneal soft tissue such as para-aortic LNs (16A2, B1), had been resected for pathologic staging. However, extensive soft tissue dissection was not provided, according to the surgeon's preference and the patients' general condition. Surgical margins, such as the bile duct, pancreatic duct, peripancreatic soft tissue adjacent to the superior mesenteric artery (retroperitoneal margins), duodenum, or stomach, were evaluated grossly and microscopically to elucidate the status of the surgical margin. These surgical margins, except for the retroperitoneal margin, were often evaluated using frozen-section analysis. If positive, additional resection was done. The final margin status was reported in the permanent pathology report. Pancreatic resection margins showing high-grade dysplasia without invasive carcinoma were considered margin-negative resections (R0).

Postoperative major complications (Mj-Cx) were defined as surgery-related complications that required additional medical or interventional management associated with prolonged hospital stays. These would include, for example, clinically relevant pancreatic leakage (amylase-rich fluid, amylase concentration in the drainage fluid more than three times the upper limit of normal serum amylase after the third postoperative day, ≥Grade B[21]), delayed gastric emptying (the need for nasogastric decompression beyond the tenth postoperative day or the inability to tolerate a regular diet on or before the 14th postoperative day), intra-abdominal abscess [a follow-up abdominal computed tomography (CT) scan that showed localized intra-abdominal fluid collection, accompanying air-bubbles, or peripheral wall enhancement with fever and leukocytosis (WBC>10,000/μl)], bleeding (requirement for more than 4 units of packed red blood cells postoperatively, associated with bloody discharge out of the drain or with a hematoma around the surgical field defined on follow-up CT scan), bile leakage (bile in the drain for more than 3 days postoperatively), or chyle ascites (milky or creamy peritoneal fluid rich in triglyceride emerging from the drain). The TMN stage was evaluated based on the AJCC Cancer Staging Manual, 6th edition.[22]

Categorical variables were expressed as frequencies and percentages and continuous variables as mean±standard deviation (or range). We compared preoperative, intraoperative, and postoperative clinical variables according to the existence of major complications. We also analyzed the impact of major complications on the survival outcome of R0 pancreatectomy for pancreatic cancer. The cumulative survival rate, according to the R status and major complications, was calculated by the Kaplan–Meier method. Subsequently, only significant variables were used in the multivariate analysis using the Cox-proportional hazards model. Differences were evaluated by the log-rank,

chi-square (Fisher's exact test, if needed), and Student's *t* tests and were considered significant when $p<0.05$.

Results

General Characteristics of Patients and Resected Pancreatic Cancers

Thirty-eight patients were female and 65 were male, with a mean age of 60.1 years (range, 42–78 years). Ductal adenocarcinoma was confirmed by microscopic examination in all patients. Forty-one patients (39.8%) underwent conventional pancreaticoduodenectomy, 37 (35.9%) underwent pylorus-preserving pancreaticoduodenectomy, and 25 (24.3%) underwent distal pancreatectomy with splenectomy. Ninety-four patients (91.3%) had T3 pancreatic cancer, followed by lower incidences of T2 (6, 5.8%) and T1 (3, 2.9%) lesions, with a mean tumor size of 3.1 cm (range, 1–7 cm). There were no R2 resections recorded in the medical records. R1 resection was performed in 20 patients (19.2%), and R0 pancreatectomy was reported in 83 (80.8%) patients. Thirty-two patients (31.1%) developed surgery-related major complications postoperatively. Among these, 28 patients underwent R0 resection, and the other four patients were treated with R1 resection. Most complications were managed conservatively (Table 1), but 30-day mortality was noted in one patient (1%) due to postoperative bleeding.

Clinical Characteristics Between Mj-Cx(−) and Mj-Cx(+)

Among preoperative clinical variables, the preoperative biliary decompressive procedure was significantly related to the incidence of postoperative major complications ($p=0.039$; Table 2). There were no intraoperative or postoperative clinical variables that were significantly different between the two groups. The length of hospital stay of the Mj-Cx(+) group was longer than that of Mj-Cx (−) group (20.5±9.1 days vs. 26.0±9.1 days, 0.027). The time lag to postoperative chemotherapy was somewhat longer in Mj-Cx(+) group compared with that of Mj-Cx(−) group but was not statistically significant (28.7±11.8 days, vs. 36.9±18.8 days, $p=0.236$).

Table 1 Postoperative Surgery-related Major Morbidity

Major complications	PPPD+PD	DPS	Frequency (%)
Bleeding	8	2	10 (9.7)
Wound infection	8	–	8 (7.8)
Delayed gastric emptying	6	–	6 (5.8)
Pancreatic fistula	2	2	4 (3.1)
Intra-abdominal abscess	2	2	4 (3.1)
Intestinal obstruction	2	1	3 (2.9)
Chyle ascites	2	–	2 (1.9)
Bile leak	2	–	2 (1.9)

Determining Prognostic Factors of Resected Ductal Adenocarcinoma of the Pancreas

Among 17 clinicopathologic variables (age, gender, preoperative biliary decompression, preoperative chemoradiation, postoperative adjuvant therapy, tumor location, tumor size, T-stage, N-stage, tumor grade, lymphovascular invasion, perineural invasion, type of pancreatectomy, major complication, intraoperative bleeding amount, intraoperative transfusion, and margin status), negative surgical margins ($p=0.0075$) and the absence of postoperative major complications related to surgery ($p=0.0116$) were all significant favorable prognostic factors for the survival of patients with resected pancreatic ductal adenocarcinoma in the univariate survival analysis. Subsequent multivariate analysis determined that these two factors were also independent prognostic factors for survival after resection of pancreatic ductal adenocarcinoma (Table 3).

Impact of Major Complications on Oncologic Outcomes of R0 Pancreatectomy

Overall, margin-negative pancreatectomy without postoperative major complications showed the most favorable oncologic outcome in resected pancreatic ductal adenocarcinoma (median survival, 35.6 months; 95% confidential interval, 25.8–45.4 months). Postoperative major morbidity had a significant adverse effect on the favorable oncologic outcome of margin-negative resection, and patients with this type of morbidity showed similar survival rates to those of the R1 resection group [R0-Cx (+) vs. R1, median survival, 22.1 months (95% confidence interval, 1.8–42.4) vs. 18.6 months (95% confidence interval, 2.0-35.2), $p=0.149$, Fig. 1a]. A detrimental effect of major complications was also observed in conventional pancreaticoduodenectomy or in the pylorus-preserving pancreaticoduodenectomy group but was attenuated in the group that had undergone distal pancreatectomy with splenectomy (Fig. 1b, c).

Characteristics of Long-Term Survivors

Among the 103 patients who underwent resection of pancreatic ductal adenocarcinoma, nine patients survived for more than 5 years (Table 4). Seven patients had pT3 pancreatic cancer, and three patients showed lymph node metastasis in pathologic specimens. All patients were

Table 2 Clinical Pathologic Characteristics According to Major Complications Following Pancreatectomy

	Variables	Mj-Cx(−), *N*=71	Mj-Cx(+), *N*=32	*p* value
Age (years)		60.1±8.1	60.1±9.8	0.980
Gender	Male	45	20	1.000
	Female	26	12	
Diabetes	No	48	24	0.442
	Yes	22	8	
Jaundice	No	39	11	0.641
	Yes	32	21	
Total bilirubin (mg/dl)		8.4±13.4	10.4±10.1	0.915
Biliary decompression	No	40	11	0.039
	Yes	31	21	
Body weight (kg)		58.4±9.0	57.5±11.5	0.608
Total protein (g/dl)		6.6±0.7	6.9±1.2	0.165
Albumin (g/dl)		3.9±0.5	3.7±0.7	0.153
ASA	I	7	4	0.107
	II	54	21	
	III	3	6	
Surgical procedure	PD	28	13	0.758
	PPPD	24	13	
	DP-S	19	6	
Operation time (min)		360.2±125.7	365.2±111.6	0.460
Transfusion	No	28	14	0.472
	Yes	39	17	
Tumor size (cm)		3.1±1.3	3.1±1.2	0.706
T stage	T1	3	-	0.663
	T2	4	2	
	T3	64	30	
N stage	pN0	39	14	0.641
	pN1	32	18	
Lymphovascular invasion	No	65	28	1.000
	Yes	5	4	
Perineural invasion	No	50	28	0.180
	Yes	21	4	
Grade	Well	47	4	0.841
	Moderate	9	16	
	Poor	1	6	
	Undifferentiated	1	–	
R-status	R0	55	28	0.230
	R1	16	4	
Hospital stay (days)		20.5±9.1	26.0±9.1	0.027
Adjuvant CTx/RTx	No	34	17	0.244
	Yes	37	15	
Time to adjuvant CTx/RTx (days)		28.7±11.8	36.9±18.8	0.165

confirmed to have undergone margin negative resection (R0 pancreatectomy), and most patients (eight patients) did not experience any major postoperative complications. Six patients survived without tumor recurrence. Only one patient died of pancreatic cancer that recurred; he was also a case of major complication after R0 pancreatectomy.

Discussion

Until now, no single treatment modality has been shown to be effective for pancreatic cancer, other than curative surgery. Although advancements in basic research and in targeted therapy have been achieved, the oncologic

Table 3 Significant Surgeon-related Factors Affecting the Oncologic Outcome After Resection of Ductal Adenocarcinoma of the Pancreas (Cox Proportional Hazards Model)

Variables	Exp(β)	95% confidence interval	*p* value
R1	2.671	1.252–5.275	0.005
Major complications	1.824	1.073–3.101	0.026

outcome of pancreatic cancer has not been improved. In addition, adjuvant therapy is generally found to be ineffective. The survival outcome of patients who have undergone resected pancreatic cancer is generally a 5-year survival rate of less than 20%, with overall 5-year survival of less than 5%. Pancreatic cancer is clearly one of the most lethal malignancies in the gastrointestinal system.

Although the present study is based on a small sample size and retrospective observation, it suggests one potential role of pancreatic surgeons in improving patients' survival after resection of ductal adenocarcinoma of the pancreas. In multivariate analysis, both margin-positive resection [Exp (β)=2.671, p=0.005] and postoperative surgery-related major complications [Exp (β)=1.824, p=0.026] were independent factors for poor prognosis following pancreatic cancer resection. In addition, analysis of long-term survivors showed that all nine patients had undergone margin-negative resection, and most of them (eight patients) recovered without major complication after pancreatectomy. Only one case of cancer-specific mortality was noted, and this patient was coincidentally also a case of major complication (pancreatic leak with abscess) after R0 pancreatectomy.

At present, only margin-negative resection in pancreatic ductal adenocarcinoma has shown strong association with favorable long-term survival.[18–20, 23] According to a recent review[12] of complication rates after pancreatic cancer resections, overall complication rate ranges from "18 to 54%". Intra-abdominal abscess occurs in "1–12%," while "3–15%" experience postoperative bleeding, "1–16%" develop pancreatic fistula, "14–30%" show delayed gastric emptying, and "2–11%" have wound infection following resection for pancreatic cancer. In our data, surgery-related major complications occurred in 32%, and about 1% postoperative mortality was noted. All common major complications rates (9.7% postoperative bleeding, 7.8% wound infection, 5.8% delayed gastric emptying, and 3.1% pancreatic fistula and abscess) seem to be within the generally reported range of incidence.

Although frequent surgical morbidities are encountered in the field of pancreatic surgery, the significance of postoperative major complications with regard to oncologic outcomes after pancreatectomy in pancreatic cancer has received little attention in the literature. Raut et al.[18], using multivariate analysis, revealed that major perioperative complications, as a group, were one of the factors that adversely affected survival in pancreatic adenocarcinoma. Winter et al.[19], by multivariate Cox proportional hazards regression (Hazard ration, 7.0, p<0.001), also suggested that bile leakage (one of the major complications) was an indicator of poor prognosis for patients with ductal adenocarcinoma of the pancreas. However, not as much significance was placed on the relationship between postoperative complications and survival outcomes. Recently, Howard, et al.[20] concluded that margin negative resection (R0) with no complications was a prognostic variable that could be affected by the surgeon. The authors hinted at the reasons for adverse effects of postoperative complications by commenting that "minimizing complications can preserve a patient's physiologic function to ensure they are capable of receiving timely and

Table 4 Characteristics of Long-term Survivors (≥5 Years)

Variables	Frequency
Age (median with range, years)	53 (43–65)
Gender (male/female)	8:1
Location (head/body/tail)	5:1:3
Tumor size (median with range, cm)	3.3 (1–7)
T stage (T1/T3)	2:7
N stage (N0/N1)	6:3
Tumor grade (well/moderate/poor)	3:4:2
Lymphovascular invasion	0
Perineural invasion	0
Mode of resection(PD/PPPD/DP-S)	2:3:4
R0 pancreatectomy	9
Complication	1 (pancreatic leak with abscess)
Adjuvant therapy	4
Disease-free status	6
Disease-specific mortality	1

appropriate adjuvant therapy." Although in our observations, there was no significant difference in the time interval to the postoperative adjuvant therapy between Mj-Cx(−) and Mj-Cx(+) groups (28.7±11.8 days, vs. 36.9±18.8 days, p=0.236), the time lag to postoperative adjuvant therapy in the Mj-Cx(+) groups is apparently much longer than that of Mj-Cx(−). This result suggests a potential negative effect of postoperative major complications, through prohibition or delay of "properly" and "timely" adjuvant therapy for possible microscopic residual tumors.[24] This situation would be evident in clinical settings where potent and effective adjuvant regimens were readily available. Patients with major postoperative complications might need additional time to return to a stable enough physiologic function to tolerate the possible toxicity of adjuvant therapy. This might allow propagation and dissemination of microscopic residual tumors, especially if immunologic impairment was also a factor.

For reasons that are not clear, the detrimental effect of major complications was observed following conventional pancreaticoduodenectomy or pylorus-preserving pancreaticoduodenectomy but was attenuated following distal pancreatectomy (Fig. 2). It is difficult to evaluate the reasons based on our limited data set; however, major morbidities are apparently more complicated and of more severity in patients requiring resection of pancreatic head cancers. For example, cases of delayed oral intake (such as delayed gastric emptying, partial obstruction, and chyle ascites), of sepsis-related complication (such as abscess, wound infection, and bile leakage), or of bleeding requiring transfusion are relatively more frequent in the postoperative period in the pancreaticoduodenctomy group than in the distal pancreatectomy group (Table 1). Poon and Wong[25] have speculated that hepatocellular carcinoma patients who develop postoperative complications might be immunosuppressed, which could enhance the development of recurrent tumors. Law et al.[17, 26] also suggested that an altered immune response associated with sepsis, stress, and inflammatory responses following complications might contribute to the growth and proliferation of residual tumor cells in colorectal cancer patients. Recently, Yeh et al.[27] examined survival in patients with pancreatic cancer who received blood transfusions in association with pancreaticoduodenectomy. Postoperative transfusion remained a predictor of survival that was independent of both nodal and margin status. All of these studies indicate the potential for adverse influences of major complications on oncologic outcome after curative resection for malignant tumors.

Therefore, the possibility of negative impacts of major complications on oncologic outcome needs to be considered in more depth. This is particularly true for pancreatic cancer patients requiring pancreaticoduodenectomy, as more complex and potent morbidities might be encountered postoperatively in these patients, which could reduce the oncologic efficacy of R0 pancreatectomy. However, the small sample size (N=25) of the distal pancreatectomy group in this study might also be a reason for this observation. This is probably the more judicious message at present, as pancreaticoduodenectomy is a more reliable and more frequent surgical approach for resectable pancreatic head cancers, especially as pancreatic cancers in the body and tail of the pancreas are usually found to be unresectable.

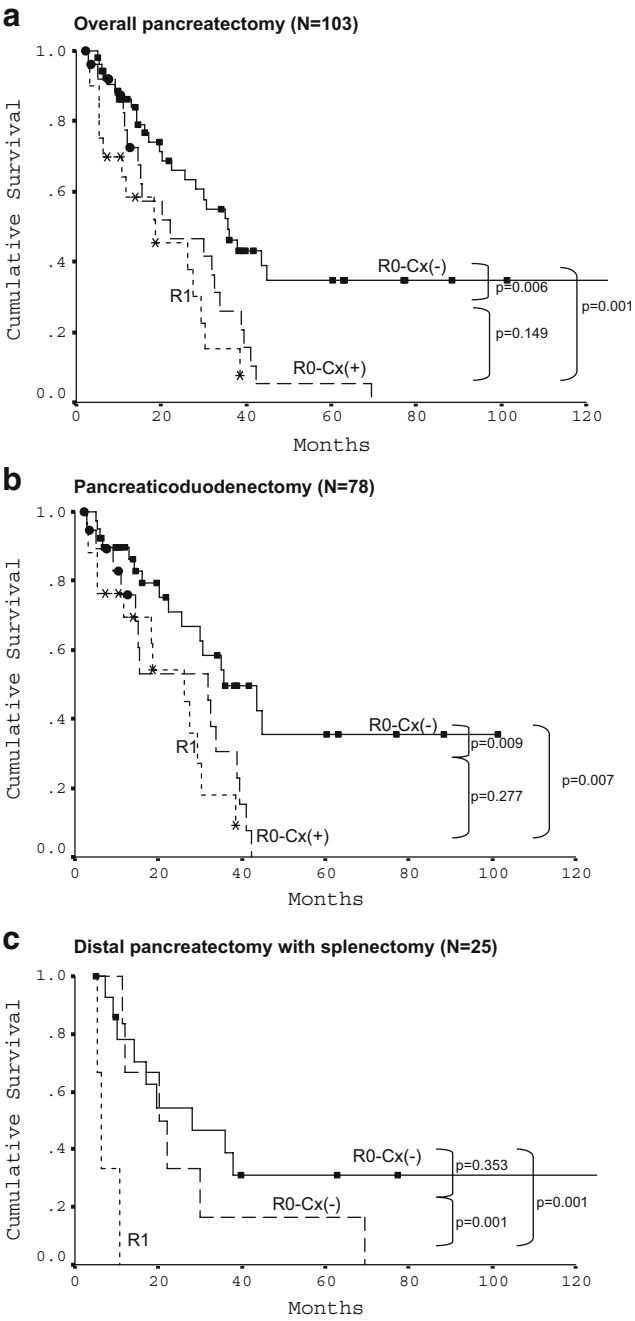

Figure 2 Impact of the quality of resection and postoperative major morbidity on survival after resection of ductal adenocarcinoma of the pancreas.

This raises the question as to which complications might provide significantly more negative impacts on oncologic outcomes of R0 pancreatectomy. This issue is also difficult to address in depth on the basis of this limited data set. However, it is evident that any complications that prove responsible for prolonging hospital stay and additional management (clinically relevant) can potentially influence the oncologic outcome. There seems to be no direct evidence supporting a potential relationship between major complications and the survival of cancer patients. Benzoni et. al.[28] recently reported on a role for pancreatic leakage in the increase in postoperative complications following pancreatic surgery. They observed that bleeding, bile fistulas, and infectious complications all could result from pancreatic leakage. These clinically relevant complications (leakage, abscess, bleeding, wound infection, prolonged DGE, prolonged delay of oral intake, etc.) may cause adverse impacts on the patient's immune system, as well as delay the earliest time for initiating adjuvant therapy. Further experimental studies and careful clinical observations are needed to confirm the validity of this potential relationship between complications and oncologic outcomes following pancreatic cancer resection.

In conclusion, although pancreatic ductal adenocarcinoma is still considered a highly malignant neoplasm with an extremely poor prognosis, this retrospective study suggests a potential role that pancreatic surgeons can take to improve survival of their pancreatic cancer patients who undergo R0 pancreatectomy. Pancreatic surgeons should continue to focus on margin-negative resection but should also do so with an eye to minimizing postoperative major morbidities for improved survival of their patients.

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ORIGINAL ARTICLE

Additional Organ Resection Combined with Pancreaticoduodenectomy does not Increase Postoperative Morbidity and Mortality

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Abstract
Background The mortality associated with pancreaticoduodenectomy (PD) has decreased substantially in recent times, but high morbidity continues to be a significant problem. With reductions in mortality, there is increasing willingness to combine organ resections with PD when indicated. There is, however, a paucity of information regarding the morbidity and mortality of multivisceral resection (MVR) that involves pancreaticoduodenectomy (MVR-PD).
Methods Patients undergoing PD between January 2002 and November 2007 by a single surgeon were reviewed and perioperative outcomes determined. Those treated by PD alone were compared to those undergoing MVR-PD.
Results There were 105 patients overall who underwent PD during the study period, with MVR-PD performed in 19 patients. Twelve (63%) patients required PD combined with right colectomy, two (11%) underwent PD combined with right nephrectomy, two (11%) required liver resection with PD, and the remaining three (16%) had various combinations of kidney, colon, adrenal and small bowel resection in addition to PD. In both groups, the main indication for surgery was pancreatic cancer; however, there were proportionally more patients in the MVR-PD group with gastrointestinal stromal tumors (two (11%) patients), sarcomas (two (11%) patients) and metastases to the periampullary region (three (16%) patients). The overall complication rate in this study was 60%. Delayed gastric emptying (39%) and pancreatic fistula (16%) were the most common complications. There was no significant difference in complications between the two groups. A non pylorus-preserving PD was more commonly performed in cases of MVR-PD (53% vs 28%; $p=0.007$), operating times were longer (9.5 vs 8 h; $p=0.002$), and surgical intensive care unit stay was greater (2 vs 1 days; $p<0.001$). The overall median length of hospital stay (7 days) and readmission rate were similar between the groups.
Conclusion MVR-PD can be performed without significant added morbidity compared to PD alone. The main indication for MVR-PD is locally advanced pancreatic cancer requiring PD combined with right hemicolectomy.

Keywords Pancreaticoduodenectomy · Multivisceral resection · Combined resection · Morbidity · Mortality · Pancreas cancer · Retroperitoneal sarcoma

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Introduction

The first pancreaticoduodenectomy (PD) was performed by Alessandro Codivilla of Imola, Italy in 1898.[1] It was, however, not until 1940 when Allen Oldfather Whipple performed what is considered the first anatomic, one-stage pancreaticoduodenal resection, defining the beginning of modern PD.[2] The mortality rate associated with this

procedure between 1940 and 1944 for the first 60 reported cases was 22%.[3–7]

The mortality and morbidity associated with PD has decreased substantially since the earliest surgical reports. The mortality rate in high-volume centers is less than 5% with several reports of 0% mortality.[8–10] With these improvements, there is now a greater willingness to combine PD with other organ resections when indicated. The morbidity associated with PD, however, continues to be significant, despite improvements in intensive care management and perioperative care, ranging from 30% to 60% in high-volume centers.[11–15] The major morbidity from PD relates to pancreatic fistula and delayed gastric emptying (DGE).

The morbidity of multivisceral resection (MVR) that combines other organ resections with PD (MVR-PD) is rarely reported. Most of the studies concern PD combined with hepatic resection for the treatment of biliary malignancy with a suggestion of increased morbidity and mortality.[16–18] There are very few contemporary studies that examine the morbidity of MVR-PD, particularly when it involves resection of organs other than the liver. We compared the outcomes of patients undergoing MVR-PD with those treated by PD alone at a high-volume tertiary academic center to determine differences in operative indications and outcomes.

Patients and Methods

Patient Population

The medical records of patients undergoing PD at the Liver, Pancreas, and Foregut Unit of the Penn State Milton S. Hershey Medical Center by a single surgeon (K.S.) from February 2002 to November 2007 were reviewed. Patients were identified from a prospective operative registry with internal review board approval. Patients undergoing PD alone were compared to those having MVR-PD.

Preoperative Assessment

Demographic data including, age, sex, American Society of Anesthesiologist (ASA) classification, body mass index (BMI), and indications for surgery were recorded for all patients. In all cases, patients had computed tomography (CT) of the abdomen, pelvis, and thorax to determine local extent of disease and assess for metastases. Tumors were considered unresectable if there was evidence of complete superior mesenteric or portal vein encasement, superior mesenteric artery involvement, or if there were metastases. MVR-PD was considered likely to be required on preoperative imaging in cases of periampullary malignancy if there was suggestion of colonic involvement and for sarcomas overlying the right kidney with evidence of duodenal or pancreatic attachment.

Operative Procedures

Operative interventions were documented. This included the type of pancreaticoduodenectomy (pylorus-preserving or nonpylorus-preserving), other organs resected, the surgical time, the estimated blood loss, and the need for intraoperative blood transfusions.

All surgical resections were performed using standard techniques. A two-layer end-to-side duct to mucosa pancreaticojejunal anastomosis was performed with an interrupted single layer end-to-side anastomosis for biliary reconstruction. A pylorus-preserving technique was the procedure of choice when possible. A two-layered retrocolic duodenojejunal or gastrojejunal anastomosis was performed. Two closed-suction drains were placed adjacent to the pancreatic and biliary anastomoses. MVR-PD was undertaken in cases where PD alone was unable to achieve oncological tumor clearance or where two or more unrelated pathologies required surgical treatment. An en bloc resection was performed when possible.

All patients were managed in a surgical intensive care unit (SICU) setting for at least 24 h postoperatively with more prolonged monitoring when indicated. Nasogastric tubes were routinely inserted at the time of operation and removed at day 1 postoperatively. A liquid diet was commenced at day 2 postoperatively and advanced, as tolerated, to a soft diet. Drain fluid amylase measurements were performed after day 5 postoperatively. Octreotide was not administered in this series. Prophylactic antibiotics were given at the time of operation and continued for only 24 h thereafter, unless otherwise indicated. Erythromycin was commenced from postoperative day 2 at a dose of 200 mg intravenous every 8 h for the prevention of delayed gastric emptying up to the point of hospital discharge, unless otherwise contraindicated.

Postoperative Outcome

The length of SICU stay, overall length of stay, complications, and readmissions were recorded for all patients. Perioperative mortality was defined as death during the resection hospitalization or within 30 days of discharge after resection. A complication was considered as any event that required an intervention such as reoperation, drainage, or antibiotics. DGE was defined according to the International Study Group of Pancreatic Surgery (ISGPS) as the inability to return to a standard diet by day 7 postoperatively or requiring reinsertion of a nasogastric tube prior to this period.[19] Pancreatic fistula was defined, also according

to the definition endorsed by the ISGPS, as any measurable amount of fluid after postoperative day 3 with an amylase level three times greater than serum amylase.[20] Patients requiring drainage of intra-abdominal collections were considered to have pancreatic fistula, unless there was clearly another explanation.

Statistical Analysis

Results were expressed as the median (range), unless otherwise stated. Comparisons between categorical variables were made by chi-square or Fisher's exact test where appropriate. Noncategorical variables were assessed by the Mann–Whitney *U* test. A statistical software package (SPSS Version 11.5, Chicago, IL, USA) was used for analysis with $p<0.05$ considered statistically significant.

Results

Patient Population

One hundred and five patients underwent PD by a single surgeon during the study period. Table 1 summarizes the patient characteristics. The median age of patients treated was 68 years (22–88 years). There were 19 patients who had MVR-PD. There were no statistically significant differences between the two groups in terms of gender, age, BMI, ASA classification, or need for preoperative biliary stenting.

Surgical Indications and Operative Outcomes

The indications for surgery and operative details are summarized in Table 2. The most common indication for surgery was pancreatic cancer in 44 (42%) cases, followed by intraductal papillary mucinous neoplasia (IPMN) in ten (10%) patients. The overall indications for MVR-PD was significantly different to PD performed alone ($p=0.006$). The main indication for surgery in the MVR-PD group was pancreatic cancer in seven (49%) cases. There was, however, a disproportionate number of patients in the MVR-PD group compared to PD alone with gastrointestinal stromal tumors (GIST; two (11%) vs one (1%); $p=0.027$), sarcomas (two (11%) vs one (1%); $p=0.027$), and metastases to the periampullary region (three (16%) vs zero (0%); $p=0.005$). In those with metastases to the pancreatic region, two were from colonic primaries and one was from a gallbladder cancer. Metastases were not suspected preoperatively or intraoperatively in these cases. In the case of one patient with a hepatic flexure colon cancer extending into the duodenum and pancreas, PD and right hemicolectomy were performed. The final pathology revealed metastases to the pancreas from the adjacent colon. Our second patient had a history of colon cancer resection 12 months previously, representing with a duodenal mass adjacent to the transverse colon. This was thought to be a primary lesion. However, following resection, colorectal metastasis was confirmed on histology.

The additional organs resected in patients treated by MVR-PD are shown (Fig. 1). PD combined with a right hemicolectomy alone was the most common procedure in this series performed in 12 (63%) cases. PD was performed with right nephrectomy alone in two patients. One of these patients had a concurrent ampullary cancer and a right renal tumor and the other had retroperitoneal sarcoma involving the right kidney, duodenum, and pancreas. Liver resection was the main additional organ resected in two patients. One patient with a neuroendocrine duodenal tumor underwent PD combined with a segmental liver resection for suspected metastasis. One patient with a periampullary mass and lymphadenopathy underwent PD for presumed distal cholangiocarcinoma. A small gallbladder cancer penetrating into the muscular layer was noted on frozen section and

Table 1 Details of Patients Undergoing Pancreaticoduodenal Resection

	Overall ($n=105$), *n* (%)	PD alone ($n=86$), *n* (%)	MVR-PD ($n=19$), *n* (%)	Difference (*p* value)
Male	52 (49)	44 (51)	8 (42)	0.457
Female	53 (51)	42 (49)	11 (58)	0.457
Age	68 (22–88)	69 (29–88)	67 (50–85)	0.608
BMI	25 (17–45)	25 (17–45)	24 (18–36)	0.720
ASA class				0.279
II	13 (12)	11 (13)	2 (11)	
III	91 (87)	75 (87)	16 (84)	
IV	1 (1)	0 (0)	1 (5)	
Biliary stent	32 (31)	25 (30)	7 (40)	0.584

PD pancreaticoduodenectomy, *BMI* body mass index, *ASA* American Society of Anesthesiologists, *MVR-PD* multivisceral resection including pancreaticoduodenectomy

Table 2 Indications for Pancreaticoduodenectomy and Operative Details

	Overall (n=105), n (%)	PD alone (n=86), n (%)	MVR-PD (n=19), n (%)	Difference (p value)
Indication				
Periampullary cancer				
Pancreas	44 (42)	37 (43)	7 (40)	0.621
Ampullary	8 (8)	8 (9)	0 (0)	0.345
Biliary	2 (2)	2 (2)	0 (0)	0.502
Duodenum	3 (3)	2 (2)	1 (5)	0.454
IPMN	10 (10)	8 (9)	2 (11)	0.869
Neuroendocrine tumor	6 (6)	5 (6)	1 (5)	1.000
Ampullary/duodenal adenoma	8 (8)	8 (9)	0 (0)	0.345
Cystadenoma	5 (5)	5 (6)	0 (0)	0.582
Chronic pancreatitis	5 (5)	5 (6)	0 (0)	0.582
GIST	3 (3)	1 (1)	2 (11)	0.027*
Sarcoma	3 (3)	1 (1)	2 (11)	0.027*
Cancer metastases	3 (3)	0 (0)	3 (16)	0.005*
Others	5 (5)	4 (5)	1 (5)	0.910
Operative details				
Estimated blood loss	400 (100–2,000)	350 (100–2,000)	500 (100–1,000)	0.272
Blood transfusions intraoperative	10 (9)	9 (11)	1 (5)	0.685
Operative time	8 (4–21)	8 (4–15)	9.5 (7–21)	0.002*
Pylorus-preserving	76 (72)	67 (78)	9 (47)	0.007*
Number of days in SICU	1 (1–6)	1 (1–6)	2 (1–4)	<0.001*
Total length of stay (days)	7 (6–34)	7 (6–34)	8 (6–19)	0.257

PD pancreaticoduodenectomy, *SICU* surgical intensive care unit, *MVR-PD* multivisceral resection including pancreaticoduodenectomy, *IPMN* intraductal papillary mucinous neoplasm, *GIST* gastrointestinal stromal tumor
*p<0.05

considered an incidental second primary tumor. Additional central hepatic resection was performed at the same operative setting. The final pathology was surprisingly consistent with gallbladder cancer with pancreatic and periportal nodal metastases. In the remaining three patients, PD combined with right nephrectomy and right hemicolectomy was required in one case of a retroperitoneal liposarcoma. One patient with a duodenal GIST required PD combined with resection of multiple loops of attached small bowel. One patient underwent PD for IPMN combined with a left adrenalectomy for treatment of a large adrenal adenoma.

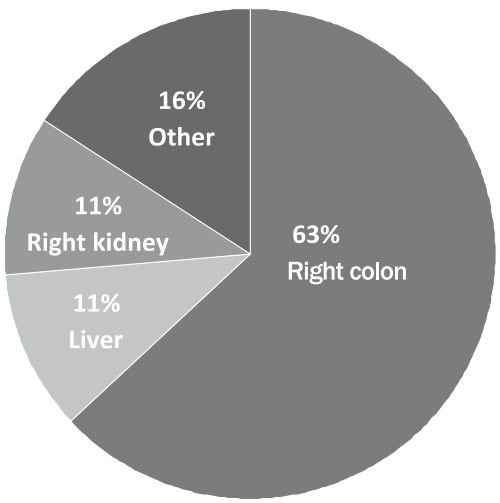

Figure 1 Chart showing the main organ resected in addition to pancreaticoduodenectomy in patients undergoing multivisceral resection (n=19).

Those undergoing MVR-PD were less likely to have a pylorus-preserving procedure than when PD was performed alone (nine (47%) vs 67 (78%); p=0.007). In cases of tumors involving but not arising from the periampullary region, pancreatic resection was usually technically easier, given that major vessel encasement was less frequently encountered. A soft texture pancreas with a nondilated duct was, however, more common in these circumstances with technically more difficult anastomoses. The overall median estimated blood loss in this series was 400 mL (100–2,000 mL) with no difference between the two main groups. Blood transfusions were required intraoperatively in 9% of cases with some cases due to low preoperative hemoglobin values. The median operative time was 8 h (4–21 h). Those undergoing MVR-PD had significantly longer operative times than those treated by PD alone (9.5 vs 8 h; p=0.002). The number of days in SICU was also greater following MVR-PD, 2 days (1–4 days), than after PD alone, 1 day (1–6 days) (p<0.001). The length of hospital stay was, however, not different between the two groups with a median length of stay of 7 days (6–34 days).

Operative Complications and Readmissions

Complications

There was no operative mortality in this series. One or more complications were noted in 63 (60%) patients. DGE 41 (39%), pancreatic fistula 17 (16%), and wound infections 11 (11%) were the most common complications. Of the 17 patients with pancreatic fistula, ten (59%) were classified as grade A, four (24%) were grade B, and three (18%) were grade C. Overall reoperation was required in two (2%) cases. One patient had a retained foreign body and another had early small bowel obstruction. There was no significant difference in complications between patients treated by PD alone and those requiring MVR-PD (Table 3).

Readmissions

There were 34 (32%) readmissions overall for one or more complications. The major reason for readmission was due to DGE in 20 (19%) patients, followed by infective complications in 13 (12%) cases. Patient in this series did not have routine feeding jejunostomy tube placements with DGE treated by intravenous rehydration and initiation of total parenteral nutrition (TPN). In cases of postoperative fluid collections requiring drainage, patients were admitted to the hospital overnight following percutaneous intervention. There was no difference in readmission rates between the two treatment groups.

Discussion

In large-volume centers, the mortality associated with a PD approaches 0%.[8–10] In a report of 1,000 pancreaticoduodenal resections performed by a single surgeon at Johns Hopkins Medical Center between 1969 and 2003, there was a 1% overall mortality.[21] Despite these reports of low mortality, the morbidity associated with PD remains significant with pancreatic fistula and DGE being the most common complications. It is not well-defined whether MVR that combines other organ resection with PD significantly alters morbidity and mortality associated with PD.

Much of the reported literature on the topic of MVD-PD is based on the treatment of cholangiocarcinoma.[16–18] In these situations, hepatic resection may be combined with PD, with controversy regarding the long-term benefits of this extensive procedure. A Japanese study of 26 patients undergoing hepatic resection with PD had zero mortality and only 23% associated morbidity.[17] Conversely, another Japanese series of 32 patients with cholangiocarcinoma treated by combined right hepatic lobectomy and PD had 15 (47%) deaths and a 91% complication rate.[22] In a Western series from the Memorial Sloan-Kettering Cancer Center of 17 patients undergoing such combined major liver resection and PD, the perioperative mortality was 18% and postoperative complications occurred in 47% of cases.[16] In our series, two patients underwent combined segmental liver resection with PD and one had a central hepatectomy and right colectomy in combination with PD. There were no complications directly related to liver resection in our series; however, the extent of liver resection was less than reported in other large series. The long-term benefit of combining major liver resection with PD, particularly for biliary malignancy, remains controversial and cannot be fully supported based on current literature and is not supported by our institution. The one exception for combined liver resection and PD is in cases of

Table 3 Complications of Pancreaticoduodenal Resection

	Overall (n=105), n (%)	PD Alone (n=86), n (%)	MVR-PD (n=19), n (%)	Difference (p value)
Patients with complications	63 (60)	50 (58)	13 (68)	0.644
Delayed gastric emptying	41 (39)	36 (42)	5 (26)	0.209
Pancreatic fistula	17 (16)	14 (16)	3 (16)	1.000
Wound infections	11 (10)	9 (11)	2 (11)	1.000
Postoperative bleeding	3 (3)	1 (1)	2 (11)	0.084
Intra-abdominal abscess	4 (4)	2 (2)	2 (11)	0.149
Pneumonia	3 (3)	2 (2)	1 (5)	1.000
Urinary tract infection	5 (5)	4 (5)	1 (5)	1.000
Thromboembolic	8 (8)	6 (7)	2 (11)	0.634
Other	5 (5)	5 (6)	0 (0)	0.361
Reoperation	2 (2)	1 (1)	1 (5)	0.331
Readmission	34 (32)	29 (34)	5 (26)	0.596
Delayed gastric emptying	19 (18)	17 (20)	2 (11)	0.518
Infective complication	13 (12)	9 (11)	4 (21)	0.247
Other	3 (3)	2 (2)	1 (5)	0.454

PD pancreaticoduodenectomy, *MVR-PD* multivisceral resection including pancreaticoduodenectomy

patients with neuroendocrine pancreatic lesions, particularly functional tumors with resectable metastases. In these cases, combined resection may improve long-term survival and provide improved symptom control in cases of functional tumors, although long-term data is lacking.

Right hemicolectomy in conjunction with PD was the most common combined procedure in our series. The literature on this approach is quite limited. Infiltration of the transverse mesentery by periampullary cancer was traditionally considered a marker of unresectability, but this should be no longer considered as a contraindication for resection. The largest series of patients undergoing PD with right hemicolectomy is from Japan, detailing 12 patients with advanced periampullary malignancy.[23] This represented 12% of patients undergoing PD in that series with no perioperative mortality and 50% morbidity. In our own series, 13 patients required PD and right hemicolectomy. In 12 of these cases, PD was performed with right hemicolectomy alone. Colon resection was performed when tumors were directly attached to the colon wall, when tumor rupture was considered high risk with disruption of tissue planes between the colon, pancreas, and duodenum, and in cases where excision of the transverse mesentery and vessels alone appeared to compromise colon viability. There was overall a higher proportion of patients undergoing MVD-PD in this series than expected, which may reflect our senior author's interest and high referral of advanced periampullary cancers, GISTs, and retroperitoneal sarcomas.

The combination of PD with additional organ resection other than the colon or liver is even less frequently reported. In our series, three patients had PD combined with nephrectomy, including concurrent colon resection in one of the cases. One of these cases was performed for two separate tumors. Another patient underwent a left adrenalectomy combined with PD for an unrelated pathology and one patient required multiple small bowel resections for the treatment of a locally advanced duodenal GIST. In all of these patients, there were no complications related to the additional organ resection.

The overall morbidity in our series was 60% with no apparent difference between those undergoing PD alone and patients requiring MVR-PD. This is comparable to a morbidity of 30–60% in other series.[11–15] DGE was the most common complication seen, occurring in 39% of patients. This was based on a strict definition set by ISGPS and is comparable to reports of 19–57% DGE in other series.[19] Patients that were otherwise well and did not tolerate a diet by day 6 or 7 postoperatively, without a feeding jejunostomy tube, were commenced on TPN and subsequently discharged home or to a rehabilitation facility. Pancreatic fistula was the next most common complication, occurring in 16% of patients based on strict international criteria. Grade C fistula occurred in only three (18%) patients with a fistula, with one being in the MVR-PD group.

The main perioperative differences between patients undergoing PD alone and those treated by MVR-PD was the length of operation and the length of stay in the intensive care unit. The median operating time was 1.5 h greater for those treated with MVR-PD than for PD alone, with significantly more patients in this group having a nonpylorus-preserving PD. Intensive care unit stay was, on average, 1 day longer in the MVR-PD group; however, the overall length of hospital stay was similar between the groups with a median length of stay of 7 days. This is significantly shorter than the 9 to 10 days reported in two large contemporary series.[15,21] The overall readmission rate in our series was 32% and was significantly higher than a report of 9% in a large United States series.[15] However, there was no significant difference between our two groups. The major causes of readmission were DGE and infective complications. The high readmission rate is partly related to our early discharge policy with a low threshold to readmit patients with DGE if they have signs of dehydration despite TPN or have prolonged vomiting. Also, patients requiring drainage procedures were generally admitted to the hospital overnight for logistic reasons rather than being treated on an outpatient basis. It should be noted that the survival benefit of MVR-PD was not assessed in our study. This is an important question and requires larger studies, likely involving multiple centers, to allow homogenous groups of patients undergoing MVR-PD to be compared to those treated by PD alone.

Pancreaticoduodenal resection appears to be a safe and well-tolerated procedure, despite high perioperative morbidity. The major causes of morbidity continue to be DGE and pancreatic fistula, which are generally of low clinical impact. MVR-PD is occasionally required to achieve complete tumor clearance or to deal with two or more concurrent pathologies. The main indication for MVR-PD is locally advanced pancreatic cancer with an increased propensity for a diagnosis of sarcoma and GIST. MVR-PD generally takes longer to perform than PD alone and is more likely to be nonpylorus-preserving. The combination of PD with a right hemicolectomy is most commonly performed with PD and nephrectomy or liver resection being less common. Morbidity related to MVR-PD is not significantly greater than the morbidity related to PD alone. MVR-PD appears to be a valid and safe treatment option in selected patients who require more extensive resection than PD alone for complete oncologic resection. This paper demonstrates the feasibility of MVR-PD, but further studies on long-term survival and indications are clearly needed.

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ORIGINAL ARTICLE

Results of Non-operative Therapy for Delayed Hemorrhage after Pancreaticoduodenectomy

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Abstract
Introduction Hemorrhage after pancreaticoduodenectomy is a life-threatening complication, which occurs in 4% to 16% of cases, even in experienced centers. Many diagnostic and therapeutic options exist but no one has yet established management guidelines. This study aimed to determine the role of conservative management in delayed hemorrhage.
Patients and methods From January 2005 to August 2008, 87 patients underwent pancreaticoduodenectomy at our center. We reviewed, retrospectively, the medical charts of all patients who had experienced postoperative hemorrhage.
Results and discussion Early hemorrhage occurred in one patient, who underwent successful reoperation. Nine patients presented with delayed hemorrhage (10.3%), including three with sentinel bleeding. Mean onset was 20 days post-surgery. We used the same initial management for each patient: all had an urgent contrast computed tomography scan. In every case, the bleeding site was arterial. Conservative treatment (embolization or covered stent) was successful in every case. We reoperated on two patients for gastrointestinal perforation, at 9 days and 2 months after embolization, respectively. We transferred seven patients to an intensive care unit, with an average stay of 8 days. Mean hospital stay was 43 days (33–60). All patients survived.
Conclusion Conservative management, combining endovascular procedures and aggressive resuscitation, is appropriate for most cases of delayed hemorrhage after pancreaticoduodenectomy.

Keywords Pancreatoduodenectomy · Hemorrhage · Covered stent · Embolization

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Table 1 Results (Population, Characteristics of Hemorrhage, Treatment)

	Age	Sex	Indication for PD	Vascular procedure	Time of onset	Bleeding site	Biochemically confirmed fistula	Collection on CT scan
Patient 1	62	M	Pancreatic carcinoma	Yes: Portal vein lateral suture	Day 15	Right Gastric Artery	Yes	No
Patient 2	57	M	Ampulloma	No	Day 20	Jejunal Artery	No	Yes
Patient 3	70	F	Pancreatic carcinoma	Yes: Portal vein resection with saphenoplasty	Day 11	Splenic Artery	No	No
Patient 4	70	M	Pancreatic carcinoma	No	Day 31	Jejunal Artery	No	No
Patient 5	55	M	Bile duct carcinoma	No	Day 16	GDA	No	Yes
Patients 6	53	M	Endocrine tumor	No	Day 18	GDA	Yes	Yes
Patient 7	64	M	Pancreatic carcinoma	No	Day 22	GDA	No	No
Patients 8	47	M	Pancreatic carcinoma	No	Day 23	GDA	No	Yes
Patient 9	56	M	Mucinous neoplasm	No	Day 24	GDA	No	Yes

Biochemically confirmed pancreatic fistula, i.e., amylase concentration in drain fluid greater than five times serum concentration

TAE Transcatheter arterial embolization, *GDA* gastro duodenal artery, *FFP* fresh frozen plasma

Introduction

Although mortality levels (0%–5%)[1–3] have fallen over the past two decades, morbidity after pancreaticoduodenectomy (PD) remains high, between 20% and 50% according to various series.[4–7] Common complications include delayed gastric emptying (19–23%), fistula from the pancreaticoenterostomy (9%–18%) and intra-abdominal abscesses (9%–10%).[7] Hemorrhage after PD (HPD) is a life-threatening complication (4%–16%),[8,9] occurring either early or late in the postoperative course. Its mortality rate varies, from 11% to 54%, even in experienced centers.[10–18] There are many diagnostic and therapeutic options for managing HPD but no established guidelines.[13,14] Treatment options include: simple resuscitation, conservative procedures such as transcatheter arterial embolization (TAE) and covered stents, and relaparotomy. Recent studies report good results for TAE[11,12,19] and covered stents[20–23] but surgery retains a key role in HPD management.[16] Our study aimed to determine the role of conservative treatment in managing HPD, with experienced radiological teams and surgeons trained in endovascular procedures at our disposal. We also defined the timing and coordination required between radiologists, surgeons, and resuscitators.

Patients and Methods

From January 2005 to August 2008, our department performed 87 PD. We retrieved all HPD cases retrospectively. The data collected concerned: population (age, sex, and indications for PD), hemorrhage characteristics and clinical impact (time of onset, clinical manifestations, bleeding site, blood loss, sentinel bleeding, pancreatic fistula), management (diagnostic procedure, units of blood transfused, need for resuscitation, treatment, length of stay in intensive care and surgery unit) and outcome. We performed the same operative procedure in all patients: a pylorus-preserving PD with an end-to-side pancreaticogastrostomy, hand-sewn with absorbable monofilament sutures. Hepaticojejunostomy and duodenojejunostomy were hand-sewn 40 cm above on the same jejunal loop. We ligated the gastroduodenal artery with non-absorbable stitches and performed a gastrostomy at the end of each procedure to prevent delayed gastric emptying. We placed a multi-channel open silicone drain close to the pancreatic and biliary anastomoses and pulled it out through the right flank. All patients received postoperative thromboembolic prophylaxis by low-molecular weight heparin. Following our department's protocol, we administered a subcutaneous injection of octreotide 12 h before surgery and gave intra-venous injections for 7 days afterwards in each case. We routinely measured hemoglobin concentrations three times a week, more often if we suspected complications. In cases where we suspected a pancreatic fistula, we measured pancreatic enzymes in the surgical drain fluid and performed a computed tomography (CT) scan. We used the recent proposals from the International Study Group of Pancreatic Surgery (ISGPS) to define the hemorrhage characteristics: "delayed" HPD classified as more than 24 h after surgery, "severe" HPD classified as a hemoglobin fall of ≥3 g/dL, clinically significant impairment (e.g. tachycardia, hypoten-

Sentinel bleeding	Treatment	Intensive care unit/ length of stay	Hb drop (g/dL)	Transfusion	Length of stay
No	TAE	No	3,1	5 units of blood	39 days
No	TAE	No	2,8	4 units of blood	36 days
No	TAE	Yes/19 days	8,2	10 units of blood; 9 FFP	60 days
No	TAE	Yes/1 day	8,6	3 units of blood	19 + 14 days
No	1°) TAE 2°) TAE	Yes/6 days	5,4	9 units of blood; 2 FFP	40 days
Day 6	1°) TAE 2°)Covered Stent	Yes/7 days		11 units of blood; 2 FFP	39 days
No	1°) TAE 2°)Covered Stent	Yes/10 days		9 units of blood; 12 FFP; 1 platelet concentrate	40 days
Day 11	Covered Stent	Yes/3 days	8,3	12 units of blood; 1 platelet concentrate	44 days
Day 20	Day 20 Endoscopy Day 24: Surgery Day 25: Covered stent	Yes/11 days	5,7	7 units of blood; 4 FFP; 1 platelet concentrate	59 days

sion, oliguria, shock, a blood transfusion requirement of greater than three units packed cells) or invasive treatment requirements (conservative or surgical). We defined pancreatic fistula as cases where drain amylase levels were more than five times higher than the serum concentration and those where CT scan revealed intra-abdominal collections, which likely imply pancreatic leak. We classified sentinel bleeding as any minor hemorrhage that did not require intervention and often preceded major hemorrhage.

Results

Among all 87 patients, only one experienced early HPD. Urgent CT scan identified the hemorrhage on the retroportal process in this 73-year-old man, who underwent successful repeat surgery and had an uneventful postoperative course.

Nine patients presented with delayed HPD (10.3%), all of which were severe. Eight patients were male and one female, with a mean age of 59 (47–70). Table 1 shows the indications for PD. We performed vascular procedures in two cases: a lateral portal vein suture and a portal vein resection with saphenoplasty (among the 87 patients, seven underwent vascular procedures). Six patients developed a pancreatic fistula (67%): two confirmed biochemically and four suspected by the presence of intra-abdominal collections on CT scan (one patient had both a biochemically confirmed fistula and a collection). The mean onset of HPD was 20 days post-surgery (11–31 days). Eight patients (89%) bled before we had discharged them from hospital. Clinically, bleeding revealed itself through the gastrostomy probe or the gastrointestinal tract. We observed hypovolemic shock in four cases (44%).

We used the same initial management for each patient: a contrast CT scan was immediately performed, in the presence of radiologists, gastrointestinal surgeons and resuscitators. In every case, bleeding was arterial and we diagnosed six cases (67%) at this stage. Three patients experienced sentinel bleeding (33%), which we localized by a repeat CT scan in one case and by angiography in two. We identified the bleeding sites as follows: the gastroduodenal artery (GDA) in five cases, a jejunal artery in two cases, the right gastric artery in one case and the splenic artery in one case (see Table 1). We performed TAE successfully on patients 1 and 2. We also performed successful TAE on patient 3, to the splenic artery, but this patient required surgery 9 days later for gastric perforation: a simple suture was performed. For patient 4, HPD occurred after we had discharged him from hospital following an uneventful postoperative course. A contrast CT scan revealed a bleeding jejunal artery, which we successfully embolized. We hospitalized this patient for a third time 2 months later and successfully operated on his jejunal perforation. Patient 5 required TAE on the GDA. This embolization caused a partial thrombus of the left hepatic artery (LHA): there was a short GDA stump. A CT scan performed the following day showed that the LHA had spontaneously recanalized. A second CT scan, at day 7, diagnosed a GDA pseudoaneurysm as well as a collection surrounding the common hepatic artery (CHA). We decided to perform a TAE of the CHA (placing microcoils both proximally and distally), to isolate the pseudoaneurysm and

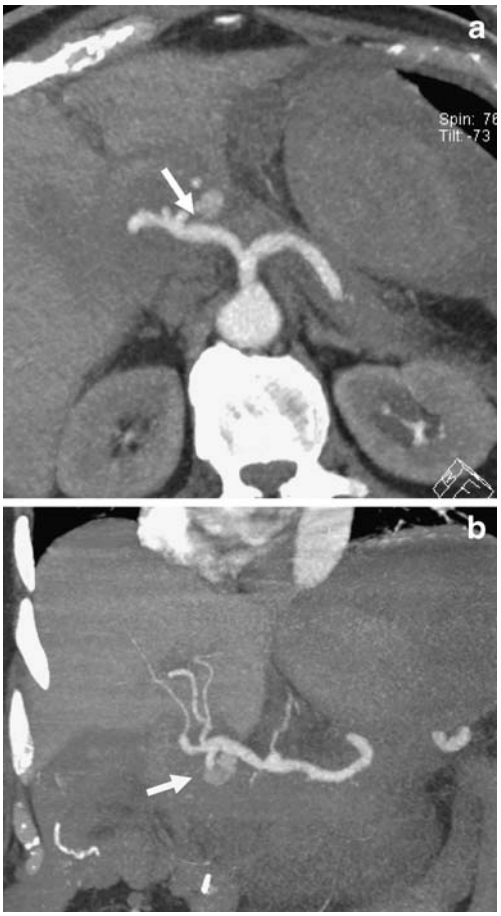

Figure 1 Contrast CT-scan performed on Patient 7. Pseudoaneurysm of the gastroduodenal artery (*arrow*) surrounded by hematoma. **a** Transverse plane, **b** coronal plane.

prevent further hemorrhage. The right subphrenic artery maintained hepatic inflow. There was no sign of hepatic failure, except for a transient cytolysis. In patient 6, we performed endovascular stenting during the same procedure as the original TAE because we could not control the GDA bleeding. Patient 7 presented with a GDA pseudoaneurysm (Fig. 1): TAE initially controlled the bleeding but then new hemodynamic failure occurred 12 days later. A new CT scan diagnosed bleeding from the GDA and we placed a covered stent in the CHA. Patient 8 presented with sentinel bleeding at day 11. At day 23, fresh hemorrhage occurred and arteriography diagnosed a GDA pseudoaneurysm; we performed endovascular stenting directly, without any complications (Fig. 2). Patient 9 had a sentinel bleed at day 20 followed by a second bleed at day 24, but CT scan was still not diagnostic. We performed an emergency relaparotomy with gastrotomy but we still could not find the bleeding site. His hemorrhage continued so on day 25 we performed arteriography that revealed bleeding from the GDA. We placed a stent in the CHA, successfully covering the bleeding stump.

We recorded a mean hemoglobin fall of 6 g/dL (2.8–8.6 g/dL). All patients were transfused; they received on average 7.8 units of blood (3–12). Five patients needed fresh frozen plasma (FFP), on average by 6 FFP (2–12). Three patients also required one unit of platelet concentrate each. We transferred seven patients to an intensive care unit, where the mean stay was 8 days (1–19 days). Three patients required intubation. HPD patients stayed in hospital for an average of 43 days (33–60 days), including 25 days after HPD (14–35 days). All nine patients survived to hospital discharge and follow up.

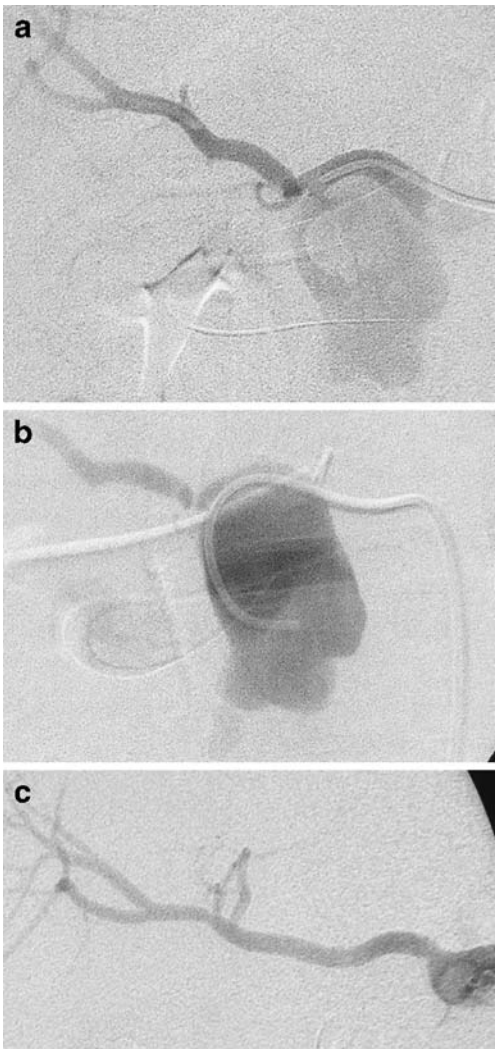

Figure 2 Arteriography performed on Patient 8. Following a sentinel bleed on Day 11, this patient presented with a new hemorrhage on Day 23. CT scan could not localize the origin. **a** Visualization of the common hepatic artery (*CHA*) and of a pseudoaneurysm of the gastroduodenal artery. **b** The catheter is in the pseudoaneurysm. **c** Placing a covered stent in the CHA, excluding the pseudoaneurysm and preserving hepatic inflow.

Comments

Our study suggests that most cases of delayed HPD, which usually carries a poor prognosis,[10–18] can be managed by endovascular procedures instead of surgery. In this series, every patient received endovascular treatment and every patient survived. The incidence of HPD in our study was 11.5% (including 10.3% delayed HPD), which is rather high, but in keeping with the literature. Blanc et al. reported a 7% incidence[14] and two recent randomized trials comparing pancreaticogastrostomy and pancreaticojejunostomy reported a HPD rate of 4% and 16%, respectively, in the pancreaticogastrostomy group.[8,9] After the last hemorrhage reported here, we stopped using bipolar diathermy forceps in PD. Since then, we have performed 20 PD, not included in this series, with no postoperative hemorrhage. Our study had a mortality rate of zero, in contrast to the high mortality rates reported in the literature.[10–18] Perhaps the small number of cases in our series can explain this. Nevertheless, it indicates a trend towards lower mortality rates with conservative management. Until the recent study of Wente et al.,[7] the international community lacked a clear definition for HPD, regarding delay of onset, localization, and severity. This explains the great variations in reported results, even in randomized controlled trials. We analyzed our results in accordance with these new definitions: "early" hemorrhage classified as occurring in the first 24 h, "delayed" hemorrhage including every HPD occurring after the first postoperative day.

It is widely accepted that early HPD is a consequence of surgical failure, requiring relaparotomy to achieve hemostasis of non-secured intra-abdominal vessels or defects in the anastomotic suture line.[13,14] In our series, our only case of early HPD responded successfully to repeat surgery. Peptic ulceration or intra-abdominal vascular lesions may explain delayed HPD. Vascular lesions result from both surgical trauma[24] (skeletonization of the visceral arteries, tight ligation of arterial stumps) and anastomotic dehiscence: pancreatic fistula (and its proteolytic activity) or local sepsis-induced erosion of the vascular wall and peri-anastomotic necrosis.[11,16,18] However, some cases show no evidence of a pancreatic leak. In our series, we confirmed a pancreatic fistula biochemically in only two cases and diagnosed intra-abdominal collections, which imply pancreatic leaks, by CT scan in five cases among nine. Two of the seven patients who underwent vascular procedures presented with hemorrhage (28.5%). However, the procedure concerned the portal vein in both cases and did not correspond to the bleeding site (right gastric and splenic arteries, respectively).

HPD bleeding sites include the GDA stump, portal vein tributaries, hepatic artery branches, superior mesenteric vein tributaries (including uncinate vessels), superior mesenteric artery branches (including jejunal arteries), the cut pancreatic surface, the suture lines of the pancreaticojejunostomy, the gall bladder fossa, the suture lines in a duodenojejunostomy after pylorus-preserving PD or the gastrojejunostomy suture lines after classical PD, and retroperitoneum.[7] In pseudoaneurysm cases, the most common bleeding sites are the GDA and right hepatic artery but others also describe bleeding from the CHA, superior mesenteric artery or splenic artery.[11] Our experience is in accordance with the literature, as bleeding originated from the GDA in five cases among nine.

There is no consensus about managing delayed HPD, except for the need for immediate diagnostic imaging (angiography, CT scan or multi-slice CT-angiography) and restoration of hemodynamic stability. Treatment can involve further surgery or employ endovascular procedures, such as TAE or covered stents. Several studies conclude that TAE is a safe and effective treatment for delayed HPD.[12,25,26] The main complication of TAE is full thrombus of the CHA, which can cause hepatic failure by hepatic duct ischemia or liver abscess formation.[13,25] If the bleeding site was too close to the CHA and there was no collateral hepatic blood flow, such as a replaced hepatic artery or a well-developed subphrenic artery, Yoshiro et al.[11] preferred to use a covered stent. In our series, we chose to embolize the CHA in one patient who also had a well-developed right subphrenic artery. Except for a transient cytolysis, the outcome was successful. Covered stents suit GDA pseudoaneurysms, with their advantage of preserving hepatic inflow.[16,20] Mansueto et al.[22] described a case of GDA bleeding where TAE was contraindicated because of portal vein thrombosis. They successfully placed a covered stent in the CHA, thus excluding the bleeding site and preserving hepatic inflow. In our series, we placed covered stents in four patients with GDA bleeding: one as first-line treatment, two after failed TAE and one after failed surgery. All procedures were successful. Hepatic necrosis has not developed at 3 years follow up for patient 7, 2 years for patients 6 and 8, and 10 months for patient 9. We therefore recommend covered stents as a first-line treatment, especially in GDA pseudoaneurysms, as long as the patient's anatomy permits it (CHA morphology sometimes prevents stent placement).

Most centers use endovascular treatment for patients with mild bleeding and no associated sepsis[12,18,20,25] but treat massive hemorrhage with urgent surgery.[16] Blanc et al.[14] found rather disappointing results concerning endovascular treatment. TAE and covered stents only treated two of 16 cases of delayed HPD successfully (occurring in stable patients with pseudoaneurysms). Four patients with active and severe bleeding underwent unsuccessful angiography. Surgeons also require a CT scan prior to reoperation to help localize the bleeding[14] and a

complete pancreatectomy is often recommended.[27–29] This procedure is associated with high mortality rates, from 24% to 80%,[28–30] except for the De Castro et al. study,[27] which reported no deaths after nine complete pancreatectomies. It is also associated with a high morbidity, causing up to 2 L blood loss and inducing unstable diabetes that considerably alters the patient's quality of life.[28] Of course, if massive hemorrhage does not respond to resuscitation, patients still require urgent surgery. Fortunately, this never happened in our series. We operated a second time on three patients with delayed HPD. Only one had a laparotomy for hemorrhage, which was unsuccessful since it did not localize the bleeding site. The two gastrointestinal perforations probably resulted from embolization: the gastric perforation occurring at 9 days was temporally related to TAE and the jejunal perforation corresponded anatomically to the embolized area. Thus, embolization carries a risk of perforation, although we believe that endovascular treatment probably remains the better choice.

It seems to us that when managing delayed HPD, timing is critical. After restoring hemodynamic stability, a contrast CT scan must take place immediately in the presence of radiologists, surgeons, and resuscitators. Then, a quick discussion between each member of the team should decide treatment. We cannot push conservative management to its limits without committed resuscitators and a well-trained endovascular team of radiologists and vascular surgeons. In our series, we chose conservative management as a second-line treatment in four cases: following TAE failure in three cases and after surgical failure in one. This choice was only possible with aggressive resuscitation.

Brodsky and Turnbull introduced the concept of sentinel bleeding in 1991.[31] This followed the study of Shankar and Russell,[32] which reported the existence of a possible warning bleed before massive hemorrhage. Sentinel bleeding precedes delayed HPD in 25% to 100% of cases.[14,16] Yekebas et al.[13] reported a 57% mortality rate when sentinel bleeding was associated with a pancreatic leak. In patients with a known pancreatic leak, the literature advises performing a helical CT scan with three-dimensional angiography if sentinel bleeding occurs.[14] In our series, sentinel bleeding occurred in three cases (33%). We performed a CT scan in each case, although it did not identify the bleeding site.

In conclusion, a recently established universal definition for HPD that includes severity, localization, and time of onset, will hopefully help improve HPD management. Nine cases of delayed HPD occurred in our series and the timing of their management was critical: we restored hemodynamic stability and performed an immediate contrast CT scan in the presence of radiologists, surgeons, and resuscitators before deciding etiological treatment. Our series shows that if aggressive resuscitation occurs, endovascular procedures can be performed in almost every case, not only as a first-line treatment for mild hemorrhage but also as a second-line procedure for massive hemorrhage (except for cases not responding to resuscitation). This conservative strategy avoids repeat surgery and its high levels of associated morbidity and mortality.

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ORIGINAL ARTICLE

Enteral Nutrition and Biliopancreatic Diversion Effectively Minimize Impacts of Gastroparesis After Pancreaticoduodenectomy

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Abstract
Background Since gastroparesis is unavoidable in a certain proportion of patients after pancreaticoduodenectomy, measures to avoid its occurrence or at least minimize its impact are needed. A prospective randomized trial was performed to test the effectiveness of biliopancreatic diversion with modified Roux-en-Y gastrojejunostomy reconstruction and of enteral feeding to minimize impacts of gastroparesis after pancreaticoduodenectomy.
Methods In total, 247 patients with periampullary tumors were randomized at the time of pancreaticoduodenectomy to have either (1) modified Roux-en-Y gastrojejunostomy reconstruction (by creating a side-to-side jejunojejunostomy between afferent and efferent loop and closing the afferent loop with a TA-30–3.5 stapler) and insertion of a jejunostomy feeding tube (modified group) or (2) conventional gastric bypass (control group). Outcomes including complications, duration of nasogastric tube placement, and length of hospital stay were followed prospectively.
Results Gastroparesis occurred in 20 patients (16.3%) in the modified group and 27 patients in the control group (21.7%, $P=0.27$). However, the International Study Group of Pancreatic Surgery grades of gastroparesis were significantly lower in the modified group (10A, 5B, 5C) than in the control group (4A, 5B, 18C, $P=0.01$).
Conclusions Modified procedure does not reduce the risk of gastroparesis but appears to reduce the severity when it occurs.

Keywords Pancreaticoduodenectomy · Gastroparesis · Gastric stasis · Delayed gastric emptying · Enteral feeding · Anastomosis Roux-en-Y

Introduction

Gastroparesis is one of the most frequent postoperative complications of pancreaticoduodenectomy (PD) especially when the pylorus is preserved.[1–5] In patients with gastroparesis, the nasogastric tube (NGT) remains in place for a long time and enteral feeding is delayed. When oral food intake is insufficient, patients often require total parenteral nutrition (TPN) support, which not only increases the cost of their hospital stay but also the risk of catheter-related infection.

The pathophysiological mechanisms contributing to development of gastroparesis after PD are unknown.[6,7] Measures designed to avoid this complication have been in vain and the latest reported incidences of gastroparesis after PD remain high (ranging between 19% and 44%) even in centers specializing in pancreatic surgery.[3,8] Since gastroparesis is unavoidable in a certain proportion of patients after PD, measures to minimize its impact are also needed.

Although gastroparesis precludes gastric enteral nutrition, jejunal enteral feeding is feasible.[9–12] To minimize the adverse impacts of gastric stasis after PD, we planned to resume enteral feeding via an intraoperatively placed jejunal feeding tube. However, enteral feeding stimulates secretion of gut hormones and in turn secretion of biliary, pancreatic,

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and gastrointestinal juices. These accumulate in the paretic stomach and make removal of the NGT more difficult. For earlier removal of NGTs in patients with gastroparesis after PD, we planned to divert the pancreatic juice and bile away from the duodenojejunostomy or gastrojejunostomy stoma via a modified Roux-en-Y gastrojejunostomy or duodenojejunostomy reconstruction. A prospective randomized trial was then conducted to evaluate the effects of these modifications in a large group of patients treated with PD. The end points were postoperative morbidity, mortality, days of NGT placement, number of patients requiring TPN, and length of hospital stay after surgery.

Methods and Patients

We did a prospective randomized clinical trial comparing the modified procedure to the conventional procedure at the National Taiwan University Hospital. Inclusion criteria were age greater than 18 years and planned PD for a lesion of either the pancreatic head or the periampullary region. Exclusion criteria were: (1) history of abdominal or pelvic radiation; (2) hepatic dysfunction (Child–Pugh >2); (3) renal dysfunction (serum creatinine concentration >3 mg/L, hemodialysis, or both); (4) cardiac dysfunction (New York Heart Association functional class > III, stroke history); (5) pregnancy; and (6) history of intestinal anastomosis of the large bowel without a diverting stoma. Before initiation of the trial in January 2003, we obtained approval for the study design from the National Taiwan University institutional ethics review board.

Between January 2003 and December 2006, a total of 307 consecutive patients were recruited into this study in anticipation of PD. Thirteen patients were excluded before randomization for the following reasons: creatinine level >3 mg/L (three patients); New York Heart Association class >3 (three patients); previous colectomy and colonic anastomosis (three patients); previous radiotherapy for prostate cancer (two patients); and ascites/portal hypertension (two patients). Forty-seven patients were intraoperatively excluded for metastatic disease or unresectable primary tumor, and their resections were converted to palliative surgery (biliary and/or gastrointestinal bypass). The remaining 247 patients underwent PD. Afterwards, randomization was performed using sealed envelopes and the patients were allocated into a modified procedure group and control group. Patients in the modified group underwent undivided Roux-en-Y reconstruction of the bowel, intraoperative placement of a jejunostomy tube, and early enteral feeding.

The type of surgery (pylorus preserving or standard PD) and the type of management of the pancreatic stump (pancreaticojejunostomy or pancreaticogastrostomy) were left to the surgeons' discretion. After PD, 20–30 cm of the proximal jejunum was brought up through an aperture in the transverse mesocolon for pancreatic and biliary reconstruction and then an antecolic gastrojejunostomy or duodenojejunostomy was created. After this, in all patients assigned to the modified group, a TA-30–3.5 stapler (Ethicon, Cornelia, GA, USA) was used to close the afferent limb just before it enters the stomach or duodenum (Fig. 1). Besides, above and below the staple line, we put two rows of reinforced horizontal mattress 2–0 silk sutures. A section 45 cm from the stomach or duodenum, along the efferent limb, was raised to the afferent limb where it was anastomosed in a side-to-side manner (Fig. 1), creating a side-to-side jejunojejunostomy. Finally, a 12-Fr, T-shaped, jejunal feeding tube was placed approximately 15~20 cm distal to the side-to-side jejunojejunostomy (Fig. 1). The jejunum was fixed to the site of the feeding tube insertion with three single stitches to the left side of the abdominal wall where the tube exits the abdomen.

For patients in the modified group, enteral feeding was routinely started within 24 h after the operation and consisted of 480 mL (20 mL/h continuously) of commercially available enteral nutrition solution, with a kilocalorie-to-milliliter ratio of 1:1 and glucose-to-lipid ratio of 70:30. The rate of delivery was progressively increased by 10 mL/day until the goal of full nutrition (25 kcal/kg) was reached. Enteral nutrition was reduced and subsequently stopped when the patient was able to eat a sufficient amount of food

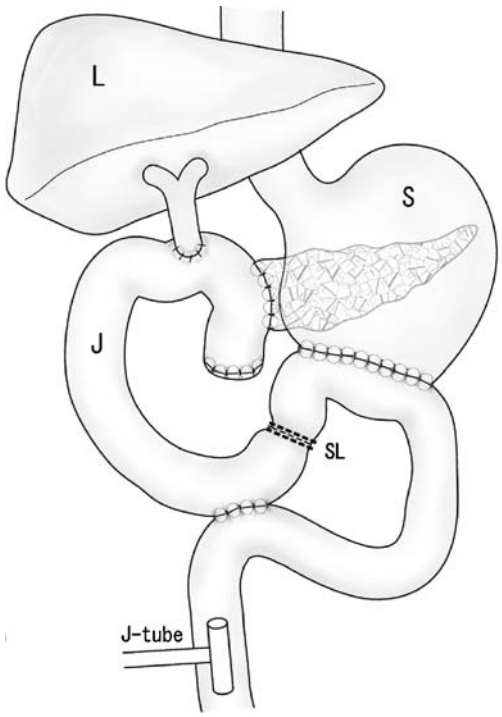

Figure 1 Modified Roux-en-Y gastrojejunostomy reconstruction and intraoperative placement of jejunostomy feeding tube. *S* stomach, *L* liver, *P* pancreas, *J* jejunum, *SL* staple line, *J-tube* jejunostomy feeding tube.

(at least 1,500 kcal/day) without vomiting. In some patients, feeding rates were reduced or stopped as a result of significant abdominal symptoms after advancement to full enteral support via the jejunostomy tube in the first few postoperative days. At that time, many were beginning oral diets and therefore jejunostomy feeding was not increased or even stopped. Patients who could not resume oral intake were encouraged daily to maintain or increase enteral feeding to the level of the nutrition goal. Patients who were judged intolerant of enteral nutrition (unable to reach at least 50% of the nutrition goal in 2 weeks after the operation) were switched to total parenteral nutrition.

For patients in the control group, conventional antecolic gastrojejunostomy or duodenojejunostomy was performed and conventional postoperative care, consisting of crystalloid fluid support, was given until the initiation and maintenance of oral intake. If oral intake had not resumed 7 days after the operation, total parenteral nutrition with nutriflex and aminomix was given via a central venous catheter. TPN was reduced and subsequently stopped when the patient was able to eat a sufficient amount of solid food (25 kcal/kg per day) without vomiting.

For patients in either group, the NGT was removed when the drainage volume was less than 200 mL in the previous 24 h. After removal of the NGT, the patient was allowed to drink 300–500 mL of liquids, and afterwards a soft diet was given for 2 days. If this was well tolerated, increasing amounts of solid food were given. The NGT was reinserted if the patient later vomited a volume of more than 300 mL on more than one occasion. Reinserted tubes were removed if the reflux was less than 200 mL per 24 h, and oral feeding (initially with a liquid diet) was tried again.

Members of the surgical staff, not involved in the trial, recorded postoperative complications. According to the recommendation by the International Study Group of Pancreatic Surgery (ISGPS),[13] gastroparesis was defined as the need for an NGT for >3 days or the need to reinsert the NGT for persistent vomiting after surgery. The severity of gastroparesis was classified by the ISGPS definition[13] as grade A: NGT required for 4–7 days or reinsertion after postoperative day (POD) 3 or inability to tolerate solid oral intake by POD 7; grade B: NGT required for 8–14 days or inability to tolerate solid oral intake by POD 14; grade C: NGT required for >14 days or inability to tolerate solid food by POD 21. Again, according to the International Study Group definition,[14] postoperative pancreatic fistula was defined as output via an operatively placed drain (or a subsequently placed percutaneous drain) of any measurable volume of drain fluid on or after POD 3, with an amylase content greater than three times the upper normal serum value.[14] Postoperative bleeding was also graded using ISGPS definitions.[15] All infectious complications were proven by microbiological analysis and positive fluid culture. If they were not postoperative complications, abdominal distension, abdominal cramps, diarrhea (defined as four or more bowel movements per day), and vomiting were recorded as adverse effects of enteral nutrition and parenteral nutrition. Displacement, clogging, breaking of the feeding tube, and local infections at the entry site of the tube were also regarded as adverse effects of enteral nutrition. Operative mortality was defined as death occurring during hospitalization or due to a postoperative complication.

To compare the control and modified groups, all surgical complications were further classified by severity using a novel grading system proposed by Dindo et al.[16,17] In brief, grade I and II complications include only minor deteriorations from the normal postoperative course that can be treated with drugs, blood transfusion, physiotherapy, and nutritional supply. Grade III complications require interventional treatment. Grade IV complications are life-threatening and require intensive care unit management. Death is the only grade V complication. Grade I and II complications were classified as minor and grades III, IV, and V were classified as major.

Statistical Analysis

The primary end point was length of hospital stay after operation. Secondary end points included rates of gastroparesis, duration of NGT placement, number of patients

Table 1 Baseline Preoperative Patient Characteristics

	Modified group (n=123)	Control group (n=124)	P
Age (years, mean±SD)	59.04± 13.33	59.49± 13.68	0.79
Sex: male/female	74/49	71/53	0.64
Proportion of body weight loss (%, mean±SD)	6.11±5.32	6.51± 5.38	0.56
Weight loss >10%	41 (33%)	43 (35%)	0.82
Serum albumin (g/L, mean±SD)	3.8±0.65	3.73± 0.62	0.35
Jaundice	77/123 (63%)	87/124 (70%)	0.21
Comorbidity			
Diabetes mellitus	25	31	0.38
Coronary artery disease	2	3	0.66
Hypertension	26	25	0.85
Peptic ulcer disease	13	11	0.65
Prior malignancy	8	8	0.78
No. of patients with comorbidities	61 (50%)	57 (46%)	0.57
No. of comorbidities/patient	1.42±0.62	1.59± 0.73	0.18

Table 2 Operative Factors

	Modified group (n=123)	Control group (n=124)	P
Preservation of pylorus	68 (55.3%)	71 (57.3%)	0.75
Additional procedure	15 (12.2%)	12 (9.7%)	0.53
Hemicolectomy	2 (1.6%)	3 (2.4%)	0.66
Vascular resection	11 (8.1%)	7 (5.6%)	0.44
Hepatectomy	2 (1.6%)	2 (1.6%)	0.99
Management of the pancreatic stump (PJ/PG)	70/53	79/45	0.27
Operative time (minutes, mean ±SD)	342±42	308±47	<0.001
Estimated blood loss (mL, ±SD)	326±253	337±208	0.44
Blood transfusions (units, ±SD)	1.5±1.1	1.6±1.1	0.51
Pathology of index operation			0.41
Pancreatic head/periampullary cancer	80 (65%)	90 (73%)	
Benign disease	16 (13%)	14 (11%)	
Chronic pancreatitis	27 (22%)	20 (16%)	

PJ pancreaticojejunostomy, *PG* pancreaticogastrostomy

requiring TPN, and complications. By setting α=0.05, with a power of 80%, a sample size of 112 evaluable patients per group was required to show a difference in length of stay of 3 days, assuming a mean duration of hospitalization of 20 days and a standard deviation of 8 days.

All values are expressed as mean±standard deviation unless otherwise specified. Statistical analysis was done with SPSS 10.0.1 for Windows 98/NT (SPSS Inc., Chicago, IL, USA). Univariate comparison of parameters between groups was made using the nonparametric chi-squared test and the Mann–Whitney U test. Duration of NGT placement, days until solid food intake was tolerated, and postoperative length of hospital stay were compared using log-rank comparisons for time-to-event data by the Kaplan–Meier method.[18] We also performed multiple logistic regression analyses, which included weight loss >10%, jaundice, comorbidity, pylorus preservation, additional procedure, type of pancreatic anastomosis, benign or malignant final pathology, and major complications, to determine the independent effect of modification in the surgical procedure on duration of NGT placement after operation and the need of TPN. A P value of <0.05 was regarded as significant.

Results

The preoperative characteristics of the two groups were comparable (Table 1). The rate of malnutrition (>10% body weight loss) was approximately 30% and the mean plasma level of albumin was close to the minimum of the normal range (3.5–5.5 g/dL). Preoperative jaundice was present in >60% of the patients. There were no significant between-group differences in the number of resections with preservation of the pylorus, management of the pancreatic stump, intraoperative blood loss, amount of intraoperative blood transfusion, or histopathologic diagnosis (Table 2). However, operative time was significantly longer in the modified group (342±42 versus 308±47 min; P<0.001). It took 20 min on average (range, 21–28 min) to perform the side-to-side jejunojejunostomy and apply the TA-30–3.5 staples, and another 13 min (range, 10–16 min) to place a jejunal feeding tube. In total, 31~44 min (mean 35 min) were needed to perform these procedures.

No complication resulted from the construction of the side-to-side jejunojejunostomy or stapling. Rare complications resulted from placement of the jejunostomy feeding tube (five patients, 4.1%, one with tube dislodgement and four with peritubular leakage). No patient required reoperation for any of these minor complications. No aspiration episodes or intestinal ischemia caused by infusion of nutrients in the gut lumen were observed. There were significantly more postoperative gastrointestinal symptoms in the modified group, although they were generally mild (Table 3). Development of significant symptoms prompted tube withdrawal or diminution in the rate of tube feeding in 55 patients whose intake by jejunostomy tube had increased in the first few postoperative days. At the same time, 35 patients were beginning oral intake and therefore their jejunostomy feeding was not increased. But in the presence of gastric stasis, patients were encouraged daily to accept the same or higher rates of jejunostomy feeding. Of the 20 patients with gastric stasis in the modified group, though

Table 3 Patients with Gastrointestinal Symptoms During Postoperative Course

	Modified group (n=123)	Control group (n=124)	P
Abdominal distension	40 (32.5%)	26 (21%)	0.04
Abdominal cramps	38 (30.1%)	24 (19.4%)	0.03
Diarrhea	15 (12.2%)	11 (8.9%)	0.36
Vomiting	7 (5.7%)	8 (6.5%)	0.80
Any adverse effect	67 (54.5%)	41 (33.1%)	<0.001

Table 4 Complications in Detail

	Modified group (n=123)	Control group (n=124)	P value
Infectious	26 (21.1%)	29 (23.6%)	0.67
Respiratory tract	2 (1.6%)	2 (1.6%)	0.99
Wound	6 (4.9%)	11 (8.9%)	0.22
Urinary tract	0	1 (0.8%)	0.32
Bacteremia	4 (6.5%)	1 (0.8%)	0.18
Pancreatic leakage	12 (9.8%)	12 (9.8%)	0.14
Biloma	1 (0.8%)	1 (0.8%)	0.99
Intra-abdominal abscess	1 (0.8%)	0	0.32
Catheter-related	0	1 (0.8%)	0.32
Non-infectious	35 (28.5%)	44 (32.3%)	0.24
Gastroparesis	20 (16.3%)	27 (21.7%)	0.27
Pancreatic fistula	6 (4.9%)	7 (5.6%)	0.79
Biliary fistula	4 (3.3%)	2 (1.6%)	0.4
Cardiopulmonary	0	3 (2.4%)	0.08
Renal dysfunction	1 (0.8%)	1 (0.8%)	0.99
Chylous ascites	3 (2.4%)	3 (2.4%)	0.99
Bleeding	6 (4.9%)	3 (2.4%)	0.3
Others	3[a] (0.8%)	1[b] (0.8%)	0.31
Total	53 (43.1%)	63 (50.8%)	0.22

[a] One afferent loop syndrome, one postprandial cramping, and one diarrhea

[b] Intussusception

infusion rates were lowered temporarily because of significant symptoms, 18 (90%) were able to increase jejunostomy feeding to the target level in 2 weeks. Only two patients needed to use a central venous catheter and TPN.

Of 123 patients in the modified group, two died: one from repeated bleeding from a pseudoaneurysm of the gastroduodenal artery stump and one from sepsis-related acute respiratory distress syndrome. In the control group, two patients also died: one from respiratory failure and one from renal failure and subsequent multiple-organ failure. Overall mortality was 1.6% and did not differ between the groups. Table 4 shows the postoperative outcomes in detail and Table 5 assesses the surgical complications by severity. No significant differences were found for major complications, infectious minor complications, noninfectious minor complications, total complications, or severity of complications. Delayed gastric emptying (DGE) occurred in 20 patients (16.3%) in the modified group and 27 patients (21.7%) in the control group. Although statistical analysis revealed no differences (P=0.27) in the frequency of delayed gastric emptying between groups, ISGPS grades of gastric stasis were significantly lower in the modified group (10A, 5B, 5C by the ISGPS definition) than in the control group (4A, 5B, 18C by the ISGPS definition, P= 0.01, Table 6). Of the 47 patients with delayed gastric emptying, 20 were in the modified group and 27 in the control group. The nasogastric tube was removed permanently within ten postsurgical days in 18 of 20 patients in the modified group but in only six of 27 patients in the control group (P=0.009). The jejunostomy feeding in-

Table 5 Classification of Surgical Complications by Severity

	Modified group (n=123)	Control group (n=124)	P
I	19 (15.4%)	21 (17%)	0.75
II	22 (17.9%)	30 (24.2%)	0.22
IIIa	3 (2.4%)	4 (3.2%)	0.64
Percutaneous drainage of abdominal abscess or pleural effusion	2 (1.6%)	3 (2.4%)	0.67
Transcatheter embolization for massive bleeding	1 (0.8%)	1 (0.8%)	0.56
IIIb	4 (3.3%)	4 (3.2%)	0.40
Reoperation for intussusception	0	1 (0.8%)	0.32
Reoperation for bleeding	3 (2.4%)	2 (1.6%)	0.64
Reoperation for afferent loop syndrome	1 (0.8%)	0	0.32
Reoperation for bile leak	0	1 (0.8%)	0.32
IVa	3 (2.4%)	2 (1.6%)	0.64
Respiratory failure	2 (1.6%)	0	0.15
Circulatory insufficiency	1 (0.8%)	2 (1.6%)	0.57
IVb	0	0	0.99
V	2 (1.6%)	2 (1.6%)	0.99
Major (IIIa, IIIb, IVa, IVb, V)	12 (9.8%)	12 (9.7%)	0.98
Minor (I, II)	41 (33.3%)	50 (40.3%)	0.25
Total	53 (43.1%)	63 (50.8%)	0.22

Table 6 Comparison of Postoperative Course Between Gastroparetic Patients in the Modified and Control Groups

Patients with gastroparesis (number, incidence)	Modified group (n=20, 16.3%)	Control group (n=27, 21.7%)	P value
Grade of gastroparesis by ISGPS definition	10A, 5B, 5C	4A, 5B, 18C	0.01
Mean days of NGT required (median, range)	8.6±7.2 (6, 3~35)	20±8.8 (19, 5~37)	<0.001
NGT removed within 10 days after operation	18 (90%)	6 (22.2%)	0.009
Mean days until regular diet tolerated orally (median, range)	16.7±7.7 (14, 7~37)	24.7±9.3 (23, 7~42)	0.002
Number of patients requiring total parenteral nutrition	2	27	<0.001
Mean days of hospital stay after operation (median, range)	29.3±7.8 (30, 18~50)	38.5±16.4 (34, 21~90)	0.001

ISGPS International Study Group of Pancreatic Surgery, *NGT* nasogastric tube

creased to the target level (25 kcal/kg BW per day) in 18 patients of the modified group. All 27 in the control group but only two in the modified group needed TPN (P<0.001, Table 6). Patients with gastroparesis in the control group had significantly longer hospital stays (control group 38.5 days; modified group 29.3 days; P=0.001, Table 6).

An NGT was needed for a significantly longer period in the group that underwent conventional Whipple resection (i.e., the control group, 7.5 days; modified group, 4.3 days; P<0.001, Table 7), especially in patients with delayed gastric emptying (control group, 20 days; modified group, 8.6 days; P<0.001, Table 6). Among all survivors, the mean length of postoperative hospital stay was also significantly longer in the control group (22.6±14.1 days median, 16 versus 18.7±9.7 days median, 15 days in the modified group, P=0.01, Table 7). Six months after operation, comparisons in gastrointestinal symptoms such as heartburn, diarrhea, constipation, and dumping syndromes revealed no significant differences between groups (Table 8). Besides, no significant difference was observed in rate of weight reduction at 6 months postoperatively between groups (Table 8).

Multiple logistic regression analyses showed modification in surgical procedure significantly related to less demand of TPN (P<0.001, odds ratio 0.083, 95% confidence interval *0.024~0.286*) and NGT placement more than 10 days (P=0.001, odds ratio 0.229, 95% confidence interval: *0.094~0.558*, Table 9) independent of preoperative presence of body weight loss >10%, preoperative presence of jaundice, preoperative presence of comorbidity, type of pancreatic anastomosis, pylorus preservation, additional procedure, postoperative presence of major complication, or malignant final pathology.

Discussion

In a retrospective review, the gastroparesis rate was 57% in patients selected and 16% in patients not selected to receive early enteral nutrition through an intraoperatively placed jejunostomy tube.[6] In contrast, other studies reported no increase or even decrease in the incidence of gastroparesis after PD with early enteral feeding through an intraoperatively placed jejunostomy tube.[19,20] The gastroparesis rate in our modified (16.3%) and control (21.7%) groups was similar (P=0.27). Therefore, early enteral feeding via an intraoperatively placed jejunostomy feeding tube and diversion of bile and/or pancreatic juice did not increase the occurrence of gastroparesis in our patients. Gastroparesis is reported to occur in 7–36% of patients after PD in recent series.[1–6] The gastroparesis rate of 21.7% in our control group was consistent with these observed rates. Of the 47 patients with delayed gastric emptying, NGT could be removed without reinsertion within 10 days after operation in 18 of 20 patients in the modified group but in only six of 27 patients in the control group (P=0.009). Of the 20 patients with gastric stasis in the modified group, though infusion rates were lowered temporarily because of significant symptoms in ten patients, 18 (90%) were able to increase jejunostomy feeding to the target level (25 kcal/kg BW per day) and only two patients needed a central venous catheter for TPN. In contrast, all 27 patients with gastric stasis in the control group needed a nasogastric tube, central venous catheter, and TPN. Multivariable logistic regression analyses also showed that our modified procedure successfully minimized the impact of gastroparesis after PD, by

Table 7 Comparison of Postoperative Course Between all Survivors in the Modified and Control Groups

All survived patients	Modified group (n=121)	Control group (n=122)	P value
Mean days of NGT required (median, range)	4.3±4 (3, 2~35)	7.5±7.9 (5, 2~37)	<0.001
Mean days until regular diet tolerated orally (median, range)	7.6±7 (5, 4~52)	10.3±9.8 (6, 4~44)	0.013
Mean days of hospital stay after operation (median, range)	18.7±9.7 (15, 8~65)	22.6±14.1 (16, 8~90)	0.01

NGT nasogastric tube

Table 8 Comparison of Prevalence of Gastrointestinal Symptoms Between Patients in Modified and Control Group 6 Months after Operation

	Modified group (N=121)	Control group (N=122)	P value
Clinical symptoms, *n* (%)			
Heartburn	5 (4)	12 (10)	0.08
Diarrhea	18 (15)	16 (13)	0.69
Constipation	21 (17)	22 (18)	0.86
Dumping syndrome	2 (0.2)	3 (0.25)	0.66
Nutritional status			
Body weight[a] (% of preoperative body weight)	89.2±12.3	90.6±13.8	0.59
Serum albumin[a] (mg/dl)	3.9±0.6	4.1±0.8	0.74

[a] Values are mean±SD

reducing the need for parenteral nutrition support and time to removal of the NGT (Table 8). Furthermore, patients with gastroparesis in the control group stayed significantly longer in the hospital (control group 38.5 days; modified group 29.3 days; P=0.001).

Postulated pathophysiological mechanisms involved in and contributing to DGE after PD included the presence of pancreatic fibrosis,[21] intraperitoneal inflammation secondary to postoperative complications[1,3,22–24] gastrointestinal reconstruction[25,26] removal of the duodenum,[27–30] or extensive lymph node dissection.[30–32] However, most of these factors were identified in retrospective studies of surgically treated patients. To our knowledge, the risk of DGE after PD has not yet been accurately predicted. Therefore, in our study, our modified procedure could not be targeted to patients destined to develop DGE after PD. Instead, patients were randomly assigned to groups receiving either modified or conventional surgery. Biliopancreatic diversion with Roux-en-Y gastric bypass and early enteral feeding via an intraoperatively placed jejunostomy tube were routinely performed for patients in the modified group. Theoretically, these additional procedures might be unnecessary or even harmful for patients who fail to develop gastroparesis after PD. However, our study showed that, even though these additional procedures extended operative time by 35 min, they could be safely performed without causing major complications. Although up to 54% of patients complained of abdominal symptoms related to postoperative early enteral feeding, both groups had similar rates of leakage from the pancreatic, biliary, or gastrointestinal anastomosis and similar morbidity and mortality rates. Therefore, modified Roux-en-Y gastrojejunostomy reconstruction and early enteral feeding via a jejunostomy tube inserted at a site distal to all anastomoses can be safely tried without jeopardizing anastomotic healing or increasing the frequency of postoperative complications. In addition, among all survivors, NGT removal was significantly earlier and postoperative hospital stay was significantly shorter in the modified group. Therefore, our data showed that modified Roux-en-Y gastrojejunostomy reconstruction and early enteral feeding via an intraoperatively placed jejunostomy feeding tube, at cost of more frequent abdominal symptoms, significantly shortened duration of NGT placement and postoperative hospital stay not only in patients with gastric stasis but also in all surviving patients. Long-term follow-up also revealed no significant differences in prevalence of gastrointestinal symptoms and nutritional status between patients in modified and control group.

Recently, it was suggested that early postoperative enteral nutrition improved postoperative outcome. Reduc-

Table 9 Association of Various Risk Factors and Rate of NGT Placement More than 10 Days After Operation or Patients Requiring Total Parental Nutrition in Patients after Pancreaticoduodenectomy as Determined in Logistic Regression Model with Multiple Covariates

Risk factors	NGT placement more than 10days after operation			Patients requiring total parenteral nutrition		
	P value	Odds ratio	95% CI	P value	Odds ratio	95% CI
Modified (yes or no)	0.001	0.229	0.094~0.558	<0.001	0.083	0.024~0.286
Weight loss >10% (yes or no)	0.787	0.885	0.366~2.143	0.821	0.896	0.346~2.320
Jaundice (yes or no)	0.265	1.637	0.688~3.896	0.156	1.935	0.777~4.818
Comorbidity (yes or no)	0.625	1.221	0.548~2.723	0.185	1.803	0.754~4.313
Pylorus preservation (yes or no)	0.694	1.188	0.504~2.799	0.518	1.361	0.535~3.462
Type of pancreatic anastomosis (PJ or PG)	0.748	0.879	0.400~1.933	0.862	1.078	0.462~2.513
Additional procedure (yes or no)	0.545	1.639	0.331~8.122	0.255	3.586	0.398~32.298
Pathology (benign or malignant)	0.241	0.561	0.213~1.474	0.465	0.689	0.253~1.873
Major complication (yes or no)	0.240	0.471	0.134~1.654	0.868	1.148	0.226~5.825d

tion in septic morbidity and reduction in infectious complications were the most frequent benefits in the majority of these studies, and the greatest benefit was seen in the most severely injured patients.[20,33,34] PD is one of the most destructive abdominal operations. Therefore, theoretically, patients should benefit greatly from early enteral feeding after PD. Indeed, some studies have shown improvements in outcomes, including reduced overall and septic complications and diminished length of stay,[19,35] while others have failed to show a benefit.[6,36] In the current study, no significant reduction in septic morbidity and infectious complications was shown in the modified group. There are two potential reasons for the differences in outcome between ours and other randomized studies. Patients in the current study might not be malnourished enough to show benefits of postoperative early enteral feeding, although they had a mean weight loss of 6% (Table 1). Feeding tube tolerance was marginal with at least 40% of patients having cramping, distension, and nausea that often necessitated decreasing or even stopping tube feeding (especially in patients without gastric stasis who resumed oral intake), as has been reported in other studies. The amount and duration of tube feeding might not be sufficient to show any benefit.

In conclusion, we prospectively studied the effects of biliopancreatic diversion with modified Roux-en-Y gastrojejunostomy reconstruction and early enteral nutrition via an intraoperatively placed jejunal feeding tube on postoperative course. Our data showed that these additional procedures could be safely performed. Modified procedure does not reduce the risk of delayed gastric emptying but appears to reduce the severity when it occurs.

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ORIGINAL ARTICLE

Implementation of a Critical Pathway for Distal Pancreatectomy at an Academic Institution

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Abstract
Objective This study was designed to identify quantifiable parameters to track performance improvements brought about by the implementation of a critical pathway for complex alimentary tract surgery.
Background Distal pancreatectomy is among the more complex general surgical procedures. This is primarily due to the possibility of blood loss from visceral vessels, splenic injury, and significant postoperative complications. The introduction of the laparoscopic approach to the distal pancreas has introduced a further level of surgical expertise required to fully address the clinical needs of this diverse patient population. Critical pathways have been one of the key tools used to achieve consistently excellent outcomes at high-quality, high-volume institutions. It remains to be determined if implementation of a critical pathway at an academic institution with prior moderate experience with distal pancreatectomy will result in performance gains and improved outcomes.
Methods Between January 1, 2003 and August 15, 2007, 111 patients underwent distal pancreatectomy. Forty patients underwent resection during the 34-month period before the implementation of a critical pathway on October 15, 2005 and 71 during the 20 months after pathway implementation. Patients undergoing both open and laparoscopic procedures were included. Peri- and postoperative parameters were analyzed retrospectively to identify those that could be used to track performance improvement and outcomes.
Results The two groups were not significantly different with respect to age, sex, race, diagnosis, operative blood loss, or mean operative duration. Postoperative length of hospital stay was significantly shorter when comparing pre- to postpathway implementation (10.2 days versus 6.7 days, $P \leq 0.037$). The rate of readmission to the hospital after discharge was significantly lower post pathway (25% versus 7%, $P \leq 0.027$). Hospital costs were also reduced.
Conclusion Implementation of a critical pathway for a complex procedure can be demonstrated to improve short-term outcomes at an academic institution. This improvement can be quantified and tracked and has implications for better utilization of resources and overall cost containment while maintaining or improving upon an already high level of care.

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Keywords Critical pathway · Distal pancreatectomy · Length of stay · Hospital charges

Introduction

Quality, performance improvement, and the means by which such can be achieved have become powerful forces in modern healthcare. Providers and institutions look for

validated tools to utilize when trying to achieve the competing and sometimes conflicting goals of high-quality care, efficient management of resources, and cost containment. As Porter and Teisberg have stated, they foresee "a health care system that harnesses the power of competition on results to drive stunning improvements in value for patients".[1] Critical pathways (or fast-track protocols) are one valuable tool that have been shown to help achieve the goal of cost-effective, high-quality health care delivery in a variety of surgical procedures.[2,3–12] Critical pathways are best described as structured multidisciplinary care plans that detail the essential steps in the care of patients with a specific clinical problem.[13] They provide a timeline of the ideal sequence of treatment-related events with daily goals to assist care providers in administering care with optimal efficiency. Multiple reports have credited these pathways with improving efficiency, reducing length of hospital stay, and helping to control costs.[2,3,6,7,11]

Distal pancreatectomy (DP; with or without en bloc splenectomy) is among one of the more complex general surgical procedures. This is primarily due to the possibility of blood loss from visceral vessels (splenic artery and splenic vein), splenic injury, and significant postoperative complications, particularly postoperative pancreatic fistula. Much effort has been put into studying this procedure in an effort to improve outcomes.[14] The introduction of the laparoscopic approach to the distal pancreas has introduced a further level of surgical expertise required to fully address the clinical needs of this diverse patient population.[15] This study was designed to evaluate the impact of the introduction of a critical pathway for DP, coincidental with the recruitment of a team focused on pancreatic surgery. It was done in anticipation of a significant increase in case volume at an academic institution with moderate previous experience with DP. The aim of the study was to determine if implementation of a critical pathway would allow for a rapid increase in case volume with fixed institutional resources while still achieving gains in performance and improved outcomes.

Methods

Patients

The records of 111 consecutive patients undergoing DP at Thomas Jefferson University Hospital from January 1, 2003 through August 15, 2007 were reviewed. A critical pathway for pancreaticoduodenectomy was implemented on October 15, 2005 at the time of the arrival of a new Chair of Surgery (C.J.Y.) and after the recruitment of a team focused on pancreatic surgery (E.P.K. and P.K.S.). Additional critical pathways for pancreaticoduodenectomy[2] and palliative double bypass (gastrojejunostomy and hepaticojejunostomy) were similarly implemented, but are not part of this report. Forty patients treated prior to the implementation of the pathway were compared to 71 patients treated after pathway implementation. Patients undergoing spleen sparing distal pancreatectomy, distal pancreatectomy with en bloc splenectomy, and patients undergoing distal pancreatectomy with en bloc splenectomy and partial or complete resection of additional attached abdominal organs (stomach, colon, kidney, adrenal gland, etc) or vascular structures (celiac axis) were all included, as they were treated according to pathway standards. Additionally, patients undergoing laparoscopic distal pancreatectomy with or without en bloc splenectomy were also included. Patients with both malignant and benign disease were included in this analysis. All patients undergoing distal pancreatectomy after pathway implementation by any surgeon at the Thomas Jefferson University Hospital were treated according to pathway standards and are therefore included in this analysis. Pathway implementation included patient education as well as numerous formal educational sessions with anesthesia, nursing, nutrition, and surgical house staff. Furthermore, pathway implementation included computerized standard order sets as part of the Thomas Jefferson University Hospital computerized provider order entry (CPOE) system.

Components of the Critical Pathway

The pathway utilized was previously developed and utilized at a high-volume institution (Johns Hopkins Medical Institution) by two of the participating surgeons (C.J.Y. and E.P.K.) and by an experienced clinical nurse practitioner (P.K.S.). The pathway was modified somewhat, prior to implementation at Thomas Jefferson University Hospital. The pathway outlines the daily progress made by a patient without postoperative complications after DP. (Table 1) Expectations with respect to all aspects of care are outlined for each postoperative day. Templates were generated for standardized order sets in the hospital CPOE system.

Pathway execution begins at the preoperative office visit, with education of patients and families about pathway goals and expectations, including the targeting of discharge for postoperative day 5. Patients do not receive a bowel prep and are admitted as same day surgery patients. Consents for operation and research studies are obtained in advance of the day of surgery. Standardized orders for perioperative prophylactic antibiotics and deep venous thrombosis prophylaxis (subcutaneous heparin and thrombo-embolic deterrent (TED) stockings) are utilized in the preoperative holding area. In the operating room, patients are routinely monitored, occasionally with a radial arterial catheter and a central venous catheter, if indicated. Sequential compression devices (SCDs) are utilized. Epidural analgesia is not utilized. A nasogastric tube

Table 1 Critical Pathway for Distal Pancreatectomy

Day of surgery
Preoperative heparin 5,000 units subcutaneously
TED stockings and sequential compression devices
Perioperative antibiotics (stopped at end of case)
Central venous access and arterial line per anesthesia and surgeon assessment
Nasogastric tube placed after induction of anesthesia
1 or 2 JP drains (2 with splenectomy)
Night of surgery spent in ICU setting
Intravenous PCA for analgesia
Intravenous PPI
Beta-blockade commenced orally preop and continued intravenously intra- and postop
Postoperative day 1
Remove nasogastric tube
Start sips of water and ice chips ≤30 ml/h
Out of bed ambulating and hourly incentive spirometry
Discontinue sequential compression devices, continue TED stockings and heparin subcutaneously
Continue intravenous beta-blockade, PCA, and PPI
Transfer to floor
Postoperative day 2
Clear liquid diet
Remove Foley catheter
Minimize all IV fluids
Begin diuresis (if clinically indicated) and continue until discharge or patient reaches preoperative weight
Continue TED stockings, subcutaneous heparin, beta-blockade, and PPI until hospital discharge
Postoperative day 3
Regular diet
Remove first drain if appropriate
Postoperative day 4
Switch all medications to oral route including analgesics
Discontinue all IV fluids
Remove remaining JP drain (if appropriate)
Distribute preprinted discharge instructions
Medical oncology and radiation oncology consults (if appropriate)
Postoperative day 5
Discharge home
Arrange follow-up appointment for 4 weeks after discharge
Discharge medications: PPI, analgesics, resume any essential preoperative medications

is placed after induction of anesthesia. Open resections are performed through a vertical midline incision. One (for spleen sparing and laparoscopic procedures) or two (for more extensive procedures) closed suction drains are placed during surgery. In most cases, the splenic artery is controlled prior to mobilization of the spleen and pancreas.

Patients are extubated in the operating room when no contraindication exists and spend the night of surgery in an intensive care setting. Electrolyte abnormalities and fluid status are aggressively monitored and corrected. Close monitoring in the ICU the night of surgery controls for any variability in the resuscitation performed during the operation and provides a consistent baseline for progression through pathway targets. Postoperative analgesia is provided with intravenous narcotics via a patient controlled anesthesia (PCA) device. This approach provides excellent pain control in this patient population, without having to account for the known side effects of epidural anesthesia (including urinary retention, postural hypotension, and leg weakness). All patients also receive an intravenous proton pump inhibitor (PPI) and an intravenous beta-blocker, in addition to subcutaneous heparin. Prophylactic antibiotics are only administered prior to incision and then redosed as indicated during the operation. Antibiotic administration is not continued beyond the end of the operation.

Patients are mobilized in the early morning of the first postoperative day. The nasogastric tube is removed that morning, and patients are started on sips of water and ice chips (≤30 ml/h). SCDs are discontinued, while TED stockings, subcutaneous heparin, beta-blockade, and PPI are continued until hospital discharge. Patients are transferred to the floor, ambulated with the assistance of staff, and encouraged to use an incentive spirometer hourly.

On postoperative day 2, patients are advanced to an unlimited clear liquid diet. The urinary catheter is removed, [16–18] and patients are assisted in increasing their frequency and duration of ambulation. Intravenous fluids are minimized, and most patients receive low-dose diuretics to aid in the mobilization of the perioperative intravenous fluid, which was administered intraoperatively and immediately postoperatively.

For most patients, a regular diet begins on postoperative day 3. If two drains are present, the first is removed if appropriate. Removal is typically a clinical decision based primarily on clinical assessment of the nature of drain output. Drain fluid is only sent for laboratory analysis when it appears sinister.

Medications, including analgesics, beta-blockade, and a PPI, are continued as intravenous formulations until postoperative day 4 to assure that a diet is tolerated. Any low-volume intravenous fluids used as carrier for analgesics or other medications are discontinued on postoperative day 4, and the second surgical drain is removed if appropriate. Medical oncology and radiation oncology are consulted if indicated. Arrangements for discharge are made. Preprinted discharge instructions are distributed to allow time for patients and their families to review and formulate questions prior to discharge.

On postoperative day 5, patients continue to increase activity levels and are discharged home if appropriate. A follow-up appointment is scheduled for 4 weeks after discharge. Typical discharge medications include any essential preoperative medications plus a PPI and analgesics (typically an oxycodone containing oral preparation).

Patient Outcomes

Data collected for analysis included demographics, pathologic diagnosis, operative blood loss and blood transfusions, length of operation, perioperative complication rates, perioperative mortality, length of postoperative hospital stay, hospital costs, and readmission rate. Data were obtained from retrospective chart review for patients treated prior to implementation of the critical pathway and from a prospective clinical data base for patients treated after implementation. Common postoperative complications analyzed included postoperative pancreatic fistula (defined as drain output of amylase rich fluid (more than three times serum value) for greater than 3 days postoperatively[19]) and wound infection (defined by standard clinical criteria and requiring wound intervention). Perioperative mortality was defined as death within 30 days of surgery or during the index admission. Readmission rate was calculated based upon readmission to Thomas Jefferson University Hospital within 30 days of discharge. Length of operation was obtained from a query of the Thomas Jefferson University Hospital operating room information management system. Financial data were provided by JeffCARE, Inc., the Jefferson Health System's Physician Hospital Organization.

Statistical Analyses

Data analyses to determine level of significance of differences in characteristics and outcomes between the two groups of patients were performed using a two-sample *t* test or Fisher's exact test, where appropriate. Data are expressed as mean ± standard error where applicable or as a percentage where noted. Statistical significance was considered to have been achieved at the $P \leq 0.05$ level.

Results

Demographics and Intraoperative Parameters

The volume of cases performed per month increased from an average of 1.2 cases per month prepathway to 3.2 cases per month postpathway. The pre- and postpathway groups were similar with respect to the analyzed demographic data. Mean age (53.6 years prepathway versus 63.4 years postpathway) was not significantly different between the groups, although the postpathway group was nearly a decade older. Similarly, distribution by sex (48% female prepathway versus 55% female postpathway) was also comparable between the groups. The pathology in the resection specimen was also similar, with 44% of the prepathway patients undergoing resection for malignant disease, compared to 56% of the postpathway patients. Five percent of prepathway patients underwent a spleen preserving procedure (as opposed to a splenectomy), comparable to a rate of 14% in the postpathway group. There were no laparoscopic patients in the prepathway group, while 14% of the postpathway group had a laparoscopic DP. This represented a statistically significant difference between the groups, but this difference was not responsible for any of the differences in outcomes between the groups, as will be explained below (Table 2).

Outcomes

Several peri- and postoperative parameters were analyzed. There were no differences in operative length (275 min prepathway versus 316 min postpathway) and estimated blood loss (623 ml prepathway versus 523 ml postpathway). The rate of postoperative complications was similar between the groups (38% versus 16%) with the most common complications being pancreatic fistula and wound infection. Perioperative mortality was also not different. Implementation of the pathway did, however, result in significantly shorter length of postoperative hospital stay (10.2 days prepathway versus 6.7 days postpathway, $P \leq 0.037$). This reduction did not come at the expense of an increased readmission rate, which was significantly reduced after pathway implementation (25% prepathway versus 7% postpathway, $P \leq 0.027$). One patient in the postpathway cohort was readmitted with a postoperative peripancreatic fluid collection requiring drainage. The others were readmitted due to wound complications or medical conditions. Total hospital costs were also reduced ($26,393 prepathway versus $22,806 postpathway); however, this difference did not reach statistical significance (Table 3).

If the data are reanalyzed after excluding the patients who underwent laparoscopic distal pancreatectomy after pathway implementation, there is no significant change in

Table 2 Demographics and Intraoperative Parameters

	Prepathway $N=40$	Postpathway $N=71$	*P* value
Surgical volume per month	1.2	3.2	0.001
Demographics			
Age (years)			
Mean	53.6	63.4	NS
Sex			
Female (%)	48	55	NS
Pathology			
Malignant (%)	44	56	NS
Procedure			
Spleen sparing (%)	5	14	NS
Other organ resection (%)	12	11	NS
Laparoscopic (%)	0	14	0.013

Table 3 Perioperative Parameters

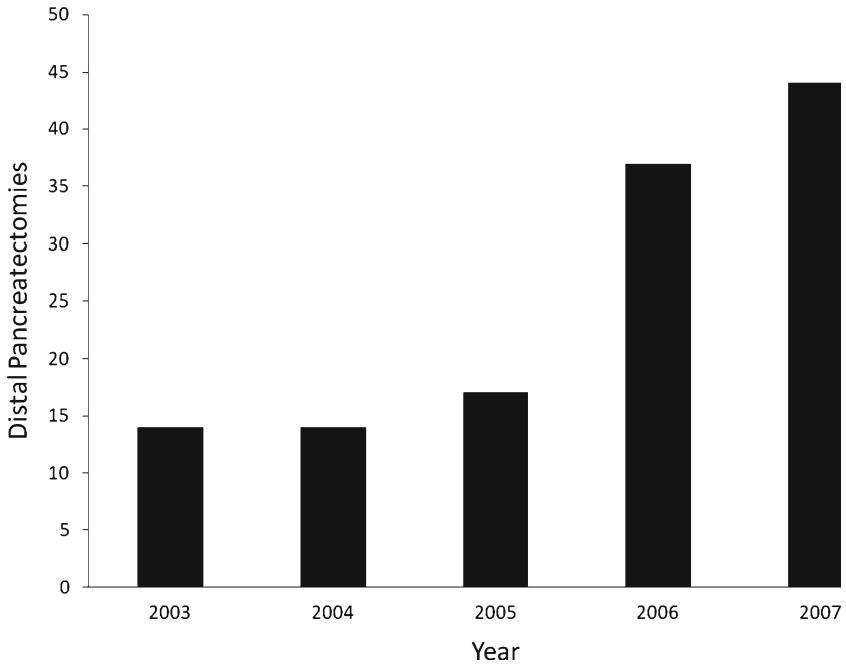
	Prepathway N=40	Postpathway N=71	P value
Operative time (min) ± SE	275±14	316±13	NS
Operative blood loss (ml) ± SE	623±186	523±73	NS
Overall rate of postoperative complications (%)	37.5	15.7	NS
Pancreatic fistula (%)	17.5	6.1	NS
Wound infection (%)	10	8.5	NS
Perioperative mortality (%)	2.3	1.1	NS
Mean length of postoperative hospital stay (days)	10.2	6.7	0.037
Total hospital charges ± SE	$26,393±4719	$22,806±1300	NS
Readmission within 30 days (%)	25	7	0.027

outcomes in the post pathway group. With laparoscopic cases excluded, operative length remains similar (275 min prepathway versus 319 min postpathway) as does estimated blood loss (623 ml prepathway versus 532 ml postpathway). Length of postoperative hospital stay remains significantly shorter after pathway implementation (10.2 days prepathway versus 6.9 days postpathway, $P \leq 0.049$). Postoperative complications, readmission rate, and hospital costs differences were all similarly unaffected.

Discussion

The provision of surgical care of the highest quality, in an efficient and cost-effective manner, is one of the primary goals at our institution as it is at many others. Additionally, providing this care in a clearly organized manner based upon best practice standards and the best available data helps provide the next generation of surgeons the skills and understanding necessary to continue to advance the field. We are strong proponents of critical pathways as powerful tools for implementing change. As evidenced here and in our previous publication,[2] they can be introduced in a very short period of time during a period of rapid rise in case volume (Table 4), and they can be associated with substantial reductions in length of postoperative hospital stay and hospital costs while maintaining or improving quality. As we observed in our pathway implementation for pancreaticoduodenectomy, they do not require substantial resources to develop, implement, and maintain as some critics claim,[20] nor do they necessarily depend on local processes and organizational structure requiring the devel-

Table 4 Distal Pancreatectomy Case Volume by Year



opment of unique pathways for each institution.[21] In fact, they can be put in place fully formed with minimal additional resources and few, if any, modifications due to local considerations. They clearly accomplish their intended purpose, enabling the provision of high-quality, efficient, cost-effective health care.

As to this particular study, several observations can be made to address several potential criticisms. First, the reductions in length of stay attributed to the implementation of this DP pathway are not simply due to an underlying, preexisting, trend toward shorter lengths of stay brought about by economic pressures. In fact, when the data for length of stay in the prepathway period are analyzed, the implementation of this pathway reversed a trend toward longer lengths of stay between January 2003 and October 2005. The implementation of the pathway consistently reduced length of stay to durations rarely seen prior to its implementation. Secondly, the introduction of laparoscopic distal pancreatectomy during the postpathway period is not responsible for the improvements attributed here to utilization of the critical pathway. The laparoscopic approach has been shown to result in a trend toward shorter lengths of stay. In this study, however, that effect is not enough to impact the conclusions. When the results are recalculated without including the ten patients who underwent laparoscopic distal pancreatectomy, the mean postpathway length of stay increases by only 0.2 days and remains significantly shorter than the prepathway period. Therefore, these laparoscopic patients are appropriately included in this study because their postoperative care is provided in accordance with the critical pathway guidelines. Lastly, the improvements attributed to implementation of this critical pathway are not simply due to the recruitment of a team focused on pancreatic surgery. All surgeons performing distal pancreatectomy at Thomas Jefferson participated in the implementation of this critical pathway. All experienced reductions in length of stay, while other quality measures such as complication rates stayed at acceptable levels.

Critical pathways are powerful tools for quality improvement and cost containment. They organize and structure care for the benefit of patients, families, nurses, and house officers. They encourage team building while educating and empowering all members of the health care delivery system. Additionally, they are excellent educational tools for residents, providing a structured map of postoperative care they can internalize and apply in the future. Their benefits clearly outweigh the minimal costs of implementation, and they are a key part of the modern management of complex surgical patients.

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ORIGINAL ARTICLE

Laparoscopic Surgery for Pancreatic Insulinomas: A Single-Institution Experience of 29 Cases

Ying Luo · Rong Liu · Ming-Gen Hu · Yi-Ming Mu · Li-Chun An · Zhi-Qiang Huang

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Abstract
Background Laparoscopic approach has been increasingly used in the treatment of pancreatic benign diseases. This report evaluates our experience with laparoscopic surgery for pancreatic insulinomas.
Methods Between July 2000 and December 2007, laparoscopic pancreatectomy was attempted in 29 consecutive patients with insulinomas. The localization of tumors, operating characteristics, and clinical outcomes were analyzed.
Results Tumors were precisely localized in 28 of 29 (96.6%) patients by a combination of preoperative imaging techniques and intraoperative ultrasonography. Laparoscopic pancreatectomy was successfully performed in 26 patients, including enucleation (n=14), hand-assisted enucleation (n=2), and distal pancreatectomy with (n=9) or without (n=1) spleen preservation. Two conversions to open procedure were required because of unfavorable locations of the tumors. The pancreatic fistula occurred in four patients who underwent tumor enucleation. The median hospital stay was 5.5 days (range, 3–18 days) after laparoscopic procedure. Twenty-eight patients with pancreatic resection were free of symptoms and remained normoglycemic after a median follow-up period of 19 months (range, 10–36 months).
Conclusion Laparoscopic pancreatic resection is a feasible and safe procedure for patients with insulinomas. Further studies are required to evaluate the potential application of the hand-assisted approach for tumors located at anatomically unfavorable positions.

Keywords Laparoscopic surgery · Pancreatic insulinoma · Enucleation · Distal pancreatectomy · Outcome

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Introduction

Insulinoma is the most common functioning endocrine tumor of the pancreas with an incidence of 4 per million every year.[1–3] Approximately 90% of insulinomas are benign and solitary and are located predominantly in the body and the tail of the pancreas. Surgical excision is the only effective treatment, with clinical cure being achieved in more than 90% of patients.[3] With the advances in techniques and equipment, laparoscopic approach has been increasingly used in the treatment of pancreatic diseases over the past years. A few retrospective studies and case reports have shown that laparoscopic pancreatectomy is technically feasible and safe, with morbidity comparable to that of open approach.[4–13] Herein, we report a study of laparoscopic surgery in 29 consecutive patients with pancreatic insulinomas, with the aim of critically evaluating our experience and results in the tumor localization and the operating procedure.

Material and Methods

Patients From July 2000 to December 2007, 29 consecutive patients with pancreatic insulinomas were referred to our institution for surgical treatment. There were 12 men and 17 women, with a median age of 42.5 years (range, 28–71 years). All patients were complaining of the symptoms of hypoglycemia. Preoperative diagnostic workup included fast test, serum insulin, and C-peptide levels. None of the 29 patients had multiple endocrine neoplasia type 1. Preoperative localization procedures were performed with a combination of non-invasive imaging techniques (Figs. 1 and 2), including transabdominal or endoscopic ultrasonography, contrast-enhanced ultrasonography with SonoVue (Bracco, Milan, Italy), and computed tomography (CT) scan. The study was approved by the local ethics committee, and informed consent was obtained from all patients.

Surgical technique During laparoscopic procedure, the patient was placed in a supine position. A 30°, 10-mm laparoscope was inserted in the subumbilical port. Under direct vision, three 5- or 11-mm ports were placed in epigastrium or left lower quadrant. The pancreas was exposed anteriorly via a window in the gastrocolic ligament, which was created by an ultrasonic dissector (Ultracision, Johnson & Johnson, Cincinnati, OH, USA). Laparoscopic ultrasonography was available to explore the pancreas. A decision was made to perform either enucleation or distal pancreatectomy with spleen preservation according to the anatomic position and the number of insulinomas, as well as their relation to the pancreatic duct and the portal and splenic vessels.

Insulinoma enucleation was carried out with a combination of Harmonic Scalpel, LigaSure, and Ligaclips along the plane surrounding the tumor (Fig. 3). For the latter eight

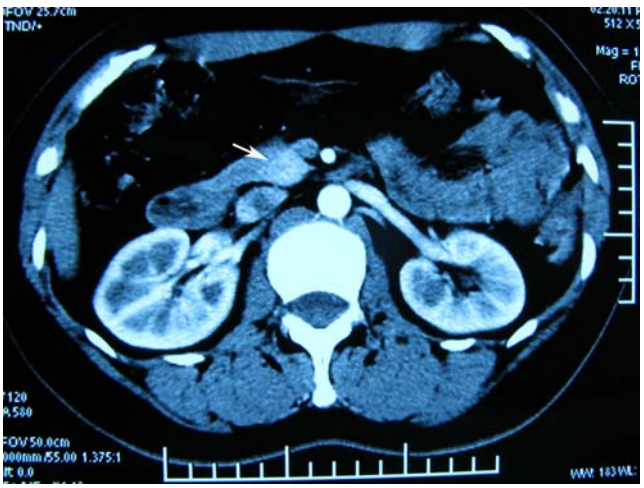

Figure 1 An insulinoma (*arrow*) located at the uncinate process of the pancreas, as shown by preoperative computed tomography.

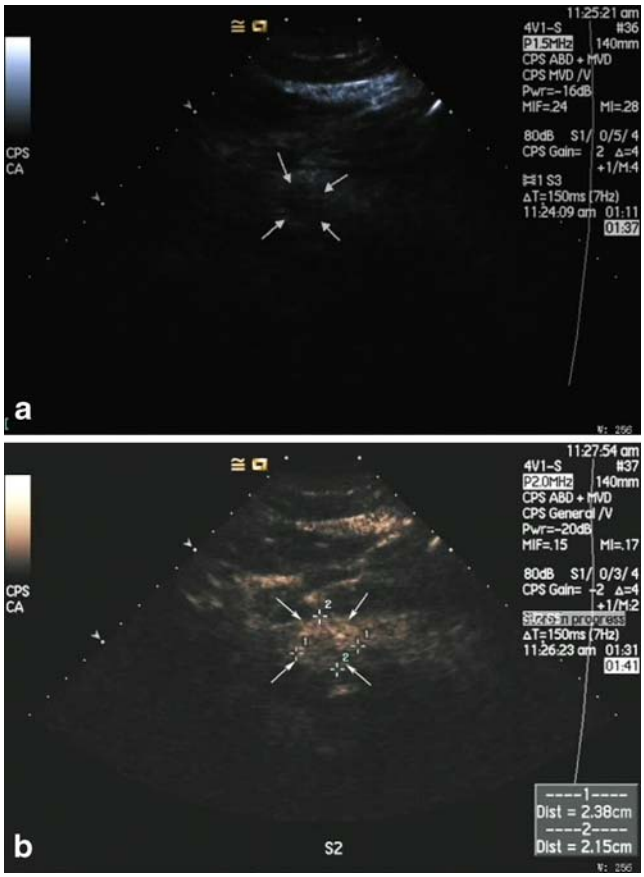

Figure 2 An insulinoma (*arrows*) located at the body of the pancreas, as shown by SonoVue-enhanced ultrasonography before (**a**) and after (**b**) contrast injection.

patients, fibrin glue and interrupted suture were employed at the tumor bed with the aim of preventing pancreatic leaks. For distal pancreatectomy, the inferior and superior border of the pancreas was mobilized, and the body and tail of the pancreas was lifted upward to isolate the splenic vessels from the pancreas. A tunnel was created between the splenic vessels and the pancreas. The pancreas was transected proximally to the tumor by an endoscopic linear stapler (Ethicon, Johnson & Johnson, Cincinnati, OH, USA). The proximal stump of the pancreas was oversewn with 4-0 Prolene to ensure hemostasis and closure of the pancreatic duct. The body and tail of the pancreas then was retracted laterally, and the dissection was continued with division of the small branches of the splenic vessels using LigaSure and Ligaclips until the splenic hilum. Next, the specimen was placed in an endoscopic plastic bag and retrieved from the extended port in the left abdomen. In addition, a hand-assisted laparoscopic procedure was performed in two patients due to unfavorable positions of tumors. A hand access device (Lap-Disk, Hakko, Tokyo, Japan) was inserted through the extended incision in the epigastrium to allow the introduction of the surgeon's left

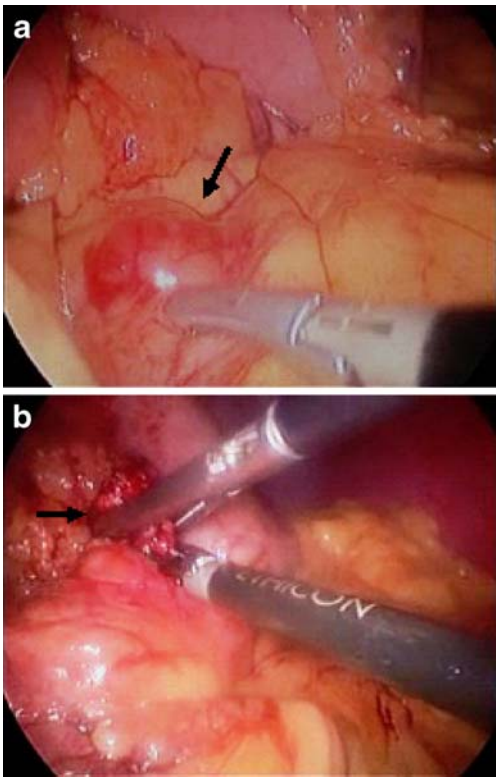

Figure 3 Endoscopic views of an insulinoma (*arrows*) at the body of the pancreas (**a**) and tumor enucleation (**b**).

hand. Two tumors were palpated in the head and the uncinate process, respectively, and were then enucleated. Finally, a silicon drain was left in the lesser sac near the transected pancreas. During the surgical procedure, the serum glucose level was tested before and at 30 min after tumor resection.

Statistical analysis Nonparametric tests were used for statistical analysis. The Mann–Whitney *U* test was used to compare continuous variables, and proportions were compared by chi-square test (SPSS/PC+; SPSS, Inc., Chicago, IL, USA). A *P* value of less than 0.05 was considered significant.

Results

All patients showed confirmed spontaneous hypoglycemia associated with hyperinsulinemia and had a positive fast test. The accuracy of preoperative localization was 44.8% (13/29) with transabdominal ultrasonography, 65.5% (19/29) with CT, 60% (6/10) with endoscopic ultrasonography, and 75% (6/8) with SonoVue-enhanced ultrasonography. The tumors were then precisely localized in 28 of 29 (96.6%) patients by a combination of these imaging techniques, four at the head, three at the uncinate process, two at the neck, fourteen at the body, and five at the tail of the pancreas, respectively. One patient was identified with two tumors at the body of the pancreas. Laparoscopic ultrasonography was performed to confirm the tumor location in 27 of 29 (93.1%) patients. One lesion located in the uncinate process of the pancreas was not detected by laparoscopic ultrasonography but was palpated in the subsequent hand-assisted approach. The size of the tumors ranged from 1.1 to 3.6 cm (mean, 1.9 cm). One lesion was not identified pre- and intraoperatively, and no additional surgical treatment was undertaken.

Laparoscopic pancreatectomy was successfully performed in 26 of 28 (92.9%) patients with confirmed tumors (Table 1). Sixteen patients underwent tumor enucleation, including two patients who underwent a hand-assisted laparoscopic procedure due to the deep location of tumors in the head and the uncinate process of the pancreas, respectively. Ten patients underwent distal pancreatectomy with (n=9) or without (n=1) spleen preservation. The resection of the spleen was needed due to intraoperative bleeding. Two patients with tumors located at the uncinate process adjacent to the superior mesenteric vein required conversion to open procedure to facilitate safe enucleation. The median operating time was 145 min (range, 55–385 min) for all laparoscopic procedures. The operating time of tumor enucleation (median, 85 min; range, 55–190 min) was significantly shorter than that of distal pancreatectomy (median, 174 min; range, 125–385 min; P=0.009). The estimated blood loss was 255 ml (median; range, 70–1,020 ml), 205 ml (median; range, 70–560 ml)

Table 1 Surgical Procedures with Regard to the Location of Pancreatic Insulinoma

Tumor location (number)	Laparoscopic enucleation	Hand-assisted enucleation	Laparoscopic distal pancreatectomy		Open enucleation
			Without splenectomy	With splenectomy	
Head (4)	3	1	–	–	–
Uncinate (3)	–	1	–	–	2
Neck (2)	2	–	–	–	–
Body (14)	9	–	4	1	–
Tail (5)	–	–	5	–	–
Total (28)	14	2	9	1	2

for tumor enucleation and 330 ml (median; range, 120–1020 ml) for distal pancreatectomy. However, there was no significant difference in the blood loss between tumor enucleation and distal pancreatectomy (P=0.083). None of 29 patients required blood transfusion. A distinct increase in serum glucose level was observed in 24 of 28 (85.7%) patients at 30 min after pancreatic resection.

There were no operative mortality and reoperation for all patients. Five of 29 (17.2%) patients developed early postoperative complications, four of which were due to pancreatic fistula defined as a drain output of any measurable volume of fluid on or after postoperative day 3, with an amylase content greater than three times the serum amylase activity. The pancreatic fistula occurred in three of eight (37.5%) patients who underwent tumor enucleation alone and in one of eight (12.5%) patients who underwent enucleation combined with oversewing of tumor bed and application of fibrin glue (P=0.569). All of the four patients were successfully treated by drainage and octreotide perfusion. The median duration of the leaks was 25 days (range, 8–68 days). The postoperative hospital stay was 5.5 days (median; range, 3–18 days) for 26 patients who underwent laparoscopic resection and 8 and 10 days, respectively, for two patients who were converted to open procedure. Excluding one patient whose lesion was not found pre- and intraoperatively, all patients with pancreatic resection were free of symptoms and remained normoglycemic after a median follow-up period of 19 months (range, 10–36 months).

Discussion

Laparoscopic resection of the pancreas is considered an ideal operative strategy for insulinomas, as they are mostly small, solitary, and benign.[6,9,14] Accurate localization is essential for the successful management of the pancreatic insulinomas. A combination with intraoperative ultrasonography and manual palpation has been shown to be the most effective measure to identify the tumors.[2,15] For a laparoscopic procedure, however, the tumor localization seems to be a concern because of the lack of tactile sensation. It may not be sufficient to localize tumors only by visualization or laparoscopic ultrasonography. It has been shown that laparoscopic approach failed to localize occult tumors in some patients, and conversion to open procedure was required.[6,11,12] In the present study, the laparoscopic ultrasonography failed to detect one small tumor located at the uncinate process of the pancreas. In addition, it has been suggested that preoperative knowledge of tumor location may facilitate the laparoscopic procedure and yield less invasiveness.[12, 13,15]

A variety of procedures, including transabdominal and endoscopic ultrasonogrphy, spiral CT, magnetic resonance imaging (MRI), angiography, and arterial stimulated venous sampling, have been recommended for preoperative localization of the insulinomas, and there was a wide range of detection rate with each one.[13,15–20] A reliable and cost-effective strategy for preoperative localization remains a matter of debate.[15,21–23] In our experience, conventional imaging techniques including transabdominal ultrasonography and CT scan were firstly recommended for all patients, with the aim of localizing the tumors and identifying possibly malignant disease preoperatively. Subsequently, those patients whose lesions had not been detected were referred to less invasive techniques such as endoscopic or SonoVue-enhanced ultrasonography. To avoid the potential complications and reduce the patients' uncomfortableness as well as medical expense, arterial stimulated venous sampling and angiography were not recommended for our patients. Our study, although involving a limited number of patients, suggests that a combination of these imaging techniques could accurately identify most lesions. The high detection rate may be associated with the larger size of tumors among our patients.

SonoVue is a new echo contrast agent for ultrasound imaging based on stabilized sulfur hexafluoride microbubbles that presents a high reflectivity at a low mechanical index and is characterized by a low solubility in water and a low diffusion in blood.[24] It allows a real-time imaging of the microcirculation that lasts several minutes, so that the early arterial and late parenchymal phases of the contrast medium diffusion can be analyzed.[24–26] The experience of identification of pancreatic insulinomas by SonoVue-enhanced ultrasonography is still limited. In our experience, the insulinomas showed early enhancement and homogeneous infusion after SonoVue injection and remained hyperechoic relative to the surrounding pancreatic tissue during the late parenchymal phase. The tumors have been successfully identified in six of eight (75%) patients by SonoVue-enhanced ultrasonography. As compared with the routine imaging techniques, the SonoVue-enhanced ultrasonography is a convenient, inexpensive, and less invasive investigation and allows the detection of a transient hypervascularity that may be missed in contrast-enhanced CT or MRI. Therefore, it may complement the preoperative imaging techniques and evaluate possibly malignant insulinomas. However, the ultrasonography is an operator-dependent procedure and is not suitable to study multiple lesions at one time because of the contrast washout.

The choice of the surgical strategy for pancreatic insulinomas depends on the location of tumors. Enucleation is preferred for solitary tumor located on the surface of the pancreas away from the pancreatic duct.[3,9,12] With regard to insulinomas deeply located in the head of the pancreas, it is technically difficult to resect tumors by laparoscopy alone because they are proximal to the main pancreatic duct and

mesenteric vessels, and the procedure requires a highly precise localization. In this study, a hand-assisted laparoscopic enucleation was successfully performed in two patients with tumors located in the head and the uncinate process of the pancreas, respectively. We found that this technique not only facilitated the mobilization of the head of the pancreas but also allowed manual palpation and control, which contributed to secure dissection of the pancreas. Moreover, the operation time and hospital stay of the two patients were not significantly prolonged. The only drawback of the procedure seemed to be the extended incision as compared with laparoscopic approach. It has been shown that the hand-assisted laparoscopic approach was greatly helpful in the complicated pancreatic surgery, such as distal pancreatectomy with spleen preservation and pancreaticoduodenectomy.[27–29] Therefore, the hand-assisted approach should be considered when the tumor is located at an anatomically unfavorable position, although its safety and efficacy need further evaluation in large-scale randomized studies.

Distal pancreatectomy is the procedure of choice for insulinomas deeply located in the body and tail of the pancreas. As with open surgery, *spleen* preservation is encouraged whenever it is technically feasible. Spleen-preserving distal pancreatectomy with splenic vessel preservation or transection has been reported, but the latter procedure was associated with the potential risk of splenic infarction or abscess requiring subsequent splenectomy.[30–32] Our experience also demonstrated the feasibility of laparoscopic distal pancreatectomy without any compromise of splenic function, although this procedure was technically demanding. During the dissection of the pancreas, multiple branches of splenic vessels were encountered and divided by a combination of LigaSure and Ligaclips with the help of the magnified view of laparoscopy. Only one case underwent distal pancreatectomy with splenectomy due to uncontrolled bleeding of splenic vein proximal to splenic hilum. In addition, it has been suggested that the hand-assisted laparoscopic approach could be attempted to perform the spleen-preserving distal pancreatectomy when technical difficulties were encountered.[33–35]

In support of previous studies,[6,9–13,36] our experience confirmed that laparoscopic pancreatectomy could benefit patients with reduced postoperative pain, shorter hospital stay, quicker recovery to normal activity, and better cosmetic appearances, as compared with open approach. The most common morbidity after laparoscopic pancreatectomy is pancreatic fistula, with a reported incidence ranging from 8% to 33%.[6,12,34,37,38] It was noted that the rate of fistula after laparoscopic enucleation was higher than that after laparoscopic distal pancreatectomy, 25% (4/16) with enucleation versus 0% (0/10) with distal pancreatectomy. The injury to the main pancreatic duct or inability to occlude smaller ducts may account for the higher incidence of fistula after tumor enucleation. To reduce the occurrence of fistula, we chose to mobilize a piece of omentum as a living pack, insert it into the tumor bed, and then *closed* the tumor bed with sutures around the omentum. The sutures should not be tied with so much tension as to tear of pancreatic substance. In addition, fibrin glue was adopted in selected cases. In our experience, application of tissue glue and oversewing of the tumor bed might be of some benefit in occluding minor ducts. All patients with pancreatic leakage were successfully managed by conservative measures.

Conclusions

With appropriate equipment and refinement of techniques, laparoscopic pancreatectomy could be successfully performed in most patients with benign insulinomas. A combination of preoperative imaging techniques and intraoperative ultrasonography aids tumor localization and laparoscopic resection. Further studies are required to evaluate the potential application of the hand-assisted approach for tumors located at anatomically unfavorable positions.

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ORIGINAL ARTICLE

Long-term Functional and Quality of Life Outcomes of Patients After Repair of Large Perianal Skin Defects for Paget's and Bowen's Disease

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Abstract
Introduction The assessment of long- term functional and quality of life outcomes of these patients following repair of large defects after surgical excision has not been reported.
Methods Between 1992 and 2004, at two institutions, 18 patients underwent repair of a perianal defect for Paget's disease (n=8) or Bowen's disease (n=10) and were alive with intestinal continuity at last follow-up. Patients were mailed the fecal incontinence quality of life scale (FIQL) and the SF-36.
Results Fourteen patients (78%) responded. Median follow-up for responders was 5 years. Mean age was 65 years with 12 females. Subcutaneous skin flaps (11) and split-thickness skin grafts (three) were used to repair the perianal defects, which were circumferential in 11 patients (79%). Nine patients reported incontinence and completed the FIQL. The FIQL scores of patients reporting incontinence were lower for lifestyle, coping/behavior, and embarrassment but not significantly different for depression compared to patients without incontinence. SF-36 scores of the patients were not significantly different from the normative population.
Conclusion Functional results after repair of large perianal defects are acceptable and overall quality of life (QOL) is similar to the normative population although a large proportion of patients have some form of incontinence that impacts certain aspects of their QOL.

Keywords Quality of life · Bowen's disease · Paget's disease · Surgery

Introduction

Paget's (adenocarcinoma in situ) and Bowen's (squamous cell carcinoma in situ) disease are uncommon premalignant conditions of the perianal region. Surgical excision of all involved perianal skin and subcutaneous tissue is currently considered the standard surgical treatment.[1–4] Depending upon the extent of microscopic and macroscopic disease, the resulting perianal defect following wide local excision can be of varying sizes. Smaller defects can be closed primarily or allowed to heal by secondary intention. However, larger defects pose a significant challenge and various techniques including split-thickness skin grafts, subcutaneous flaps, and myocutaneous flaps have been described to gain adequate tissue coverage.[5–9] While the oncologic results of this approach have been reported to be satisfactory, patient-reported outcomes such as long-term functional results and quality of life (QOL) have not been adequately evaluated.

We assessed the long-term functional and QOL outcomes of patients undergoing repair of large perianal defects after WLE for Paget's disease (PD) and Bowen's disease (BD) using standardized and validated questionnaires.

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Patients and Methods

Eighteen patients underwent repair of a perianal defect involving at least half the circumference of the perianal region for PD (n=8) or BD (n=10) between 1992 and 2004 at the Mayo Clinic in Rochester, Minnesota and Jacksonville, Florida and were alive at last follow-up. Functional and QOL outcomes were evaluated by mailing all 18 patients a standardized bowel function questionnaire, the fecal incontinence quality of life scale (FIQL)[10], and the SF-36 survey instrument.[11] Fourteen patients responded (78%). Median follow-up of responders was 5 years. The functional and QOL outcomes of this patient cohort form the basis of our report. The study was approved by the Institutional Review Board.

Fecal Incontinence Quality of Life Scale (FIQL)

The FIQL is a 29-item questionnaire divided into four categories: lifestyle (ten items), coping/behavior (nine items), depression/self-perception (seven items), and embarrassment (three items). Its psychometric properties have been adequately evaluated and it has been shown to be valid and reliable. Scoring of the FIQL scale was done in accordance with the original study.[10]

SF-36

The Short Form-36 is a generic QOL instrument composed of 36 questions divided into eight groups in two categories: physical health (general health, physical functioning, role-physical, and bodily pain) and mental health (mental health, vitality, role-emotional, and social functioning).[11] The SF-36 health survey is one of the most widely used generic health status instruments to assess health-related quality of life.[12] It has been validated and reproduced in several studies for patients undergoing colorectal surgery.[13,14] The SF-36 was scored according to the author's manual.[15,16]

Statistical analysis was performed using SAS version 8.2 (SAS Institute Inc., Cary, NC, USA). Outcomes comprised of discrete nominal variables were compared using chi-square tests or Fisher's exact tests when low expected cell counts were observed. Continuous variables were analyzed using two-sample t tests or Wilcoxon rank sum tests when the data were not sufficiently Gaussian. The SF-36 mental and physical component summary scores were standardized to a mean of 50 and standard deviation of 10; comparisons of these scores with an external reference population were performed using a one-sample t test. Significance was assumed at the $P<0.05$ level.

Results

Fourteen patients (78%) responded. Mean age at surgery was 65 years (range 48 to 84) with 12 females and a median follow-up of 5 years (range 1 to 12 years). Subcutaneous skin flaps (n=11) and split-thickness skin grafts (n=3) were used to repair the perianal defects, which were circumferential in 11 (78%) patients. Of the patients who responded, five patients (36%) did not report incontinence to either stool or mucous during the day or night, while nine patients (64%) reported some form of incontinence and, therefore, completed the FIQL.

The FIQL scores of patients reporting incontinence were lower for lifestyle (2.9 vs. 3.6, $P<0.002$), coping/behavior (2.5 vs. 3.3, $P<0.001$), and embarrassment (2.5 vs. 3.4, $P=0.01$), but not significantly different for depression (3.4 vs. 3.7, $P=0.31$) compared to controls without incontinence (Table 1).[10] Mean SF-36 physical and mental summary scores of patients were not significantly different from the normative population (43 vs. 50, $P=0.051$ and 50 vs. 50, $P=0.96$) or between patients reporting incontinence and those who did not (41 vs. 48, $P=0.21$ and 49 vs. 52, $P=0.93$).

In order to minimize the possibility of a response bias, we compared the available demographics of the responders and non-responders. Patients responding to the FIQL and SF-36 questionnaires were older than patients who did not respond (median age 65 vs. 51 years, $P=0.03$) but appeared similar in gender, type of surgery, and underlying pathology. Although the small number of non-respondents precluded meaningful comparisons for these latter parameters.

Discussion

In our study, we found that, following wide local excision and repair of large perianal defects for PD and BD, functional results are acceptable and overall QOL is similar to the normative population as measured by validated instruments. A large proportion of patients, however, report

Table 1 Comparison of Fecal Incontinence Quality of Life (FIQL) Subscales Between Patients with Fecal Incontinence and Control Patients without Fecal Incontinence

	Patients with incontinence (n=9)	Control patients[10]
Lifestyle	2.9	3.6*
Coping/behavior	2.5	3.3*
Embarrassment	2.5	3.4*
Depression	3.4	3.7

*Statistically significant

some form of fecal incontinence. This is likely due to several factors including age-related deterioration of anal sphincter function, iatrogenic injury to the sphincter complex, and loss of perianal sensation and soft tissue fibrosis that can occur during the excisional and reconstructive phases of surgical treatment. Fecal incontinence in these patients impacts certain aspects of QOL as measured by the FIQL, although their overall QOL as assessed by the SF-36 was similar to patients without fecal incontinence.

Our inability to detect a significant difference between the QOL of patients with and without fecal incontinence may seem counterintuitive, as fecal incontinence is usually considered to have an adverse impact on QOL.[17,18] In our study, patients with fecal incontinence reported lower QOL on several domains of the FIQL, although their SF-36 physical and mental summary scores were not different from the scores of patients that did not report fecal incontinence. An explanation for this may be the "frame-shift phenomenon" in which patients change their perspective and "threshold" for what is considered "a good quality of life" when faced with a potentially life-altering or life-threatening diagnosis.[14] This discrepancy between functional outcome and QOL has been previously reported in the literature for other colorectal patient cohorts.[13,19] Ko et al.[13] assessed functional outcomes and QOL of patients undergoing an ileorectal anastomosis (IRA) and ileal pouch anal-anastomosis (IPAA) for familial adenomatous polyposis (FAP) and found that patients undergoing an IPAA, despite having more frequent bowel movements than patients undergoing IRA, had a similar QOL as IRA patients as measured by the SF-36.

Another possible reason for this discordant finding could be a lack of sensitivity of the SF-36 to detect a clinically significant difference in the QOL of patients with and without fecal incontinence. This is supported by the observation that the FIQL, which is a disease-specific QOL instrument, was able to detect differences in certain QOL domains for patients with fecal incontinence as compared to controls without fecal incontinence. It is therefore important to use disease-specific, as well as generic, QOL instruments when assessing the QOL of patients undergoing surgical interventions for specific diseases.

A third limitation of our study is that we did not have documentation of the preoperative QOL or continence status of the patient cohort. From population-based studies, it is known that a proportion of the US population in their fifth and sixth decade of life report some element of idiopathic fecal incontinence.[20,21] Therefore, it is difficult to determine if the reported fecal incontinence was a preexisting condition, a result of the surgery, or due to age-related deterioration of sphincter function. However, repair of large perianal skin defects in patients with any degree of incontinence is likely to make already compromised function worse and should be considered a relative contraindication.

Traditional parameters such as operative morbidity, mortality, and oncologic outcomes are considered to be important in assessing the efficacy of an intervention. However, recent research has suggested that patient-reported outcomes may be just as significant.[22,23] This is based on the paradigm that patients are the ultimate consumers of all therapies and are the ones who experience the benefits and the consequences of any treatment. Therefore, patient-reported outcomes determine the true effectiveness of an intervention. Based upon available literature, the natural history of perianal PD and BD following surgical therapy is one of relative indolence.[2–4,24–26] The disease course is marked by frequent local recurrences and the disease-specific mortality is low in the absence of invasive disease.[2,4,24–26] At the same time, the surgical treatment of PD and BD can have a significant impact on fecal continence and possibly QOL as seen in our study. Therefore, while the oncologic outcome of the current surgical treatment of PD and BD seems to be satisfactory, the patient-reported outcomes are not always optimal.

In recent years, several pharmacologic therapies, including Imiquimod[27–30] and 5-Fluorouracil (5-FU)[31–33], have been shown to be effective in treating PD and BD. Imiquimod is an immune response modifier that is an agonist for the toll-like receptor 7 (TLR-7). It is also thought to induce cutaneous cytokines, thereby enhancing both innate and acquired immunity and thus having potent anti-viral and anti-tumor activity.[34] So far, the evidence for the efficacy of imiquimod in treating PD has been mainly in the form of case reports. It has been shown to be effective in treating PD of the scrotum[28,35], vulva[36], perianal region[35,37], thigh[38], and suprapubic region.39 Several prospective and retrospective studies have reported the efficacy of imiquimod and 5-FU in treating BD.[29,31,32,40] Based upon these promising results, several authors[30,37,40] have suggested that pharmacologic therapies be considered as an alternative to the surgical treatment of PD and BD. Results from our study support this contention by demonstrating the adverse impact of surgery on the long-term function of patients. Due to the relative rarity of perianal PD and BD, it is unlikely that controlled trials will be possible to determine the superiority of one treatment modality over the other. The current literature, however, does provide evidence-based support for pharmacologic therapy as an alternative to surgical treatment of perianal PD and BD. In patients with extensive perianal disease, these therapies may avoid the need for radical excision with soft tissue reconstruction that can, in turn, lead to adverse functional outcomes. Concurrently, it is important that these pharmacologic therapies be carefully monitored for their long-term oncologic efficacy, adverse effects, as well as patient-reported outcomes.

The long-term functional and QOL outcomes of patients following repair of large perianal defects for PD and BD are

acceptable although a large proportion of patients will report having fecal incontinence. Effective pharmacologic therapies, which are less likely to have an adverse impact on functional outcomes, should be considered in the management of perianal Paget's disease and Bowen's disease as long as they maintain similar oncologic efficacy.

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ORIGINAL ARTICLE

Long-Term Follow-Up of Patients with Fulminant *Clostridium difficile* Colitis

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Abstract
Purpose The purpose of this study was to determine the long-term survival rate, rate of gastrointestinal continuity restoration, and rate of recurrence following an attack of fulminant *Clostridium difficile* colitis.
Material and Methods Fulminant *C. difficile* colitis was defined as any patient who had a bout of *C. difficile* colitis and required surgical intervention after failing medical therapy. These patients were found through a pathological database search. Follow-up phone calls were made to any patient who survived at least 30 days after being discharged from the hospital following surgical intervention (long-term survivor group).
Results A total of 49 patients were involved in the study. The 30-day mortality rate was 57% (28/49), with an in-hospital mortality rate of 49%. The 5-year survival rate for the long-term survival group was 38% (8/21) and 16.3% for all patients. Gastrointestinal continuity was restored in 20% of the patients. There was one documented recurrence of *C. difficile* colitis
Conclusion Patients who have a bout of fulminant *C. difficile* colitis have a poor prognosis of surviving longer than 5 years. Restoring gastrointestinal continuity is uncommon and usually reserved for patients with few co-morbidities. Recurrent *C. difficile* colitis after surgical resection is a rare occurrence

Keywords *Clostridium difficile* · Pseudomembranous colitis · Toxic megacolon · Colectomy · Survival

Introduction

Clostridium difficile is an anaerobic bacterium, which is the most commonly diagnosed cause of infectious hospital diarrhea.[1] Although it was described as early as 1935 by Hall and O'Toole, its link with disease was not identified until 1978.[2] Most patients are asymptomatic or suffer from mild diarrhea; however, approximately 3–8% will have a fulminant course with high fevers, severe abdominal pain, toxic megacolon, or even perforation.[3,4] Despite aggressive surgical treatment with a partial or subtotal colectomy, the in-hospital mortality remains between 30% and 80%.[5–8] Those patients who do survive a bout of fulminant *C. difficile* colitis have not, to our knowledge, extensively been followed-up long term. The aim of this study is to determine the long-term outcomes of the patients who survived an episode of fulminant *C. difficile* colitis. Outcomes analyzed included survival, the incidence of restoration of gastrointestinal continuity, and recurrence of *C. difficile* after surgery.

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Material and Methods

Fulminant *C. difficile* colitis was defined as any patient who required surgical intervention for their disease after failing medical management and had a pathological diagnosis which included pseudomembranes or psuedomembranous colitis.[5] An institutional pathological database (Tamtron Power-Path system; IMPAC, Columbus, OH, USA) was used to search the pathological diagnoses pseudomembranes and pseudomembranous colitis. Seventy-three colectomy specimens were identified with *C. difficile*-associated pseudomem-

branous colitis as the final pathological diagnosis. Medical records of these patients were reviewed to determine their work-up before surgery. Patients with a history of inflammatory bowel disease as well as those who were lost to follow-up were excluded from the study. Follow-up phone calls were then placed to patients or their families. Specific questions asked included whether patients were alive (if speaking with a family member) or, if they expired, the date of expiration if applicable, if the patient still had a stoma, and whether they were ever diagnosed by a physician with recurrent *C. difficile* colitis after surgery. Medical records were reviewed to confirm a recurrence of *C. difficile*. These methods were approved by the Mount Sinai School of Medicine institutional review board.

Results

A total of 49 patients were eligible for our study. Patients with inflammatory bowel disease (12) and those who were lost to follow-up (12) were excluded. Preoperatively, patients were treated with different combinations of oral and intravenous metronidazole as well as oral vancomycin for anywhere from 24 h to 23 days, except for one patient who was treated for 52 days. Intravenous immunoglobulin was given to four patients for 1 to 3 days. Table 1 illustrates the clinical instability of patients before any operative intervention. Diagnostic tests for the eligible patients included computed tomography (CT) scans and lower endoscopy (Table 2). Patients who survived the hospitalization for *C. difficile* and were alive >30 days after discharge from the hospital were included in the long-term survival group. The discharge date range was from April 1995 to March 2006. Follow-up calls were made on July 1, 2008. This resulted in a total of 28 patients in the 30-day mortality group and 21 patients in the long-term survival group. The 30-day mortality rate was 57%, with an in-hospital mortality rate of 49%.

There were 21 patients in the long-term survival group who previously underwent the following procedures for fulminant *C. difficile* colitis: subtotal colectomy with end ileostomy (18), right hemicolectomy with ileostomy (one), left hemicolectomy with colostomy (one), and ileocolectomy (one). No patient underwent a proctectomy. One patient who underwent a subtotal colectomy had a recurrence of *C. difficile* after the surgery. Four patients had their stomas reversed at a later date for an overall reversal rate of 20%. All data for patients in the long-term survival group can be found in Table 3.

Overall survival of the patients in long-term survival group was calculated using a Kaplan–Meier curve (Fig. 1). The five-year survival rate for these patients was 38%. The overall 5-year survival rate of all patients included in the study was 16.3% (8/49).

Table 1 Clinical Status of Patients Before Operative Intervention

Clinical status	Number of patients
Intubated	23
Vasopressors	21
Mental status changes	29

Table 2 Results of Diagnostic Tests for Patients Eligible for the Study

CT scan	24
Pancolitis	15
Segmental colitis	9
Free air	2
Lower endoscopy	25
Pseudomembranes present	20
No pseudomembranes present	5

Discussion

C. difficile colitis is an increasing problem whose incidence has risen over 100% since the early 1990s.[9] Our in-hospital mortality rate of 49% is comparable to other hospital mortality rates in the literature.[5,6] However, this mortality rate is still quite high, and we feel this is due to the population of patients we studied. The average age of our patients was 70.5 years, and many of them had multiple co-morbidities. As shown in Table 1, many patients were clinically unstable at the time of operation. The patients with inflammatory bowel disease that were excluded were generally younger and healthier, and if they were included, our overall in-hospital mortality rate would have been reduced to below 40%. This number is similar to the 34% reported by Byrn et al.,[5] from our institution.

Table 3 Demographic Data of All Patients in the Long-Term Survival Group

Mean age (range)	70.5 years (35–90)
Sex (M/F)	9:12
Subtotal colectomy (%)	18 (86)
Other surgical procedure (%)	3 (14)
Hypertension (%)	12 (57)
Coronary artery disease (%)	9 (43)
Diabetes (%)	8 (38)
Immunosuppression (%)	7 (33)
Number of reconnections (%)	4 (20)
Number of recurrences (%)	1 (5)

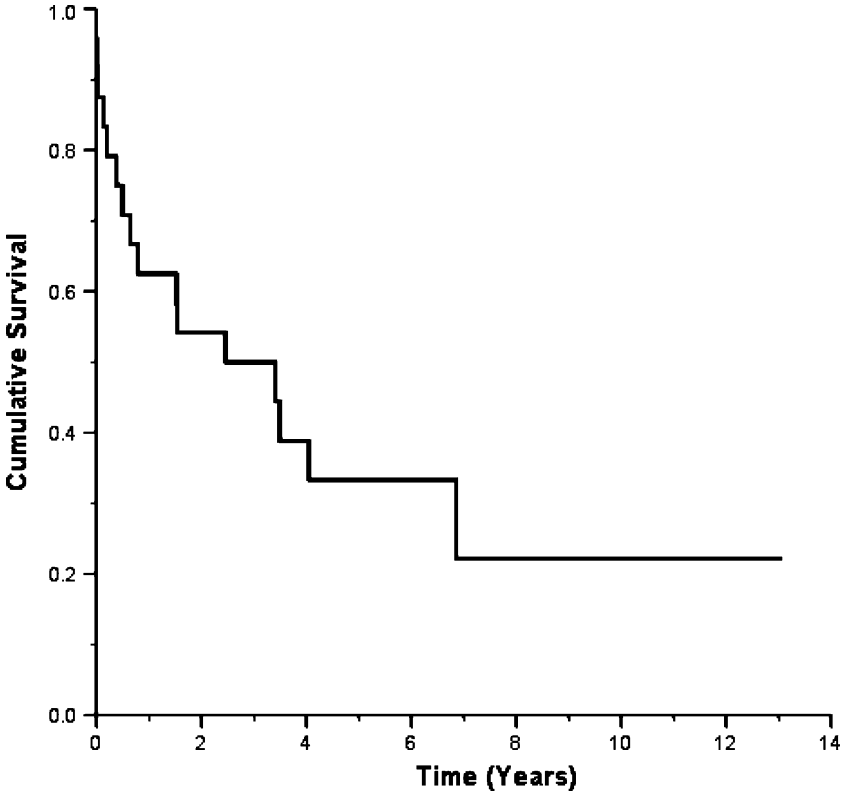

Figure 1 Long-term survival of 21 patients after colectomy for fulminant *C. difficile* colitis.

Despite the high incidence of death in patients with fulminant *C. difficile* colitis, surgical intervention is usually required and may reduce the mortality rates in some patients.[3,10] It is important for patients and their families to understand that surgery for fulminant *C. difficile* colitis carries a high rate of mortality, but sometimes, it is the only chance a patient has at survival.

Our data on long-term survival after an episode of fulminant *C. difficile* colitis demonstrates a 38% 5-year survival rate for those patients in the long-term survival group. Patients who suffer an attack have significant co-morbidities requiring major surgical interventions or are immunosuppressed.[11] This patient population, as shown in Table 3, has significant co-morbidities that preclude long-term survival. We acknowledge that patients in the long-term survival group, as shown in Table 4, expired from causes other than the fulminant *C. difficile* colitis. Therefore, fulminant *C. difficile* colitis is a poor prognostic sign for patient survival, with a 5-year survival rate of 38% for patient surviving >30 days after hospital discharge and a 5-year survival rate of 16.3% for all patients.

Table 4 Causes of Death for Patients in the Long-Term Survival Group

Cause	Number of patients
Multisystem organ failure	5
Cardiac failure	3
Metastatic cancer	2
Respiratory failure	1
Unknown	2

Restoring gastrointestinal continuity was possible in only 20% of the long-term survivors. Most surgeons are hesitant to perform an elective, major operation under general anesthesia for patients who are generally elderly with multiple co-morbidities. Of the four patients who were reconnected, three of them were under 70 years of age. All three patients were generally healthy except for being immunosuppressed secondary to chemotherapy for breast cancer, a previous heart transplant, and being HIV positive. The heart transplant patient had hypertension; otherwise, there were no other co-morbidities. Patients should be informed, before surgery for fulminant *C. difficile* colitis, that there is a strong possibility they will have a permanent stoma. However, with younger patients who have few co-morbidities, such as those immunosuppressed but otherwise healthy, there is a chance of stoma reversal once they have fully recovered from their colitis.

One patient in the long-term survival group had a documented recurrence of *C. difficile*, and this was in the rectal stump following a subtotal colectomy with ileostomy. The recurrence was documented with a stool sample positive for *C. difficile* toxin 46 days after discharge from the hospital. The patient was treated with intravenous metronidazole but expired from multi-organ system failure 1 month later.

The three patients who underwent a segmental resection did so with a presumed diagnosis of ischemic colitis based upon CT scan results, and only the portion of the colon that appeared to be diseased was removed. Those that underwent endoscopy had no pseudomembranes present. No recurrence was noted in this subset of patients.

Despite the overall low recurrence rate and the lack of recurrence in partial colectomy patients, it has been well documented that the subtotal colectomy with ileostomy has less of a chance of requiring another surgery for recurrence and a better overall mortality.[4,12,13] Thus, we advise any patient with a preoperative diagnosis of fulminant *C. difficile* colitis to undergo a subtotal colectomy with ileostomy.

A major limitation of this study is the small sample size of patients in the long-term survival group. Fulminant *C. difficile* colitis only occurs in 3% to 8% of patients diagnosed with *C. difficile* colitis with a 57% 30-day mortality rate. In addition, patients with inflammatory bowel disease were excluded because we felt they were a different population. Inflammatory bowel disease patients were often younger and healthier than most patients who develop fulminant *C. difficile* colitis. These characteristics might have affected the survival curve and reconnection rates. These patients should probably be evaluated long-term in a separate study.

A second limitation of the study is that all data were obtained from a single institution. The patients at the Mount Sinai Hospital may represent a different patient population not encountered in smaller, community hospitals. Thus, these results may not be applicable to surgeons practicing at these hospitals.

Conclusion

Patients without inflammatory bowel disease, who suffer a bout of fulminant *C. difficile* colitis, have a 57% 30-day mortality rate and an in-hospital mortality rate of 49%. Patients who survive longer than 30 days after discharge from the hospital eventually expire from something other then the *C. difficile* colitis. Fulminant *C. difficile* colitis is a marker for patients having a 5-year survival rate of 38% if they survive longer then 30 days after hospital discharge. Gastrointestinal continuity in these patients is feasible 20% of the time and is usually reserved for patients who are younger and have few co-morbidities. Recurrence of *C. difficile* (5%) following surgery is very low. The recommended procedure for patients with fulminant *C. difficile* colitis should be a subtotal colectomy with end ileostomy.

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ORIGINAL ARTICLE

Comparison of One-Stage Managements of Obstructing Left-Sided Colon and Rectal Cancer: Stent-Laparoscopic Approach vs. Intraoperative Colonic Lavage

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Abstract
Purpose We evaluated the operative outcomes of laparoscopic surgery following self-expandable metallic stent compared to one-stage emergency surgical treatment.
Methods From April 1996 to October 2007, 95 consecutive patients with left-sided malignant colorectal obstruction were enrolled. Twenty-five patients were assigned to the preoperative stenting and elective laparoscopic surgical treatment group (SLAP) and 70 to the emergency open surgery with intraoperative colon lavage group (OLAV).
Results Among the 25 patients in the SLAP group, a primary anastomosis was possible in all patients and a diverting stoma was needed in one patient. The operative time was shorter in the SLAP group (198.53 vs. 262.17 min, P=0.002). Tumor size, number of retrieved lymph nodes, and pathological stage were similar in both groups. The rate of anastomotic failure was similar and postoperative complications occurred less in the SLAP group (5.9% vs. 31.4%, P=0.034). The passage of flatus and oral intake were resumed earlier in the SLAP group (2.88 vs. 3.68 days, P=0.046 and 5.18 vs. 6.65 days, $P<$ 0.001, respectively). The postoperative hospital stay was shorter in the SLAP group (10 vs. 15.4 days, P=0.013).
Conclusions In patients with left-sided malignant colon and rectal obstruction, laparoscopic surgery after SEMS could be safely performed with successful early postoperative outcomes.

Keywords SEMS · Laparoscopy · Malignant obstruction · Colorectal

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Introduction

The treatment for malignant left-sided colon obstruction consists of multiple-staged operative procedures to avoid an increased incidence of anastomotic leakage caused by inadequate bowel preparation. Recently, obstructed left-sided colon cancer has been managed by a single-stage resection of the diseased colon or rectum with a primary anastomosis, with or without intraoperative colon lavage.[1,2] In selected patients, tumor resection with a primary anastomosis can be performed with satisfactory results using intraoperative colon lavage or a subtotal colectomy.[3–5] However, the morbidity and mortality of surgery for a left-sided obstructed colon is high, whether it includes a stoma or not.[6] In this setting, therefore, a technique that alleviates obstruction, while allowing the surgery to be delayed, may be useful. Dohmoto first described the placement of self-expandable metallic stents (SEMS) for the relief of colon obstruction in 1991.[7] The stents were used for patients with

disseminated disease or unacceptable surgical risk. This approach to patient management can be used as definitive palliative treatment to avoid a colostomy.[8–11] A step forward in the use of these stents is their application in transient colon decompression in cases of potentially curable colorectal cancer obstruction prior to definitive surgery. This allows for preoperative study of the colon proximal to the lesion and the assessment of the stage of the tumor. A colon stent, as a bridge to elective surgery, may also lead to a shorter hospitalization, fewer surgical procedures, and less time in intensive care compared to the conventional emergency surgery for an obstructed colon cancer.

Since the introduction of laparoscopic colorectal resection, in the last decade, many studies have shown the benefits of this method compared to traditional open surgery for colon cancer. The advantages include decreased surgical trauma, reduction of perioperative complications, faster postoperative recovery, and survival rates similar to those obtained with conventional surgery. The use of SEMS for patients with acute colon obstruction allows the surgeon to forgo the traditional emergency surgery, with the associated high risks, and perform an elective operative procedure laparoscopically in a more controlled setting. The use of SEMS as a bridge to elective, one-stage laparoscopic resections with a primary anastomosis, for colon obstruction, could provide the combined advantages of the two techniques. However, there is limited information on laparoscopic surgery after self-expandable stents compared to one-stage open surgery using intraoperative bowel preparation in patients with left-sided malignant colorectal obstruction. Therefore, the main goal of this study was to compare the operative outcomes of laparoscopic surgery following the use of SEMS with those of one-stage emergency surgical treatment using intraoperative colonic lavage.

Methods

From April 1996 to October 2007, 125 of 2,049 patients with left-sided colon and rectal cancer presented with acute malignant obstruction. Twenty-three patients underwent staged surgery. The patients treated with a subtotal or total colectomy were excluded from this study. In addition, patients were excluded from the study if they manifested clinical or radiographic evidence of bowel perforation, peritonitis, or had hemodynamic or pulmonary instability. The stent-laparoscopic (SLAP) group included 25 patients who were treated by successful colon stenting followed by laparoscopic colorectal resection. In the open lavage (OLAV) group, 70 patients underwent resection of the colon or rectum with primary anastomosis after intraoperative colon lavage. We compared the demographic findings, pathology results, and postoperative outcomes between the two groups. This study was approved by the Institutional Review Board (Fig. 1).

A SEMS was introduced using a colonoscope under the guidance of fluoroscopy a week before surgery as described previously.[12,13] Plain abdominal X-rays were performed 24 h after the stent insertion to confirm the stent expansion and position. Successful stent-induced decompression was determined by resolution of symptoms and was confirmed by improvement in radiologic examination. Around 1 week after the stenting procedure, the patients were clinically improved and underwent elective laparoscopic resection (Fig. 2).

Operative Procedure for the SLAP Group

The decompressed colon was prepared with 90 mL of Solus® (sodium phosphate) solution 24 h before surgery. The patients were placed in the Trendelenburg position and were slightly tilted to the right and downward. The colon or rectum was laparoscopically mobilized in the medial to lateral fashion and the colon distal to the tumor was divided using endolinear staplers. A vertical periumbilical incision was made to remove the specimen and to introduce the anvil of a circular stapler. An anastomosis was made using the circular stapler in an end-to-end manner or double-stapled method in case of a discrepancy in the size of the colon or rectal lumen.

Open Surgery with On-Table Lavage

After full mobilization of the left colon, including the splenic flexure and/or rectum, antegrade colon irrigation was performed as follows. A Foley catheter was inserted into the cecum through the appendix, or ileum in cases with a prior appendectomy, and a corrugated tube was introduced into the colon at least 15 cm proximal to the tumor. Then, 2–4 L of warm saline was poured through the Foley catheter until clear fluid came out of the corrugated tube. However, more recently, we have been using a commercially available retrograde irrigation catheter (NICI, MI Tech, Seoul, Korea), which replaced the corrugated tube and could avoid proximal Foley catheterization. Others were conducted by a same method for treatment of colorectal cancer.

For the statistical analysis, the unpaired Student's t test, chi-squared test, and Fisher's exact test were used as indicated. A P value of less than 0.05 was considered significant.

Results

Preoperative colon stenting was attempted in 30 patients and succeed in 25 patients; the success rate (clinically and

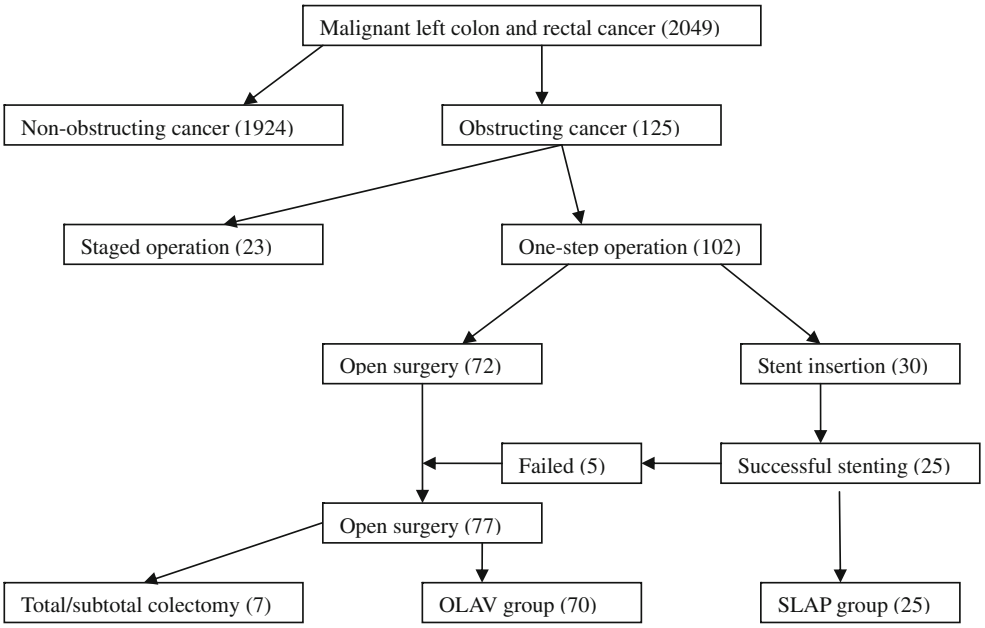

Figure 1 Algorithm of enrolled patients (number of patients).

technically) was 83.3%. One of the remaining five patients with unsuccessful stenting had a colon perforation (3.3%) and was excluded from the study. In the other four patients, the stent could not be inserted because the colon was completely obstructed without any pinhole through which the guidewire could be passed.

The age and gender distribution were similar in both groups. The location of the tumor was mainly in the sigmoid or rectum. There were more descending colon and rectal cancers in the OLAV group than in the SLAP group; however, this difference did not reach statistical significance. The mean operative time was significantly shorter in the SLAP group (186.2 min) than in the OLAV group (262.17 min). The size of the tumor and length of the distal resection margin were similar in both groups. The length of the proximal resection margin was longer in the OLAV group. (P=0.031) The mean number of harvested lymph nodes was similar and acceptable in both groups (SLAP= 28.88 vs. OLAV=24.42). The disease stage included mostly advanced stages and was similar in both groups (Table 1). A protective ileostomy was needed in two patients, one in the SLAP group and one in the OLAV group. One patient treated by SLAP was converted to an open low anterior resection due to a severely edematous rectum.

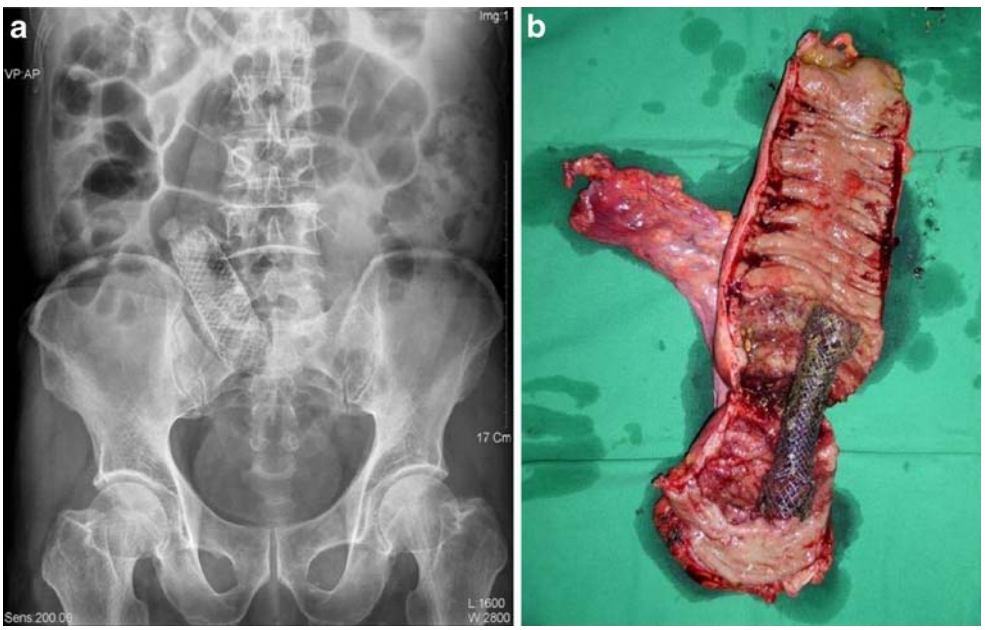

Figure 2 **a** Plain abdominal X-ray showing relief of colonic obstruction with the self-expanding metallic stent in situ. **b** Surgical specimen containing the stent.

Table 1 Clinicopathological Characteristics of the Patients (in Percent)

	SLAP group (n=25)	OLAV group (n=70)	P value
Age, years	61.6 (46–80)[a]	61.7 (23–90)[a]	0.95
Sex			0.62
Male	15 (60.0)	47 (62.7)	
Female	10 (40.0)	23 (37.3)	
Location			0.52
Splenic flexure	1 (4.0)	6 (8.0)	
Descending colon	0	11 (14.7)	
Sigmoid colon	17 (68.0)	31 (41.3)	
Rectum	7 (28.0)	21 (36.0)	
Operating time, min	186.2 (80–345)[a]	262.2 (140–540)[a]	0.002
Tumor size, cm	6.4 (5–10)[a]	5.8 (3–14)[a]	0.25
Proximal resection margin, cm	13.4 (3–32)[a]	19.1 (3–59)[a]	0.03
Distal resection margin, cm	7.9 (2–18)[a]	9.3 (2–36)[a]	0.27
No. of retrieved lymph node	28.9 (2–75)[a]	24.4 (4–92)[a]	0.27
TNM stage			0.74
I	0	1 (1.3)	
II	11 (44.0)	30 (40.0)	
III	9 (36.0)	30 (40.0)	
IV	5 (20.0)	9 (12.0)	

[a] Range

Regarding the postoperative progress, the time to the first flatus and resumption of oral intake was faster in the SLAP group than in the OLAV group. In addition, the postoperative hospital stay was significantly shorter in the SLAP group (9.24 vs. 15.70 days). However, the total length of the hospital stay was similar in both groups (Table 2).

Only one patient in the SLAP group had postoperative complication; this patient had a long-standing ileus and was treated by conservative management. On the other hand, there were significantly more postoperative complications such as wound infection, postoperative ileus, and anastomosis leakage in the OLAV group. Two serious complications including bleeding and acute myocardial infarction led to postoperative mortality in the OLAV group. There were no postoperative deaths in the SLAP group.

Discussion

The incidence of obstruction from a colorectal cancer has been reported to be 10–20% of all colorectal cancers. The traditional treatment for patients with acute colon obstruction, in many centers, is urgent surgery. Emergency surgery in these patients is associated with high rates of morbidity and mortality.[14–16] A subtotal colectomy and primary anastomosis, as a one-stage procedure for left-sided colon obstruction, has reduced the mortality rates to 4.2–7.4% in some reports.[15,17] Although several options exist for the management of colorectal cancer obstruction, the current trend is toward a one-stage resection and anastomosis of the colon or rectum. The use of SEMS for patients with acute colon obstruction enables the surgeon to operate under less urgent conditions and thereby reduce the patient-related risks. Moreover, this approach allows for a primary anastomosis in adequately prepared colon, which avoids the stoma-related complications and inconvenience.

Laparoscopic surgery has been adopted as an alternative treatment modality for many surgical diseases. However, this minimally invasive approach has not yet been accepted for the treatment of colon obstruction, especially for patients with malignant disease. However, with increasing evidence supporting the safety of the laparoscopic approach to colorectal resection for malignant disease and the successful management of colon obstruction using SEMS, it is likely that this approach will gain popularity for the management of this condition. The theoretical advantages include the following. The combination of decompressive stenting followed by an elective laparoscopic colectomy may be considered a model for minimally invasive therapy. An endoluminal procedure, followed by minimally invasive surgery, could replace the aggressive and mutilating surgery currently used as the standard of care. It would replace an emergency procedure, with all of its related risks, with the controlled setting of an elective laparoscopic colectomy procedure. Stenting, performed by flexible endoscopy or under radiological control, is a well-described and easily

Table 2 Operative Outcomes and Postoperative Recovery (in Percent)

	SLAP group (n=25)	OLAV group (n=70)	P value
Gas passage after surgery, days	3.1 (2–5)[a]	3.7 (2–6)[a]	0.04
Starting of oral alimentation after surgery, days	4.9 (4–7)[a]	6.7 (4–21)[a]	<0.001
Hospital stay after surgery, days	9.2 (7–19)[a]	15.7 (6–54)[a]	<0.001
Total hospital stay, days	18.2 (10–32)[a]	17.4 (7–54)[a]	0.68
Postoperative complications	1 (4.0)	23 (30.7)	0.006
Leakage	–	1 (1.3)	
Ileus	1 (4.0)	6 (8.0)	
Wound complication	–	8 (10.7)	
Postoperative mortality	0	2 (2.6)	0.03

[a] Range

performed procedure in skilled hands. According to the results reported recently, the technical success rate of inserting a stent into an obstructed colon ranges from 70% to 90% with a slightly lower rate of clinical success.[18] Endoscopy with simultaneous fluoroscopic guidance is preferred to either approach alone. In our study, the overall success rate of stenting was 83.3%, similar to other reports. Most cases where the stenting fails have been attempted by the radiological approach only. In this study, the protocol was changed to the endoradiological approach during the later part of this series.

Undoubtedly, placement of the stent makes the laparoscopic procedure more difficult. During surgery, the stents make the colon segment much more bulky, and hence, add to the technical difficulty. In some cases, indeed, colonic decompression was insufficient and it makes laparoscopic surgery more difficult. Nevertheless, the procedure remains feasible in the hands of a well-trained laparoscopic colorectal surgeon, as has been documented in preliminary reports.[19,20] In the present study, the operative time was significantly shorter in the SLAP group (198.53 vs. 262.17 min, P=0.002). There were no differences in the length of the distal resection margin and the number of retrieved lymph nodes between the two groups. Proximal resection margin was longer in OLAV group. In the OLAV group, colonic edema sustained after on-table lavage though the lumen was cleared and proximal resection should be performed including insertion site of corrugated tube; it was 15 cm proximal to the lesion. Therefore, proximal resection margin might be longer than needed.

One of the most obvious advantages of laparoscopic surgery is the early recovery of bowel movements. This may be due to the reduced amount of manipulation and trauma to the intestine during surgery. The preoperative stent decompresses the ileus of the small and large bowel, which can enhance the benefit of laparoscopy. For effective intraoperative colon lavage, applying pressure onto the bowel and at times mobilization of the colon at the splenic flexure are needed. A shorter time to the passage of flatus and beginning oral intake, in the present study, also support earlier recovery of bowel movements in the SLAP group compared to the OLAV group. Despite the fact that the average total hospital stay was similar in both groups, the postoperative stay was shorter in the SLAP group. With regard to postoperative complications, the anastomotic failure rate was not statistically different and the overall postoperative complication rate was lower in the SLAP group (5.9% vs. 31.4%, P=0.034). Only one patient suffered from a prolonged ileus in the SLAP group. However, in the OLAV group, prolonged ileus and wound complications were more frequent. Indeed, in the OLAV group, two patients died of acute myocardial infarction and septic shock. This suggests that emergency surgery was associated with higher risk for complications, especially in patients with medical comorbidities.

There are inconsistent findings from many studies on the oncologic outcomes of patients with obstruction due to colorectal cancer compared to patients with colorectal cancer without obstruction. Our preliminary results, comparing obstructing to nonobstructing colon cancer, showed an unfavorable outcome for patients with an obstruction (unpublished data). This was due to the relatively advanced stage of the cancer in cases with an obstruction, difficulty in obtaining an adequate resection in the emergency setting, possible increased frequency of lymphatic or hematogenous spread by excessive bowel manipulation, and relatively compromised immunity of the patients. Therefore, the oncologic results as well as the postoperative recovery with the elective laparoscopic procedure, following the SEMS, might improve the overall patient outcome.

This study has some limitations. We tried to perform SEMS in some patients, and for selection of patients who underwent SEMS insertion, inevitable selection bias could be intervened. In patients who had completely obstructed disease, SEMS insertion was not attempted, and in such cases, operative procedure was more difficult. Therefore, selection of patients for SEMS insertion might give favorable effect on operative outcome in the SLAP group. And, the retrospective study design was based on a prospectively collected database. Therefore, subjective consideration could be intervened in analyzing the data. Nevertheless, the present study has provided meaningful data about laparoscopic surgery after stent insertion in obstructive left-sided colorectal cancer.

The results of the present study suggest that the use of a colon stent to relieve obstruction allows the surgeon to perform an elective laparoscopic procedure in a controlled setting. The advantages of laparoscopic surgery include a reduced number of expensive sequential operations, a reduction in stoma requirements, and a reduction in overall morbidity and mortality compared to the one-stage emergency surgery. The results of this study demonstrated that the management of acute colon obstruction with SEMS decompression followed by a laparoscopic resection was safe and effective. The results of this study support the use of stent placement followed by elective laparoscopic surgery as first-line therapy for appropriate patients who present with evidence of acute, complete, left-sided, malignant colon obstruction.

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ORIGINAL ARTICLE

Conservative Management of Acute Appendicitis

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Abstract
Background The acute appendicitis is the most common abdominal emergency, and the primary treatment has been appendicectomy. Antibiotics are started preoperatively and continued postoperatively as needed.
Methods This prospective study was carried out at Sher-i-Kashmir Institute of Medical Sciences, Soura, Srinagar, Kashmir, India to determine the role of antibiotics as the only treatment in acute appendicitis and the analgesic consumption needed. Total of 80 patients were included in the study with a duration of abdominal pain less than 72 h. Out of 80 patients, 40 patients received antibiotics intravenously for 2 days followed by oral treatment for 7 days, while another 40 patients considered as controls were randomized to surgery.
Results Patients managed conservatively were discharged within 3 days except for two—patients who required surgery after 12 and 24 h, respectively, because of peritonitis due to perforated appendicitis. Four patients were readmitted within 1 year as a result of recurrent appendicitis and had to undergo surgery when appendicitis was confirmed. The diagnostic accuracy within the operated group was 90%. Two patients had perforated appendicitis at operation.
Conclusion Our conclusion is that antibiotic treatment in the patients with acute appendicitis is quite effective, and these patients may not need surgery. The patients managed conservatively with antibiotics alone experience less pain and require less analgesia but have high recurrent rate.

Keywords Acute appendicitis · Peritonitis · Antibiotics · Ultrasonography

Introduction

McBurney reported his study of eight patients with acute appendicitis with special reference to early appendicectomy in 1889.[1] Coldrey in 1959[2] treated 471 unselected patients conservatively with low mortality and morbidity rates, and the idea was as controversial as it is today. Of 500 patients with suspected acute appendicitis, 425 were treated conservatively, with use of traditional Chinese medicines and antibiotics in some.[3] Seven of 100 patients at follow-up had recurrent appendicitis. In both studies, patients were assessed by history and clinical examination; the treatment differed without standardization, and there was no consecutive follow-up. The administration of preoperative antibiotic treatment can be used as a means of delaying appendectomy, particularly during twilight hours, while the incidence of perforation, complications, and hospitalization in children operated within 6 h was the same as that of those who underwent operation between 6 and 18 h after admission.[4]

Conservative management of appendiceal mass has been advocated successfully[5–11] although some recommend interval appendicectomy[5,9] in case of a cecal neoplasm or recurrent appendicitis supervenes. Conservative treatment of acute appendicitis has been described in American submariners[12] and onboard Soviet ships at sea (247

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patients).[13] There have been only a few prospective randomized trials.[14]

This prospective randomized controlled study compared the results of conservative treatment with antibiotics and surgery in patients with acute appendicitis.

Material and Methods

Patients

Eighty patients were studied between August 2003 and July 2005, with further follow-up for 1 year. The patients were randomly allocated into two groups by systematic random sampling with an equal size of 40 to maintain balance. This included 54 males and 26 females in the age group of 17–64 years. The time of onset of abdominal pain was ascertained, and patients were examined by the same surgeon before inclusion in the study. Some patient data are available in Table 1.

Patients were evaluated on the basis of modified Alvarado's Score, which includes various signs, symptoms, and laboratory findings associated with acute appendicitis.[15] This modified Alvarado's Score is summarized below:

	Points
Symptoms	
Migratory right iliac fossa pain	2
Nausea, vomiting	1
Signs	
Tenderness right iliac fossa	2
Rebound tenderness	1
Fever	1
Rovsing's sign/positive cough test/rectal tenderness	1
Laboratory findings	
Leucocytosis	2

Depending on the signs, symptoms, and laboratory findings, number of points are added and treatment decided.

Score of 1–4	Acute appendicitis unlikely
Score of 5–6	Acute appendicitis probable and patient needs observation.
Score of 6–7	Acute appendicitis definite and patients needs immediate surgery.

Ultrasonography and laboratory tests like estimation of total white blood cell (WBC) count and C-creative protein (CRP) level were used as diagnostic tools to identify patients with a high probability of acute appendicitis.[16,17] Inclusion criteria included typical history and clinical signs as described in Alvardo's score, positive findings at ultrasonography and either increased WBC and CRP values, or high CRP or WBC levels on two occasions within a 4-h interval. Ultrasound was positive in 64 (80%) patients. Computed tomography (CT) scanning of the abdomen was not done in any patient because of high cost for CT in this part of the world.

Conservative Treatment

Ciprofloxacin 500 mg 12 hourly and metronidazole 500 mg 8 hourly were given for 2 days. Patients received only intravenous fluids during this period. Pain was registered every 6 h using visual analog scale and oral temperature was measured twice daily. Patients were discharged within 3 days and received oral treatment with ciprofloxacin 500 mg twice daily and tinidazole 600 mg twice daily for 7 days

Surgery

Patients who underwent surgery were treated with antibiotics only in the event of perforation or in cases of abdominal spillage for 48 h. Operated patients were discharged once the conditions were satisfactory. Visual analog scale scores were registered every 6 h, and oral temperature was measured twice daily. The excised appendices were sent for histopathological examination.

Follow-Up

Patients were seen at 7, 12, and 30 days after admission. During the follow-up, blood sample was taken for determination of WBC and CRP levels, pain registered as visual analog scale scores, and oral temperature measured.

Methods

Compressive technique described by Puylaert[18] was applied in ultrasonography where positive findings for acute appendicitis included a diameter greater than 6 mm and a non-compressible appendix. An invisible appendix was considered as negative.

The upper limits of the reference intervals used were $9.0\times10^9/1$ for WBC and 10 mg/l for CRP levels.

Pain was registered by patients using a visual analog scale every 6 h during hospital stay.[19] Pain was also checked daily by the same surgeon with a visual analog scale score and at follow-up. This score ranged from no pain (0 mm) to unbearable pain (100 mm). Pain was treated with diclofenac sodium intramuscularly during hospitalization. Patients who

Table 1 Patient Data

	Antibiotics	Surgery
No. of patients	40	40
Mean (range) age (years)	28.7 (17–56)	32.6 (18–64)
Sex ratio (M:F)	13:7	14:6
Duration of pain (hours)	23.0 (16.4)	21.3 (14.3)
Total white blood cell count on admission (x 10^9/1)	14.2(4.9)	14.7(4.4)
C-reactive protein concentration on admission (mg/l)	43 (29)	42 (34)
Temperature on admission (°C)	37.4 (0.6)	37.6 (0.7)
Number of patients treated with antibiotics	40	8
Diclofanac sodium dose (mg)	75 [50]	200 [100]
Hospital stay (days)	23.2 (0.3)	1.2 (2.1)
Wound infection	–	3
Recurrent appendicitis	4	–
Follow-up (months)	18.3 (9.0)	18.4 (7.1.)

Values are mean (SD)

needed analgesia at home were prescribed oral paracetamol and diclofenac potassium.

Ultrasonography was performed on days 12 and 30. On ultrasonography, 38 patients treated conservatively with antibiotics alone; the appendix could be visualized in 15 symptom-free cases on the 12th day .Out of 15 patients, the appendix was still visualized after 1 month in nine patients. Four of these nine had recurrent appendicitis within a year. All conservatively treated patients with suspected recurrent appendicitis underwent surgery.

Statistical Analysis

Statistical comparisons between groups were made using Student's *t* test for uncorrelated means and within groups by use of the pairwise Student's *t* test for correlated means. Descriptive statistics was employed to characterize the data; $p<0.05$ was considered significant. The appropriate sample size was determined by considering a power of 80% and an alpha error of 5%.

Results

In all patients, there was a significant increase in CRP levels from admission to randomization and a significant decrease in WBC count.

Conservative Treatment Group

There was a significant decrease in analgesic consumption in patients managed with antibiotics ($p<0.001$) and significantly less pain was observed after 12 h of conservative treatment ($p<0.001$). Significantly lower pain scores were also noted by the surgeon. The WBC count declined significantly faster in patients treated with antibiotics, and mean temperature was significantly lower on days 1 and 2 ($p<0.05$) with not more than 0.5°C difference. However, the pattern of CRP levels in both groups was the same.

Surgery Group

Of the patients who underwent surgery, 36 patients had proven appendicitis at histological examination (Table 2). Four patients had normal appendix. Among these four patients, two patients had ruptured ovarian cyst with hemoperitoneum, while one female had pelvic inflammatory disease and one male had Meckel's diverticulitis.

Follow-Up

There was a significant decrease in pain on days 7 and 12 in patients treated with antibiotics ($p<0.01$). The WBC also continued to decrease in this group on day 7. However, no

Table 2 Histopathological Diagnosis in Patients who Underwent Surgery

Diagnosis	No. of patients
Appendicitis	
Catarrhal	7
Phlegmonous	12
Gangrenous	15
Perforation	2
Normal appendix	
Ruptured ovarian cyst with haemoperitoneum	2
Meckels diverticulitis	1
Pelvic inflammatory disease	1

difference in CRP levels and mean temperature was noted between the two groups at these visits. Three patients with gangrenous appendicitis were readmitted after 1 week of surgery because of wound infection and were treated with antibiotics for 5 days.

Four patients treated with antibiotics were readmitted with recurrent appendicitis and were subsequently operated in the same admission. Surgery was performed after a mean of 8 (range 4–12) months of conservative management. However, no chronic findings were noted at histopathological examination.

Discussion

The basic pathophysiology of appendicitis is obstruction of the lumen of the appendix followed by infection. In 60% of patients, obstruction is caused by hyperplasia of submucosal follicles. This form of obstruction is mostly observed in children and is known as catarrhal appendicitis. In phlegmonous appendicitis, there is diffused inflammation of connective tissues around the appendix due to infection. Initially, there is only inflammation and congestion of the appendix. Once the elema and congestion increases, there is interference with the blood supply resulting in gangrene of the appendix. This stage of appendicitis is known as gangrenous appendicitis.

The surgical diagnosis of acute appendicitis is customarily made on clinical grounds using history, physical examination, and white blood cell count. In the atypical patients, i.e., the patients with prolonged symptoms, inconsistent history or misleading physical examination, diagnostic studies should be helpful in establishing appropriate diagnosis[20] ultrasonagraphy and CT scan have demonstrated utility in diagnosing appendicitis. CT scan has been found 95–100% accurate in diagnosing appendicitis; as a result, routine use of CT has been advocated by some authors.[20] The study conducted by Horton et al.[20] have reported 100% specificity and 97% sensitivity with CT scan and 90% specificity and 76% sensitivity with ultrasonagraphy. In our study, ultrasound was positive in 80% patients. We did not subject any patients to CT scan because of very high cost.

Patients with suspected acute appendicitis need high diagnostic accuracy as the negative appendicectomy carries significant morbidity from wound sepsis, intestinal obstruction, pneumonia, and infertility from fimbrial damage.[21,22] Diagnostic scoring systems have been applied in order to reduce the negative appendicectomy rate as reported earlier.[15,23] There is a greater risk for abdominal adhesions after laparotomy for healthy appendices compared with that for acute appendicitis.[24,25] The appendix can be a useful conduit for reconstructive surgery (e.g., epaticoportoappendicostomy[26] or ureteroplasty[27]).

Estimation of WBC and CRP levels[16] and ultrasonography[17,28,29] may help achieve a more accurate diagnosis. The WBC was significantly decreased in both groups between the level found on admission and at randomization as previously reported.[14] During this period, the level of CRP significantly increased, emphasizing the importance of repetitive analysis in patients with suspected acute appendicitis.[14]

Probably, clinical follow-up at day 30 after antibiotic treatment is sufficient. Our study like others[14] demonstrates that 10-day antibiotic treatment is sufficient in patients treated conservatively, which is a shorter period than that described by others.[12] Conservative treatment started within 6 h of abdominal pain was not less effective as reported by others.[13]

After conservative treatment, patients were followed up until normal findings were found at ultrasonography. These results are in close agreement with those of Singh et al.[29] A mucocele can be recognized by ultrasonography.[17,30] Carcinoid, the most common tumor of the appendix,[31,32] might not have normal findings at ultrasonographic follow-up, as it is a firm solid lesion most often located at the tip of the appendix (Table 3).[31] The incidence of carcinoid is three to seven in every 1,000 appendicectomies;[31,32] the tumor occurs more frequently in women (2.5:1) and is often asymptomatic.[32]

The recurrence rate in our study correlates well with those reported by others.[2,3] However, the inclusion criteria were more liberal, and follow-up periods was short. Recurrence of appendiceal abscess after 3 months is rare.[6,7]

Conservative approach for acute appendicitis seems to be of special benefit to peripheral health centers especially in developing countries with poor health services and other areas still lacking operating facilities. Being cost effective, it can also be applied in busy emergency setups, thereby avoiding unnecessary surgery and associated morbidity and mortality. Larger studies in a larger population are needed to establish the superiority of antibiotic treatment over surgery in acute appendicitis.

Table 3 Ultrasonographic Follow-Up Findings (n=38)

Duration (days)	Appendix visualized (no. of patients)
12	15
30	09

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ORIGINAL ARTICLE

Intestinal Stem Cell Organoid Transplantation Generates Neomucosa in Dogs

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Abstract
Background and Aims Intestinal stem cell organoid transplantation generates functional intestinal neomucosa and has been used therapeutically to improve nutrient absorption and cure bile acid malabsorption in rats. We hypothesized that intestinal organoids can be harvested and transplanted to generate intestinal neomucosa in a large animal model.
Materials and Methods In group 1, 2-month old beagles (n=6) underwent autotransplantation of intestinal organoids prepared from a segment of their own ileum. In group 2, intestinal organoids were harvested from fetuses and allotransplanted into 10-month old mother animals (n=4). Tissues were harvested after 4 weeks and analyzed by hematoxylin and eosin histology and fluorescent microscopy.
Results Large numbers of viable organoids were harvested in both groups. In group 1, no neomucosal growth was identified in any of the engraftment sites after autotransplantation of juvenile organoids. In group 2, neomucosal growth with large areas of crypts and villi was identified in 11 of 12 polyglycolic acid scaffolds after allotransplantation of fetal organoids. The neomucosa resembled normal canine mucosa in structure and composition.
Conclusions Intestinal stem cell organoid transplantation can be used to generate neomucosa in dogs. This is the first report of successful generation of intestinal neomucosa using intestinal stem cell organoid transplantation in a large animal model.

Keywords Intestinal stem cell transplantation · Tissue-engineered intestine · Bioscaffolds · Polyglycolic acid

Abbreviations

ASBT	apical sodium bile-acid transporter
CFDA	carboxyfluorescein diacetate
DiI	1,1′-dioctadecyl-3,3,3′,3′-tetramethylindocarbocyanine perchlorate
DMEM	Dulbecco's modified Eagle medium
DTT	dithiothreitol
EDTA	ethylenediamine tetra-acetic acid
H&E	hematoxylin and eosin
HBSS*	Hanks' buffered saline solution
NAC	*N*-acetyl cysteine
OCT	optimal cutting temperature
PBS	phosphate-buffered saline
PEG	polyethylene glycol
PGA	polyglycolic acid

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Introduction

Massive loss of small bowel leads to a short bowel syndrome with significant morbidity, including malnutrition, diarrhea, electrolyte abnormalities, profound dehydration, and failure to thrive.[1–3] Current therapeutic options for short bowel syndrome are limited. They include total parenteral nutrition, bowel lengthening procedures, and small bowel transplantation, all of which carry significant morbidity and mortality.[4] Many patients with these conditions

could be more effectively treated if healthy mucosa were available in larger quantities as a replacement or functional supplement. Hence, methods to generate neomucosa, for example, by transplanting intestinal mucosal stem cells, represent a potentially appealing alternative.

Intestinal stem cell "organoids" are multi-cellular aggregates of intestinal mucosal progenitors and putative mucosal stem cells, which surround a core of mesenchymal stromal cells.[5] Organoids are the smallest transplantable unit of this mucosal tissue identified to date. Transplantation of intestinal organoids has been shown to generate intestinal neomucosa in rats that resembles native intestine in both structure and function.[6–11] We have recently shown that transplantation of rat ileal organoids into debrided segments of jejunum generates a "neo-ileum" that completely reverses bile acid malabsorption in rats that have undergone ileal resection.[10] In other studies, Grikscheit et al. anastomosed tissue-engineered mucosal cysts to the native intestine at the time of an 85% enterectomy in rats and showed that it reduced postoperative weight loss compared with animals that underwent only small bowel resection.[11] Based on these studies, it is clear that intestinal organoid transplantation has potential therapeutic benefits.

In spite of these successful rodent studies, successful generation of neomucosa using intestinal organoid transplantation has never been reported in large animals. In the present study, we show that the isolation and transplantation of intestinal organoids can be used to generate neomucosa in a dog model.

Materials and Methods

Animals

Beagles were obtained from Marshall Farms (North Rose, NY, USA). Animals were allowed an acclimatization period of 1 week before participation in experiments in accordance with Institutional Animal Care and Use Committee guidelines. All animals were housed in accordance with the National Institutes of Health guidelines for the care of laboratory animals, maintained under a 12-hour light/dark cycle (6 A.M. to 6 P.M.) and received standard dog chow twice a day (Nestle Purina, St. Louis, MS, USA) and water ad libitum.

Study Design

Preliminary pilot experiments were performed on three 2-month-old beagles (P1, P2, and P3) to optimize the method of intestinal organoid isolation (Table 1). We aimed to obtain clusters that were microscopically similar to those produced with our previously successful rodent protocols.[8,10,12,13]

We then conducted two different types of experiments involving autotransplantation of organoids and allotrans-

Table 1 Study Overview

Study group	Animal ID	Organoid source	Organoid labeling	Organoids implanted	Implantation location	Bioscaffold	Implantation results
Pilot	P1	Adult ileum	No	No	n/a	n/a	n/a
	P2	Adult ileum	No	No	n/a	n/a	n/a
	P3	Adult ileum	No	No	n/a	n/a	n/a
Autotransplantation	Auto-1	Adult ileum	No	Yes	Subcutaneous Tissue	None	No mucosa
	Auto-2	Adult ileum	No	Yes	Omentum	PGA	No mucosa
	Auto-3	Adult ileum	CFDA	Yes	Surgically debrided intestine	None	No mucosa
			Unlabeled control	Yes	Surgically debrided intestine	None	No mucosa
			CFDA	Yes	Chemically debrided intestine	None	No mucosa
			Unlabeled control	Yes	Chemically debrided intestine	None	No mucosa
	Auto-4	Adult ileum	CFDA/Dil	Yes	Surgically debrided intestine	None	No mucosa
			Unlabeled control	Yes	Surgically debrided intestine	None	No mucosa
			CFDA/Dil	Yes	Omentum	None	No mucosa
			Unlabeled control	Yes	Omentum	None	No mucosa
	Auto-5	Adult ileum	DsRed lentivirus	Yes	Surgically debrided intestine	None	No mucosa
			Unlabeled control	Yes	Surgically debrided intestine	None	No mucosa
	Auto-6	Adult ileum	DsRed lentivirus	Yes	Omentum	PGA	No mucosa
			unlabeled control	Yes	Omentum	PGA	No mucosa
Allotransplantation	Allo-1	Fetal intestine	No	Yes	Omentum	PGA	Mucosa
	Allo-2	Fetal intestine	No	Yes	Omentum	PGA	Mucosa
	Allo-3	Fetal intestine	No	Yes	Omentum	PGA	Mucosa
	Allo-4	Fetal intestine	No	Yes	Omentum	PGA	No mucosa

Experimental details for each subject in the pilot, autotransplantation, and allotransplantation groups are shown

plantation of organoids, respectively. In experimental group 1, *autotransplantation* experiments were performed (Table 1). Two-month-old male beagles were used as both donors for intestinal stem cell isolation and as recipients for transplantation. The group consisted of six animals (n=6), Auto-1, 2, 3, 4, 5, and 6. In experimental group 2, *allotransplantation* experiments were performed. Ten-month-old pregnant female beagles were used. The group consisted of four mother animals (n=4), Allo-1, 2, 3, and 4. Their fetal pups (gestational days 40–50) were removed via cesarean section and used as the donors for the intestinal organoid isolation. The mother animals were used as non-syngeneic recipients of the intestinal organoids. All four animals had organoids seeded onto tubularized polyglycolic acid (PGA) biopolymers (Synthecon, Houston, TX, USA), which were wrapped in omentum (Table 1).

Surgery

Animals were fasted 24 h before surgery and kept *nothing per os* from the night before surgery. All pharmaceutical drugs were obtained from McKesson Pharmaceutical (San Francisco, CA, USA) unless otherwise noted. On the morning of the surgery, each animal was sedated with subcutaneously administered acepromazine (0.025 mg/kg; Butler Animal Health Supply, Dublin, OH, USA) 1 h before anesthesia. A transdermal fentanyl patch (25 μg/72 h) was placed on the dorsal skin for perioperative pain control. After intravenous administration of atropine (0.05 mg/kg; Butler Animal Health Supply, Dublin, OH, USA) and diazepam (0.275 mg/kg), the animal was endotracheally intubated and maintained on inhaled isoflurane (0.8–2.0% in oxygen; Butler Animal Health Supply, Dublin, OH, USA) anesthesia for the duration of the procedure. Cefazolin (20 mg/kg) was administered intravenously before making the skin incision. All suture materials were obtained from Ethicon (Sommerville, NJ, USA).

Group 1—Autotransplantation

To harvest ileal organoids, a midline laparotomy was made under sterile conditions. The distal 40 cm of ileum was resected and transferred to the laboratory for ileal organoid isolation. The proximal and distal resection sites were reanastomosed to restore the continuity of the gastrointestinal tract. The animals were maintained under anesthesia while the organoid isolation was performed.

Isolation of Juvenile Organoids

Intestinal organoids were isolated using a modification of a technique described by Avansino et al.[8] In brief, the 40-cm length of excised ileum was rinsed with 1 l of pre-warmed sterile 0.9% saline, followed by 4 l of pre-warmed polyethylene glycol (PEG) (5.9% in water) (Braintree Laboratories, Braintree, MA, USA) solution to remove the large amounts of mucus present in the juvenile canine intestine. The rinsed ileum was then opened longitudinally, and the mucosa was scraped off with a glass slide and minced into pieces. The tissue was transferred to a large tissue culture flask and washed three times in calcium- and magnesium-free Hanks' buffered saline solution (HBSS*; Mediatech Inc., Herndon, VA, USA), with 100 IU/ml penicillin+100 μg/ml streptomycin (Gibco, Gaitersburg, MD, USA) and 4 mM L-glutamine (Invitrogen, Carlsbad, CA, USA). A fourth wash included 2 mM *N*-acetyl cysteine (NAC; Abbott Laboratories, Chicago, IL, USA) as a mucolytic agent. The epithelial clumps were shaken gently for 10 min at room temperature. A final wash was performed in HBSS*. The tissue was minced into ≤1 mm pieces and transferred into an HBSS* solution containing 0.1 mg/ml dispase type 1 (Roche, Indianapolis, IN, USA) and 300 U/ml collagenase type XI (Sigma, St Louis, MO, USA) and shaken on the orbital incubator at 250 rpm at 37°C for 40 min. The suspension was transferred into HBSS* with 2 mM NAC and shaken at room temperature for 5 min. The contents were allowed to sediment for 1 min, and the upper mucous layer was removed and discarded. The supernatant was transferred into HBSS* and gently inverted and allowed to sediment for 2 min. The upper mucus layer was removed and discarded and the step repeated. Two parts of this cleared supernatant were mixed with one part of Dulbecco's modified Eagle's medium (Gibco, Gaitersburg, MD, USA) to which 2% D-sorbitol (Sigma, St Louis, MO, USA), 2.5% fetal bovine serum (FBS; Hyclone, Logan, UT, USA), and 100 IU/ml penicillin+100 μg/ml streptomycin (Gibco, Gaitersburg, MD, USA) had been added (DMEM-S). The mixture was centrifuged at 1,600 rpm for 4 min at room temperature, and the supernatant was decanted. The pellet was washed in DMEM-S six times. The intestinal organoids were then seeded directly or first labeled (see below) and then seeded.

Labeling of Intestinal Stem Cell Clusters with Fluorescent Cell Markers

Carboxyfluorescein diacetate succinimidyl ester (Vybrant ® CFDA SE) and 1,1′-dioctadecyl-3,3,3′,3′-tetramethylindocarbocyanine perchlorate (Vybrant ® DiI) cell labeling solutions were obtained from Invitrogen (Carlsbad, CA, USA). The intestinal organoids were suspended at a density of 20,000 clusters per milliliter in DMEM-S and labeled for 10 min at 37°C following the manufacturer's recommendations. The suspensions were centrifuged at 1,500 rpm for 5 min at 37°C and the supernatant discarded. The organoids were gently resuspended in 37°C DMEM-S and washed three times. The

organoids were then resuspended in DMEM-S and seeded. An aliquot of organoids were left unlabeled to control for any possible adverse effect that the labeling process may have had on organoid viability. Organoid cell viability was tested with Trypan blue (Invitrogen, Carlsbad, CA, USA) exclusion.

Lentiviral Transduction of Organoids with DsRed

Intestinal organoids (20,000 clusters ~2×10^6 cells) were suspended in 600 μl of pre-warmed 37°C DMEM supplemented with 10% FBS, 100 IU/ml penicillin+100 μg/ml streptomycin (Gibco, Gaitersburg, MD, USA), and diethylaminoethyl-dextran (DEAE-dextran; 16.7 μg/ml; Amersham Biosciences, Piscataway, NJ, USA). The DsRed lentiviral transfer vector RRLsin.cPPT.hPGK.DsRed.Wpre (a kind gift from Dr. Hans-Peter Kiem, University of Washington) expresses the fluorescent protein DsRed from the internal human phosphoglycerate kinase promoter containing a woodchuck hepatitis pre-element as well as a central polyurine tract.[14] Freshly thawed and pre-warmed lentivirus in DMEM was added to the warm intestinal stem cell solution and gently inverted. The final solution volume had a final concentration of 1.08×10^6 IU of lentivirus per milliliter and 10 μg/ml of DEAE-dextran. The mixture was incubated at 37°C for 30 min with gentle inversion. The cells were then washed six times in DMEM (with 10% FBS and 100 IU/ml penicillin and 100 μg/ml streptomycin) to remove any remaining virus. The pellet was resuspended in DMEM and used for seeding. An aliquot of the transduced organoids were transferred into tissue culture for 48 h to confirm transduction efficiency.

Biopolymer Preparation and Sterilization

Non-woven sheets of PGA (2-mm thick, 95% void volume, 60 mg of PGA/ml, fiber diameter of 13 μm) were obtained from Synthecon (Houston, TX, USA). The PGA polymer sheets were tubularized into 1-cm long tubes with an internal radius of 8 mm using 6-0 Vicryl suture. The tubes were sterilized for 30 min in 80% ethanol and subsequently rinsed with 1.5 l of sterile phosphate buffered solution (PBS) (Fisher, Pittsburgh, PA). The tubes were placed into a 0.3% collagen type 1 solution in PBS (Vitrogen 100, Cohesion Tech, Palo Alto, CA, USA) for 30 min and then rinsed with PBS. They were finally vacuum-dried (Speed Vac, Savant Instruments, Farmingdale, NY, USA) for 30 min at 25°C and stored at 4°C under sterile conditions in a vacuum desiccator until use.

Intestinal Organoid Seeding

Animals underwent seeding of the intestinal organoids into (a) subcutaneous tissue (n=44), (b) omentum (n=6), (c) biopolymer scaffolds wrapped in omentum (n=15), (d) segments of mid-jejunum whose surface mucosa had been chemically debrided with perfusion of the chelating agent ethylenediamine tetra-acetic acid (EDTA; n=4), and (e) segments of mid-jejunum whose mucosa had been surgically debrided with a no. 2 surgical curette (n=10). The intestinal organoids were quantified, resuspended in DMEM-S, and seeded with a pipette at a density of 20,000 organoids per square centimeter in all graft beds (Fig. 1).

Implantation of Organoids into Subcutaneous Tissue In dog Auto-1, 44 separate 5-mm incisions were made along four rows on the back of the animal, and 20,000 organoids in 500 μl HBSS* were seeded into each subcutaneous pocket with and without matrigel.[15] The skin was closed with a 4-0 monocryl suture. The organoids were left in the subcutaneous pockets for 4 weeks. For 22 of the organoid implantations, 5 μl of India ink (Fisher Scientific, Fair Lawn, NJ, USA) were mixed with the organoid suspension to aid in the identification of the implantation site during microscopic examination.

Implantation of Organoids into Omentum In dog Auto-4, both labeled (n=3 sites) and unlabeled (n=3 sites) organoids were seeded into the omentum. The omentum was wrapped and secured around the organoids with 6-0 polypropylene suture.

Implantation of Organoids into Biopolymer Scaffolds In dog Auto-2, non-labeled organoids were seeded onto the inner lumen of three PGA tubes. In dog Auto-6, the inner lumen of PGA tubes were seeded with either DsRed

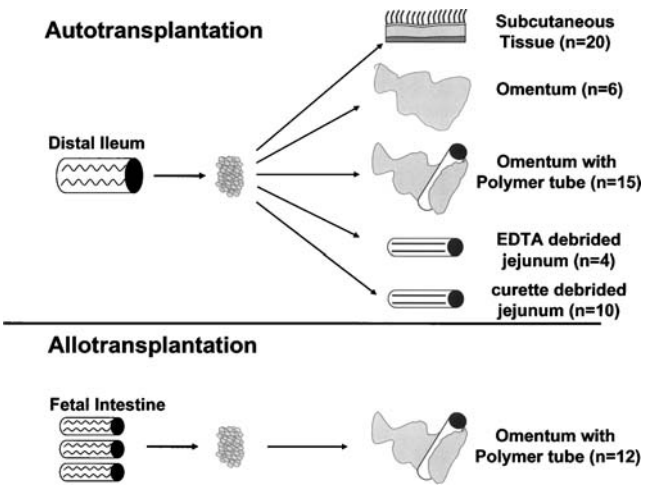

Figure 1 Experimental design. The isolation and implantation of organoids in the autotransplantation and allotransplantation groups. *Numbers in parentheses* represent total number of implantations in respective graft bed.

lentiviral vector transduced organoids (n=6 tubes) or unlabeled organoids (n=6 tubes). The seeded PGA tubes were placed on ice for 30 min to allow attachment of the organoids. The tubes were wrapped and secured in omentum with 6-0 silk suture, marked with 6-0 polypropylene sutures, and placed in the abdomen for 4 weeks (Table 1).

Chemical Debridement of Jejunal Mucosa In dog Auto-3, a 20-cm segment of jejunum 80 cm proximal to the ileocecal valve was isolated with its mesenteric blood supply intact and the continuity of the gastrointestinal tract restored by re-anastomosis. Both ends of the jejunal segment were cannulated. The mucosal epithelium from the isolated jejunum was chemically stripped using a modification of the technique described by us previously.[8] In brief, the mesenteric blood vessels were cross-clamped, and the jejunal segment was flushed vigorously with 1 l of 0.9% saline, 4 l of 5.9% PEG solution, 0.9% saline containing 1 mM dithiothreitol (DTT) for 5 min, then 1 mM DTT/27 mM citrate for 15 min and 1 mM DTT/3 mM EDTA for 60 min at a flow rate of 80 cc/min at 39°C. The debrided segment was flushed with 3 l of HBSS* (Mediatech Inc., Herndon, VA, USA) and then seeded with ileal organoids. The proximal and distal ends of the segment were sutured closed with 4-0 polypropylene suture. The segment was placed in the abdomen for 4 weeks.

Surgical Debridement of Jejunal Mucosa (Surgical Mucosectomy) In dogs Auto-3, 4, and 5 (Table 1), a 20-cm segment of jejunum 80 cm proximal to the ileocecal valve was isolated with its mesenteric blood supply intact and the continuity of the gastrointestinal tract restored by re-anastomosis. The jejunum was opened along its antimesenteric border. Using a no. 2 surgical curette, the mucosa was then scraped off. Bleeding from the graft bed was controlled by compression with gauze soaked in epinephrine solution (10 μg/ml). Then, the intestinal organoids were seeded onto the surface of the denuded intestine, the intestine was sewn closed along its antimesenteric border and its ends with a running 4-0 polypropylene suture, and the segment was placed in the abdomen for 4 weeks.

Once the intestinal organoids were seeded in the respective graft beds, the abdomen was closed in three layers.

Histology

The animals were killed 4 weeks after organoid seeding with pentobarbital overdose (100 mg/kg; Butler Animal Health Supply, Dublin, OH, USA). The seeded subcutaneous tissue, omental tissue, biopolymer implants, and intestinal tissue were harvested and cut transversely into 5-mm sections. Half of the tissue was mounted in OCT compound (Ted Pella Inc., Redding, CA, USA) and used for frozen sections. The other half of the tissue was fixed in 4% phosphate-buffered formalin for 24 h and paraffin-embedded. Frozen sections were cut (5-μm thickness) on a cryostat (Leica, Wetzlar, Germany) and mounted on glass slides. The tissue was mounted with Vectashield hard mount with 4′,6-diamidino-2-phenylindole (DAPI; Vector Laboratories, Inc., Burlingame, CA, USA) to stain the nuclei. Every tenth slide was evaluated for a fluorescent signal (DsRed, CFDA, or DiI) that would indicate engraftment of seeded cells. Immediately adjacent sections were stained with hematoxylin and eosin (H&E) and evaluated for presence of neomucosa. Likewise, paraffin-embedded tissue was mounted on glass slides, stained with H&E and evaluated for the presence of neomucosal growth.

Group 2—Allotransplantation

To harvest organoids, fetuses were obtained from an anesthetized pregnant female. A midline laparotomy and a hysterotomy were made under sterile conditions. Each fetus was removed, and its small intestine was harvested and transferred to the laboratory for organoid isolation. Then, the uterus of the mother was removed. The mother animal remained under anesthesia until the stem cell preparation was complete.

Isolation of Fetal Organoids

The intestinal organoids were isolated as described above for experimental group 1 with the following exceptions. PEG and NAC were not utilized, as the fetal intestine did not contain significant mucus. Enzymatic digestion with dispase and collagenase was performed for 25 min at 22°C.

Biopolymer Preparation and Sterilization

The PGA biopolymer tubes were prepared and sterilized as described above for experimental group 1. Due to the availability of biopolymers at the time of the individual experiments, dog Allo-1 had five biopolymer tubes implanted, dogs Allo-2 and Allo-3 each had three biopolymer tubes implanted, and dog Allo-4 had only one biopolymer tube implanted.

Intestinal Organoid Seeding

The intestinal organoids were seeded on the luminal surface of the PGA at a density of 20,000 organoids per square centimeter and implanted into omentum as described for group 1. An unseeded PGA tube was implanted as a negative control. The abdomen was closed in three layers.

The biopolymer implants were left in the abdomen for 4 weeks before retrieval.

Immunosuppression

Transplant recipients underwent induction and maintenance immunosuppression to prevent rejection of the intestinal organoids. Each animal received 250 mg of IV solumedrol intraoperatively before implantation of the fetal intestinal organoids. Starting on postoperative day 1, the animals were maintained on oral cyclosporine dosed at 100 mg twice daily (Novartis, New York, NY, USA). Animals received 500 mg methylprednisolone as an intravenous infusion immediately before cell implantation intraoperatively. Postoperative oral prednisone was tapered as follows: 20 mg per os daily × 4 days, 10 mg per os daily × 4 days, then maintenance dose of 5 mg per os daily until the end of the experiment. Systemic cyclosporine levels were checked on postoperative days 5 and 14.

Histology

The animals were killed at 4 weeks after seeding as described for group 1. All tissues were fixed in 4% phosphate-buffered formalin for 24 h and paraffin-embedded and analyzed for presence of neomucosa as described. The total amount of neomucosa per biopolymer tube was calculated by determining the percentage of the available surface area of each tube that was actually covered by neomucosa.

Results

Surgery

All animals survived to the end of the experimental period without complications.

Isolation of Organoids

In the dogs of the pilot group, the ileum used to isolate the ileal organoids contained and released large amounts of mucus during the preparation. This mucus hindered effective enzymatic digestion and release of organoids. A modified isolation protocol using PEG and NAC was devised, which effectively removed the mucus. The harvested organoids microscopically resembled the neonatal rat organoids that we have harvested in previous experiments.[8,10,12] The modified harvest protocol was used for all dogs in the autotransplantation group. An average of 1,430,000±530,000 organoids per ileum was obtained. Fetal intestine used in the allotransplantation experiments did not require the use of PEG and NAC in the digestion protocol, as the fetal intestine did not contain any appreciable mucus. The digestion yielded on average 213,000± 22,000 organoids per isolation. The organoids obtained from fetal intestine were microscopically indistinguishable from the organoids obtained from the juvenile ileum. Furthermore, when the number of organoids harvested was controlled for by weight of donor tissue, the organoid yield per gram tissue was similar between the autotransplantation and allotransplantation groups. Organoid preparations took 180 to 200 min in all cases, and there was no difference between groups. The recipients were kept under anesthesia while organoid suspensions were prepared.

Labeling of Intestinal Stem Cell Clusters with Fluorescent Markers

In dog Auto-3, an aliquot of organoids were labeled with CFDA before implantation. In dog Auto-4, aliquots of organoids were labeled with either CFDA or DiI before implantation. All organoids labeled with fluorescent vital stains were readily seen under fluorescent microscopy before implantation. Uniform staining of the organoid clusters was achieved with CFDA and DiI (Figs. 2a, b).

Lentiviral Transduction of Organoids with DsRed

In dogs Auto-5 and Auto-6, aliquots of isolated organoids were transduced with DsRed lentivirus before being implanted. Some of these aliquots were directly implanted, while others were transferred into tissue culture to confirm transduction efficiency. After 48 h in tissue culture, transduced organoids expressed the red fluorescent marker DsRed, confirming that the transduction was successful. The cells in the organoids expressed the DsRed marker with high intensity (Figs. 2c, d).

Intestinal Organoid Implantation and Explant Histology

Autotransplantation

In autotransplantation experiments, organoids were implanted into five different graft beds. In the subcutaneous tissue, no evidence of intestinal mucosal growth was observed in any of the 20 engraftment sites. The India ink particles were observed in 22 of the implants marked with the pigment, confirming that the subcutaneous tissue analyzed contained the implantation sites.

In the omentum, both CFDA-labeled, DiI-labeled, DsRed-lentivirus-labeled, and unlabeled control cells were seeded. Groups of DiI- and CFDA-labeled cells were identified in the graft beds by fluorescent microscopy.

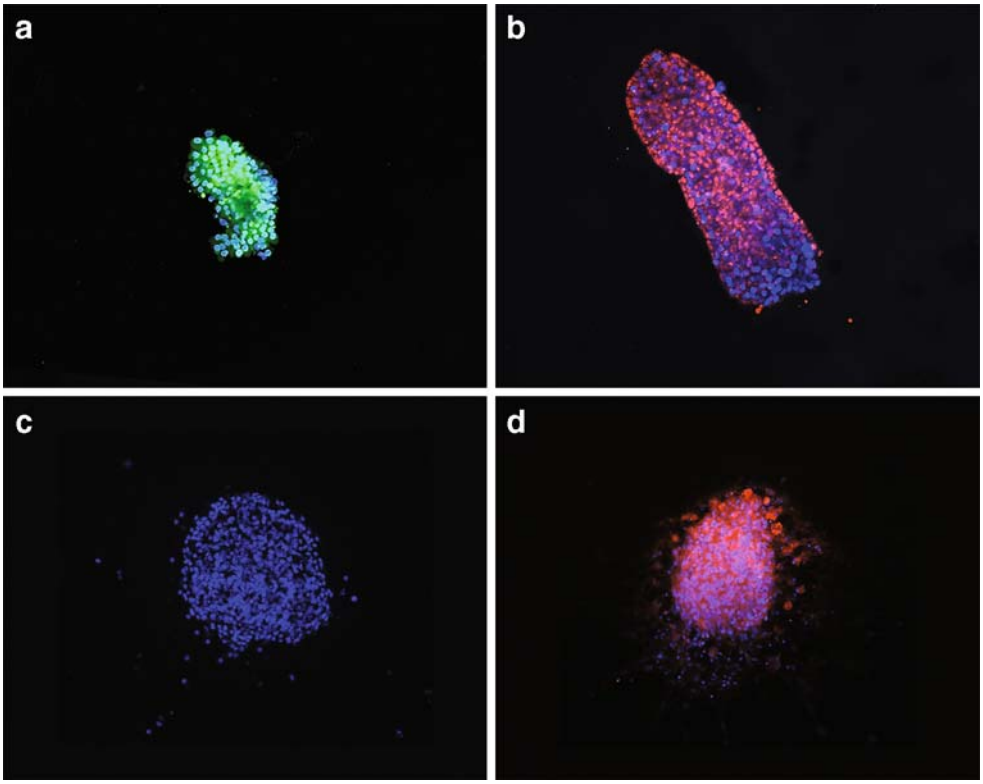

Figure 2 Fluorescent labeling of ileal organoids. In autotransplantation experiments, organoids were successfully labeled with **a** CFDA, **b** DiI, or transduced with DsRed Lentivirus. The organoids expressed DsRed after 48 h in tissue culture (**c** 0 h, **d** 48 h). All slides at ×20 magnification.

However, H&E analysis did not reveal any intestinal mucosa (Figs. 3a–c). Examination of the 15 PGA biopolymer tubes that were wrapped in omentum also did not reveal any mucosa. The lumens of the tubes were obliterated, and the scaffold material revealed abundant inflammatory cells and multinucleated giant cells (Fig. 3d).

Chemical debridement of the intestine with 60 min of EDTA perfusion resulted in the dislodgement of approxi-

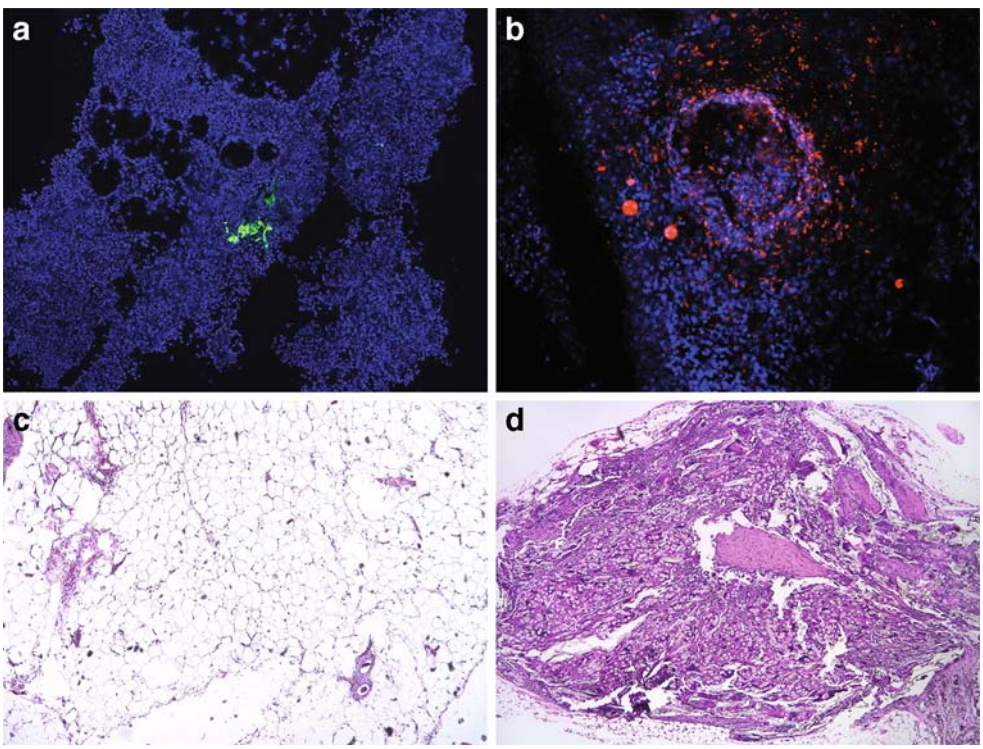

Figure 3 Organoid implantation into omentum in autotransplantation. Fluorescent (×10, *top*) and H&E (×4, *bottom*) images are shown. Groups of CFDA (**a**) and DiI (**b**) labeled cells were present in the omentum. However, H&E analysis showed absence of intestinal mucosa (c). PGA biopolymer tubes wrapped in omentum revealed no intestinal mucosa (**d**).

mately 80% of the crypt mucosal cells from the basement membrane. This amount of debridement had been shown to produce an excellent graft bed in rodents.[8,12] In dog Auto-3, organoids had been implanted into graft beds that were debrided in this way for 60 min. In sites where labeled organoids had been seeded, some fluorescent cells were observed. However, these fluorescent cells did not co-localize to the DAPI-stained mucosa. This indicated that the regeneration of mucosa in these debrided areas was not the result of organoid engraftment but, rather, restitution from the remaining quantities of native mucosa (Fig. 4a).

A total of ten (n=10) aliquots of organoids were seeded into surgically debrided intestine (Auto-3, Auto-4, and Auto-5). In all sites that were seeded with unlabeled ileal organoids, there was no presence of ileal bile acid transport protein staining by immunostaining with anti-ASBT antibody that cross-reacts with the dog transporter, which might have indicated successful engraftment of ileal organoids.[8,16] In sites where labeled organoids had been seeded (DiI, DsRed), no engraftment of fluorescent cells was observed 4 weeks (Figs. 4b, c).

Allotransplantation

Animals had cyclosporine levels drawn on postoperative days 5 and 14. The levels were within therapeutic range (blood concentrations of 400–600 ng/ml), and no dosing adjustments were necessary. After 4 weeks, H&E histology revealed the presence of intestinal mucosa in 11 of 12 biopolymer tubes. Only the one biopolymer tube implanted into Allo-4 failed to generate neomucosa. On gross examination, the biopolymer tubes were completely enveloped with omentum with clearly visible, well-developed blood vessels entering the bioscaffolds. The lumen of 11 of the 12 biopolymer tubes, which proved on histology to have intestinal neomucosa, grossly had large amounts of mucus. On histology, the intestinal mucosa was indistinguishable from native dog intestine in structure and composition, with fully formed crypts and villi (Fig. 5). The enterocytes-and mucus-producing goblet cells were present in the same location and proportions as in native intestine. Furthermore, an extensive submucosal smooth muscle layer was generated, which resembled the native submucosal muscle layer.

Each 1-cm^2 long PGA scaffold had a total available surface area of 502.4 mm^2 (internal surface area of each tube=$2\pi rh$, where r=8 mm and h=10 mm). In the 11 of 12 biopolymer scaffolds in which neomucosa was observed, an average of 303 mm^2 per tube of neomucosa was generated. The unseeded control biopolymer tubes demonstrated fibrovascular ingrowth without any evidence of intestinal mucosa.

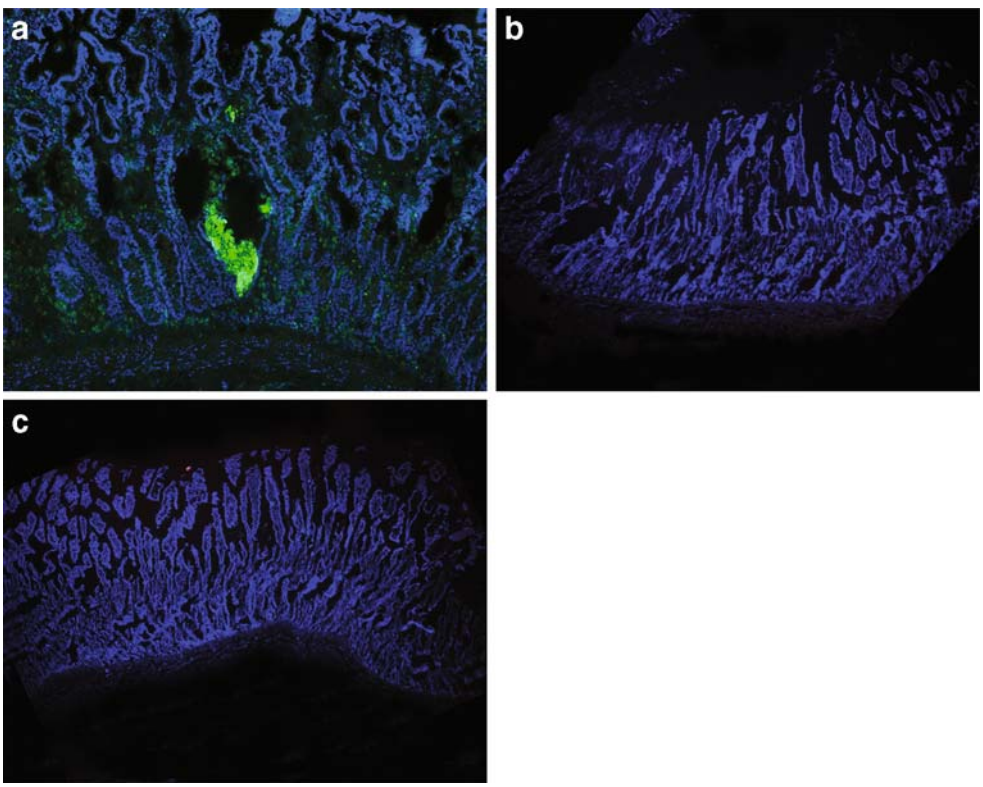

Figure 4 Organoid implantation into denuded intestine in auto-transplantation. In chemically debrided intestine, groups of CFDA labeled cells were observed; however, the signals did not colocalize to the DAPI-stained enterocytes (**a**; ×10). In surgically debrided intestine, no DiI (**b**) or DsRed (**c**) labeled cells were identified in the graft beds (×2.5).

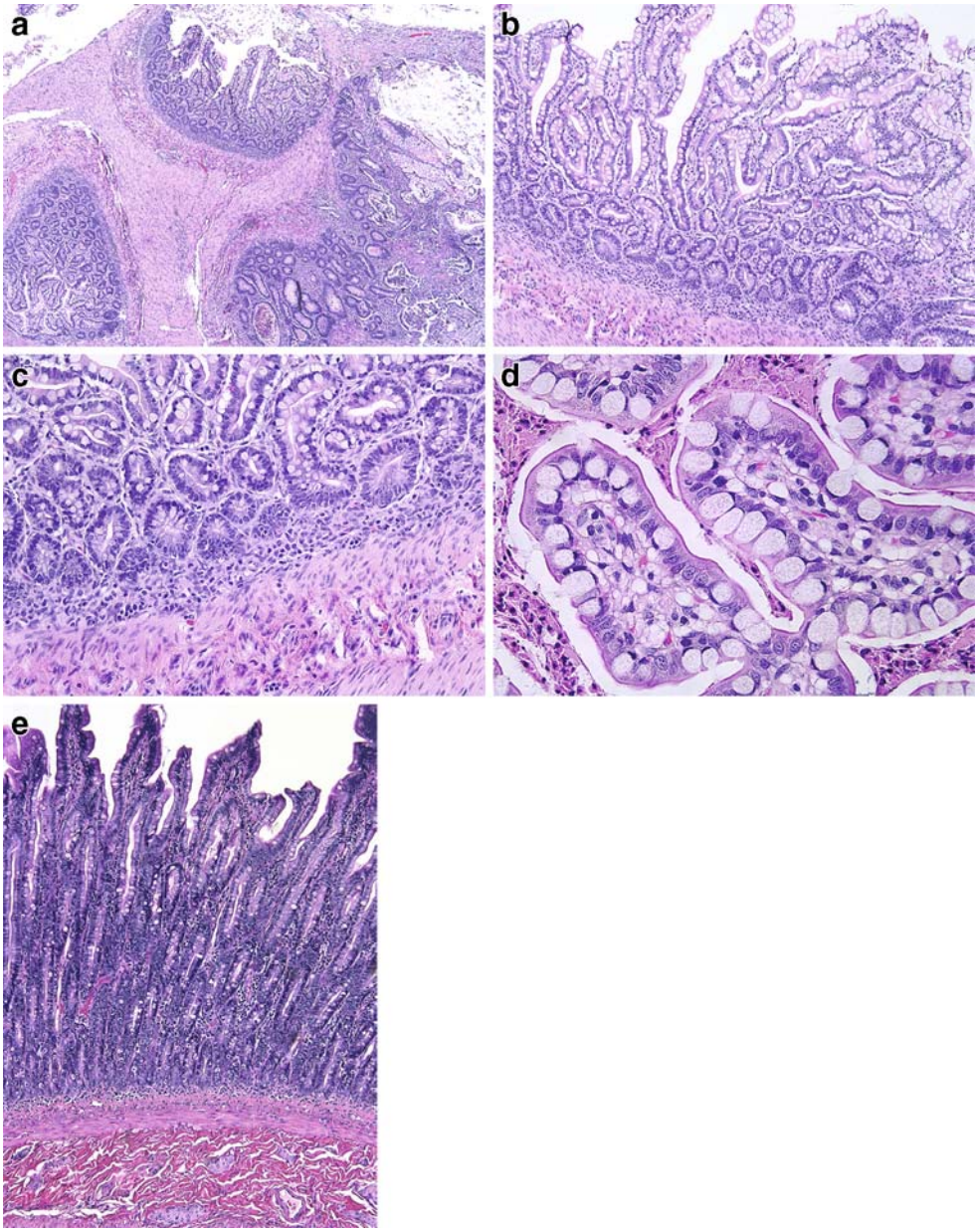

Figure 5 Neomucosal growth in allotransplantation. Neomucosa generated on PGA biopolymer tubes (**a**) resembled normal canine intestine in both structure and composition. Fully developed crypts and villi were present with proportions of enterocytes and goblet cells (**b**–**d**) similar to normal intestine (**e**).

Discussion

This study represents the first report of the successful generation of intestinal neomucosa using intestinal organoid transplantation in a large animal model. There have been several recent reports of generation of an intestinal mucosal layer in dogs. In these studies, mucosal defects were created in the small bowel and then bridged by decellularized, porcine-derived small intestinal submucosa or an acellular collagen sponge. These scaffolds then became epithelialized from the adjacent native mucosa.[17,18] However, this regenerated mucosa was not the result of organoid transplantation; rather, it reflected the remarkable wound healing capacity of the intestinal epithelium when a mucosal injury or defect is created. The ability of intestinal mucosal stem cells to divide and generate more mucosal surface area in response to either injury or to loss of mucosal surface area is well known.[19–23] There has been some thought that, perhaps, regeneration of intestinal mucosa on biopolymer scaffolds in this way can generate large amounts of mucosal surface area. However, there are limits to the amount of mucosal regeneration that can take place in response to mucosal injury or loss, and these repair mechanisms cannot replace larger stretches of lost intestine. Loss of intestine leads to mucosal hypertrophy and that results in some functional compensation.[24] However, loss of 70–75% of the small intestine overwhelms this intestinal adaptation response and leads to short bowel syndrome.[4] With organoid transplantation, the amount of intestinal mucosa that can be generated would, in principle, not be

similarly limited. In the future, it may be possible to amplify the intestinal stem cell clusters in vitro to generate vast amounts of intestinal neomucosa.

In this present study, we optimize methods of intestinal organoid isolation from canine juvenile ileum as well as fetal intestine. With both isolation techniques, we were able to obtain large amounts of viable intestinal organoids. When fetal intestinal organoids were allotransplanted onto PGA biopolymer tubes, a significant amount of intestinal neomucosa was generated. This neomucosa resembled native canine intestine in structure and composition. There were the normal proportions of enterocytes and goblet cells, and we observed the development of a well-formed submucosal muscle layer similar to the native canine intestine. In contrast, autotransplantation of juvenile organoids into different graft beds (subcutaneous tissue, omentum, biopolymer scaffolds, and debrided intestine) failed to produce intestinal neomucosa in any of the engraftment sites.

In the autotransplantation experiments, the recipient bed preparation techniques were chosen based on our previous experience with successful organoid transplantation in rodent models. The omentum has been well established to support the growth of intestinal neomucosa after organoid transplantation in rodents.[11,13,25–27]. Furthermore, we have previously reported successful intestinal resurfacing in rodents.[8] In these autotransplantation experiments, a total of 79 seeding experiments were performed with intestinal organoids that were either unlabeled or labeled with different vital stains. In organoids labeled with DiI or CFDA, we observed strong staining of the organoid clusters at the time of seeding. After 4 weeks time, many recipient graft beds still contained fluorescently labeled cells. However, the pattern of fluorescence did not suggest the presence of intestinal mucosa, and subsequent H&E staining confirmed its absence. It is possible that these fluorescently labeled cells represent the persistence of a mesenchymal component of the organoids. A weakness of our studies may be that no further tests were performed to investigate the ratio of labeled mesenchymal and labeled mucosal cells. Thus, we cannot exclude the possibility that rare non-labeled mucosal cells engrafted into a recipient bed but eluded detection. However, in our experiments, the stained cells were mainly used as a guide to help us focus where we would expect to find neomucosa in the recipient segment. The ultimate determination of the presence of neomucosa was made by analysis of H&E-stained slides. In these slides, we specifically looked for mucosal cell formations in the graft beds. In all of the experiments where the organoids were labeled with vital stains, an aliquot of unlabeled organoids was implanted. Since neomucosa was not found in any of these control engraftment sites, it is unlikely that the labeling of organoids itself affected the long-term viability or the implantation of the organoids.

In contrast to the autotransplantation experiments where juvenile organoids were used, the use of fetal intestinal organoids transplanted onto PGA biopolymer tubes generated neomucosa in almost all samples. Only the one PGA tube implanted into Allo-4 failed to generate neomucosa. This is not easily explained; it is unlikely that this lack of engraftment was due to rejection, since there was no histologic evidence for this. In this experimental series, we chose to transplant the organoids onto PGA tubes wrapped in omentum, since this had developed into a gold-standard for testing of neonatal organoids in rodents in our laboratory during the time period the dog studies were conducted. We avoided cell labeling in this case as a possible confounding factor, since any mucosa grown in the confined luminal space of the PGA tube would evidently be derived from the transplanted organoids.

Why autotransplantation of juvenile organoids failed to generate neomucosa whereas allotransplantation of fetal organoids succeeded is not easily explained. However, this result is comparable to previous experience in rodents[5,7] (Stelzner, unpublished data). As noted above, generation of small intestinal neomucosa has been reported in different animal species previously when neonatal donors were used. In contrast, successful use of adult organoid donors has never been reported in the literature to our knowledge. It is therefore conceivable that juvenile or adult small intestinal canine organoids do not give rise to a neomucosa, e.g., because they are in some way too differentiated. However, this hypothesis would have to be addressed in future studies.

In both groups, large amounts of organoids were harvested, and equal amounts were seeded onto similar graft beds. It is conceivable that the fetal intestinal organoids are more primitive and more vigorous than the juvenile intestinal organoids. Evidence to support this assumption for enterocytes is sparse, but Guillot et al. has recently shown that fetal mesenchymal stem cells express more pluripotency markers, have longer telomeres, and are more readily expandable and senesce later in culture than their adult counterparts.[28,29]. The present pilot study has additional limitations since the autotransplantation group is in other aspects not comparable to the allotransplantation group. For example, it is possible that the immunosuppressive medications enhanced organoid implantation or acted as a growth stimulus for the mucosa. Investigation of such drug actions would have exceeded the scope of this study of and would need to be further elucidated.

We have demonstrated in this study that generating intestinal neomucosa with organoid transplantation is feasible in large animals. As with any potential clinical therapy, demonstration of a “proof of principle” is generally

accepted as an important milestone before considering human studies. Some obstacles still remain before intestinal organoid transplantation could be used for therapy in human applications such as the treatment of short bowel syndrome or malabsorption syndromes. Currently, no methods exist to successfully harvest and transplant adult intestinal epithelial stem cells, which would appear more widely applicable than transplantation of fetal cells.[5] The lack of availability and banking of neonatal or fetal cells from human donors also currently limits the feasibility of this approach for clinical applications. This is not different from several other areas of stem cell transplantation. Furthermore, intestinal organoid transplantation only generates the intestinal *mucosal* layer. Recently, Nakase et al.[30,31] reported that transplantation of smooth muscle cells onto collagen sponge scaffolds results in generation of both an intestinal smooth muscle layer as well as enteroendocrine cells and nerve tissue in the tissue-engineered small intestinal segment. However, generation of a functional, peristaltic neuromuscular unit has still not been reported. Finally, a very large number of transplantable cells would need to be available before attempts at producing bioengineered human intestinal mucosa can be made. In our previous rat model, we were able to produce enough neomucosa using organoid transplantation to cure a clinical malabsorption syndrome.[10] This is very encouraging; however, good methods to amplify the stem cell mass to bioengineeer adequately large neomucosal segments in humans are not yet available. A concerted effort to make progress in these areas is necessary for intestinal organoid transplantation to become part of our clinical armamentarium.

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ORIGINAL ARTICLE

Somatostatin Limits Intestinal Ischemia-Reperfusion Injury in Macaques via Suppression of TLR4-NF-κB Cytokine Pathway

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Abstract
Objective Intestinal ischemia-reperfusion (IIR)-induced gut injury remains a challenge for critically ill patients despite the oxidative stress theory that has been elaborated. This study aimed to test whether Toll-like receptor 4 (TLR4) is involved in gut injury during IIR and whether somatostatin (SST) affects TLR4-nuclear factor-κB (NF-κB) cytokine pathway in the intestinal mucosa of macaques.
Design Fifteen macaques were randomized into control, IIR, and SST + IIR groups. Pieces of isolated ileal epithelium from each animal were incubated with lipopolysaccharide (LPS), interferon-γ, or SST. Expression of TLR4 and NF-κBp65 was evaluated by immunohistochemical staining, Western blot analysis and reverse transcription polymerase chain reaction. Cytokine levels were measured by ELISA. Radioimmunoassay was used to determine of SST levels.
Measurements and Main Results Significant overexpression (IIR vs control) of ileal TLR4 (0.17±0.03 vs 0.05±0.02), NF-κBp65 (0.55±0.11 vs 0.15±0.05), and TNF-α (213.2±29.2 vs 56.0±10.04) after IIR was greatly decreased ($p<0.05$) by prophylactic use of SST (TLR4: 0.06±0.02; NF-κBp65: 0.26±0.09; TNF-α: 97.1±32.3) in vivo. TLR4 expression in the ileal epithelium treated with LPS and SST (1,330±93) was significantly lower than that in the ileal epithelium treated with LPS alone (2,088±126) in vitro. SST levels in plasma (3.67±0.41 ng/ml) and ileal mucosa (1,402.3±160 ng/mg protein) of the IIR group were significantly lower than those (6.09±1.29 ng/ml, 2,234. 8±301.8 ng/mg protein) in the control group ($p<0.05$).
Conclusions Endogenous SST is a crucial inhibitor of massive inflammatory injury in the intestinal mucosa via direct suppression of the TLR4-NF-κB cytokine pathway induced by LPS in ileal epithelium. IIR attacks caused shortages of endogenous SST in the plasma and intestinal mucosa of macaques in this study. Therefore, preventive supplements of SST may limit intestinal injury of macaques by IIR.

Keywords Somatostatin (SST) · Toll-like receptor 4 (TLR4) · NF-κB · Intestinal ischemia-reperfusion (IIR) · Macaques · Cytokine

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Critically ill patients are susceptible to injury of the intestinal mucosa, changes in gut permeability, and failure of intestinal defense mechanisms. These conditions put patients at risk of infection and multiple organ dysfunction syndrome (MODS).[1] It has been reported that the splanchnic circulation is particularly vulnerable to hypoperfusion, as occurs with low-flow states such as hemorrhagic shock, infection, acute pancreatitis and transplantation.[2] The mechanisms underlying intestinal ischemia-reperfusion (IIR)-induced gut injury are likely to be complex and multifactorial, although the oxidative stress-nuclear factor-κB (NF-κB) pathway has been considered to play a major role in the pathogenesis of lesions in the intestinal mucosa barrier.[3,4]

The intestinal epithelium is continually exposed to diverse bacteria and bacterial products. The biological response to endotoxins is mediated through the Toll-like receptor 4 (TLR4)-MD-2 receptor complex (TLR4 complex), which results in NF-κB activation and the release of cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-α TNF-α.[5,6] Despite the density of commensal bacteria and their products in the intestinal epithelium, the host has evolved various mechanisms of tolerance to these organisms that allow a peaceful coexistence with resident bacterial flora. However, it is not clear whether TLR4, which is involved in the initiation of the host immune response to microorganisms, is essential for the control of the innate immune responses involved in gut injury during IIR.

Although stimulators for the expression of TLR4, such as lipopolysaccharide (LPS) and cytokines, have been widely reported,[7–9] the regulation of TLR4 expression is still largely unknown. Somatostatin (SST), a multifunctional neuropeptide, is widely distributed in the central nervous system and gastrointestinal tract. Its suppression of the downstream agents of the TLR4-NF-κB pathway, such as IL-1, IL-6, TNF-α, in a paracrine fashion,[10,11] suggests that SST may also inhibit the expression or activation of TLR4 or NF-κB, the upstream molecules of these cytokines. It would be wise to control the initiators of the cytokine cascade rather than suppress cytokines in the later stage of the cascade in attempts to prevent the maladaptive outcomes of innate immunity during an IIR attack. In addition, our previous study has shown that SST ameliorates the development of MODS via suppression of intestinal mucosal mast cells.[12] These results suggest a probable shortage of endogenous SST in the intestinal mucosa of critically ill patients.

Various intervention studies on IIR or MODS have been widely performed in rodent animal models.[13] Discrepancies between species have limited the application of some of this new knowledge in clinical practice. The resemblance of macaques to humans, in regard to anatomy, physiology, and biochemical metabolism, makes these nonhuman primates suitable experimental animals for investigating the pathophysiology of diseases relevant to humans. Therefore, to provide more useful suggestions for the clinical prevention of MODS, a macaque IIR animal model was used in this study.

This study aimed to investigate (1) whether TLR4 is essential for the control of innate immune responses to gut injury during IIR, (2) whether endogenous SST is an inhibitor of the expression or activation of the TLR4-NF-κB cytokine chain, (3) whether endogenous SST is low in ileal mucosa and plasma during critical states of illness, and (4) whether preventive supplements of SST may limit the massive inflammatory injures induced by IIR attacks.

Materials and Methods

Experiment Animals

Healthy adult rhesus macaques (4–7 years, body weight 6.9±1.7 kg, male/female=9/6) were obtained from the Animal Center of Sichuan University. All macaques were maintained in the facility after a quarantine inspection. The experiments in this study were performed in accordance with the guidelines of the Sichuan University Institutional Animal Care and Use Committee. All animals were fasted for 12 h, kept in an environment at a temperature of 20~22°C with alternative illumination every 12 h, and drinking water was withdrawn 2 h before the experiment began.

Surgical Procedures of IIR in Macaques

Animals were anesthetized with xylazine (0.2 ml/kg, i.m.) and maintained with diazepam (0.1 ml/kg, i.v.) and carbrital (30 mg/kg, i.v.) as needed. A catheter was placed in a peripheral vein to infuse 0.9% saline and 20 g glucose (0.1~0.2 ml/kg/min, i.v. gtt) for 24 h. Animals were given a midline laparotomy of 5 cm in length. Then, the superior mesenteric artery (SMA) was isolated and occluded with a microsurgical clip. After occlusion for 1 h, the clip was removed, and intestinal perfusion was reestablished. The animals were not given special volume resuscitation during and after the SMA occlusion, and infusion of saline and glucose was maintained at the same speed as mentioned above. Venous blood samples were taken again, and the animals were killed 24 h after IIR via removal of the vital organs.

Experimental Grouping

Fifteen macaques were randomly divided into three groups, with five animals (male/female=3/2) in each group. For the control group, animals underwent a sham operation with the same treatment mentioned above, except the IIR procedure was not performed. In the IIR group, animals underwent an IIR procedure. In the SST + IIR group, SST-14 (Serono Singapore Pte Ltd, Singapore) was given to animals intravenously with a syringe pump at a dosage of 5 μg/kg/h from 5 min before occlusion of the SMA until the end of the experiment. The dosage (5 μg/kg/h) of SST was referred from the recommendation of 250 μg/h for human being.[14] Other treatments for this group were the same as those in the IIR group.

Morphological Evaluation of Macaque Intestine

Specimens from the terminal ileum (5 cm from the distal end of the ileum) and the right colon were taken from each

animal and fixed with 10% formaldehyde. After embedding these specimens in paraffin, sections were cut and then stained with hematoxylin and eosin for histological evaluation in a single-blinded fashion. For semiquantitative evaluation of lesions, ten arbitrary microscopic fields were viewed in each sample. The scoring system was based on the area of the inflammatory lesion: +, <1/3 total area; ++, 1/3–2/3 total area; and +++, >2/3 total area.

Visualization of TLR4, MD2, and NF-κBp65 by Immunohistochemistry

Sections of the terminal ileum and the right colon were deparaffinized and treated in a microwave for 15 min. For nonspecific blocking, 10% goat sera was added, and sections were incubated for 20 min at room temperature, then the following polyclonal antibodies were added into individual sections: rabbit anti-human TLR4 (1:100), rabbit anti-human MD2 (1:100), and rabbit anti-human NF-κBp65 (1:100; Santa Cruz Biotechnology Inc, CA, USA). After incubation with polyclonal antibodies for 120 min at 37°C and overnight at 4°C, the sections were stained with a ready-to-use streptavidin-catalase immunohistochemical reagent system as a detection reagent. Color reactions were developed with diaminobenzidine (DAB; Zhongshan Bioagent Company, Beijing, China). A semiquantitative immunohistochemical analysis of raw data with Image-Pro Plus 4.0 software was used to score integrated optical density (IOD) from the nuclear area of ileal epithelium. Each value was the mean ± SD of five visual fields in which duplicate measurements were made.

Isolation of Intestinal Mucosa Epithelial Cells

Epithelial cells from the intestinal mucosa of animals in the control group were isolated in accordance with previously described procedures.[15,16] Briefly, the dissected terminal parts of the ileum were immediately placed in cold Hanks fluid and 1 mM DTT for 15 min to remove mucus. Then, samples were cut into small pieces and put into 20 ml EDTA and 10 mM D-Hanks fluid (pH 7.4). The bottle was shaken for 10–20 min at 37°C. After sediment from the tissue samples had settled, the supernatant was collected, filtered, and then centrifuged three times at 4°C, 1,500 rpm for 5 min. The supernatant was discarded, and the sediment was gently resuspended in cold Hanks fluid. With this procedure, more than 95% of cells were identified as mucosal epithelial cells which were confirmed by alkaline phosphatase rapid staining. The positive staining for intestinal epithelia cells was indicated as gray-black cell membrane. The cells were shown to be alive by negative staining with 0.2% Trypan-blue. The culture durations of isolated cells were usually limited ≤ 24 h before the experiment in vitro. Their viability could be guaranteed for 2~3 days and was checked again at the end of following experiments.

Quantification of TLR4, MD2, and NF-κB with Western Blotting

Protein was extracted from isolated ileum epithelial cells in accordance with Kaiser's method.[17] The extracted protein (30 μg) was incubated in loading buffer and heated at 100°C for 10 min. Samples were loaded onto an 8% sodium dodecyl sulfate-polyacrylamide gel, then transferred to nitrocellulose (65 mA, 90 min), and the nitrocellulose was incubated with rabbit polyclonal TLR4 antibody (1:500), MD2 (1:500), or NF-κBp65 (1:1,000), at 4°C overnight. Filters were then washed three times in blocking solution and incubated with horseradish peroxidase-linked immunoglobulin followed by exposure to an enhanced chemiluminescence Western blot luminal reagent (Promega Biosciences Inc, San Luis Obispo, CA, USA) and exposed to photographic film. Band densities were quantified using Quantity One software 4.5.0 (Bio-Rad Laboratories, Hercules, CA, USA). Each value was expressed as the ratio of the IOD of the TLR4, MD2, or NF-κB band to that of β-actin.

Cytokines Measured by Enzyme-Linked Immunosorbent Assay

Plasma and intestinal levels of IL-1β, IL-6, and TNF-α were measured by an enzyme-linked immunosorbent assay (ELISA) kit (Senxiong Company, Shanghai, China). The plasma levels of cytokines were normalized as picograms per milliliter. The ileal concentration of cytokines was normalized as picograms per gram of protein.

Table 1 The Sequences of Primers and PCR Products

mRNA	Sense	Antisense	Size(bp)
TLR4	TGCAATGGATCAAGGACCAGAGGC	GTGCTGGGACACCACAACAATCACC	449
MD2	GAAGCTCAGAAGCAGTATTGGGTC	GGTTGGTGTAGGATGACAAACTCC	422
IL-1β	AAACAGATGAAGTGGTCCTTCCAGG	TGGAGAACACCACTTGTTGCTCCA	388
TNF-α	AGGGCTCCAGGCGGTGCTTG	TGGTAGGAGACGGCGATGCGG	418
β - actin	CACCACACCTTCTACAATGAGC	GTGATCTCCTTCTGCATCCTGT	695

Table 2 The Inflammatory Lesion Scores in Three Groups

Group	M/F	+	++	+++
Control	3/2	44	6	0
IIR	3/2	7*	23*	20*
SST + IIR	3/2	30**	14**	6**

M male, *F* female
*$p<0.05$ vs control, **$p<0.05$ vs IIR group

Detection of mRNA for TLR4, MD2, IL-1β, and TNF-α with the Reverse Transcription–Polymerase Chain Reaction

Total RNA was extracted from isolated ileum epithelial cells using the TRIZOL reagent (Roche, Burlington, NC, USA). Quantification and purity of extracted RNA were determined by the ratio of absorbance at 260 and 280 nm (A260/A280), which was ensured to be between 1.8 and 2.2. Reverse transcription (RT) and polymerase chain reaction (PCR) amplification were conducted by using PTC-100 PCR (Bio-Rad Laboratories Inc, Hercules, CA, USA). In accordance with the protocols of RT–PCR core kit (TaKaRa, Shiga, Japan). The sequences of primers and PCR products are listed in Table 1.

After denaturation of samples at 94°C for 1 min, PCR was carried out for 40 cycles (94°C for 30 s, 55°C for 30 s, 72°C for 60 s). The amplification was terminated by a final extension step at 72°C for 2 min. A positive control (human small intestine RNA) and an internal control (β-actin) were amplified at the same time. PCR products were quantified by running them on a gel and scanning the gel in an imaging system (Bio-Rad Gel Doc 2000). The data were normalized as a ratio of gray scale (IOD) of objective band over β-actin.

Effects of LPS, IFN-γ and SST on Ileal TLR4 Expression and Cytokine Levels In Vitro

Isolated ileum epithelial cells were incubated in DMEM medium (10% bovine serum, 100 U/ml penicillin, 100 U/ml streptomycin, 10 U/ml gentamycin) at 37°C for 3 h and grown in a six-well plate with 1×10^6 cells/ml in each well.

The isolated ileum epithelial cells were incubated separately with (1) LPS (10 μg/ml; Sigma, St Louis, MO, USA); (2) IFN-γ (20 ng/ml; Roche, Indianapolis, IN, USA); (3) SST-14 (2.2 μM/ml, Sigma); (4) LPS (10 μg/ml) + SST (2.2 μM/ml); (5) LPS (10 μg/ml) + IFN-γ (20 ng/ml); and (6) LPS (10 μg/ml) + IFN-γ (20 ng/ml) + SST (2.2 μM/m) for 24 h. Control wells were incubated with DMEM medium only. After incubation, the supernatant of each well was collected to measure TLR4 and cytokines by Western blotting, RT–PCR and ELISA.

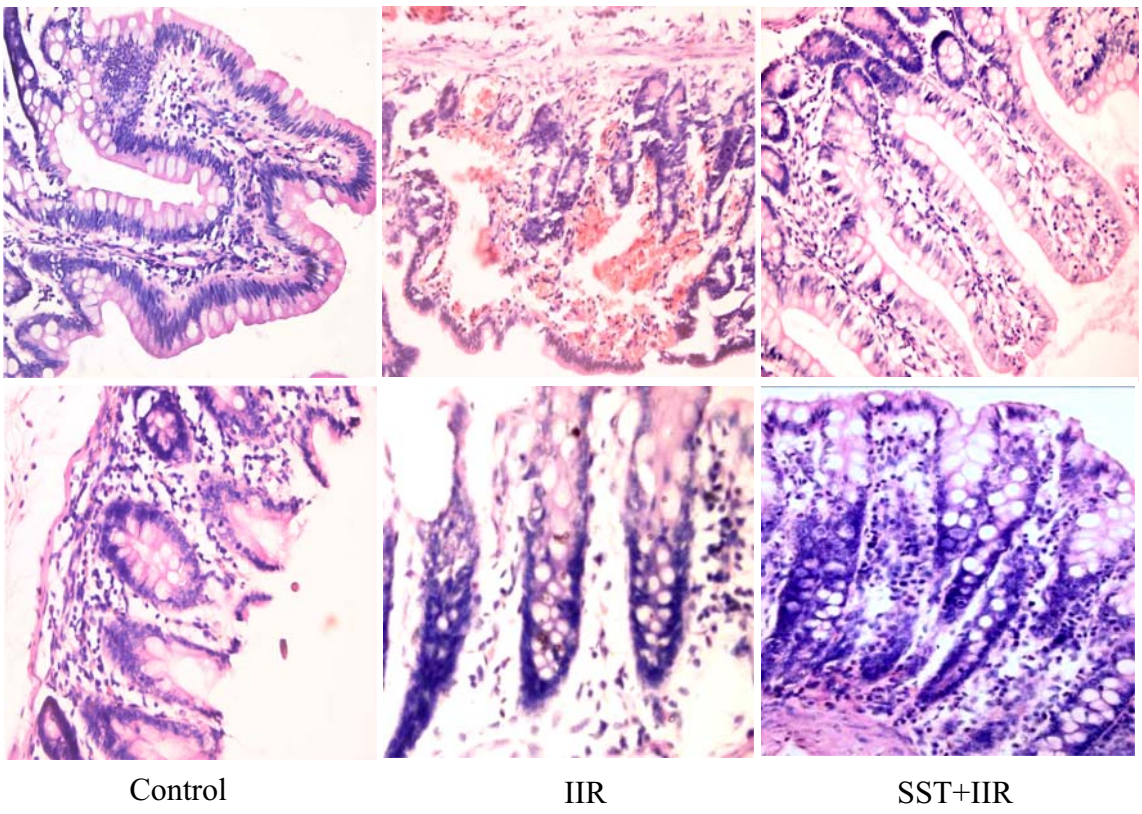

Figure 1 Histological sections of ileum (*upper line*) and right colon (*lower line*) from the three groups (Haematoxylin and Eosin stain, ×400).

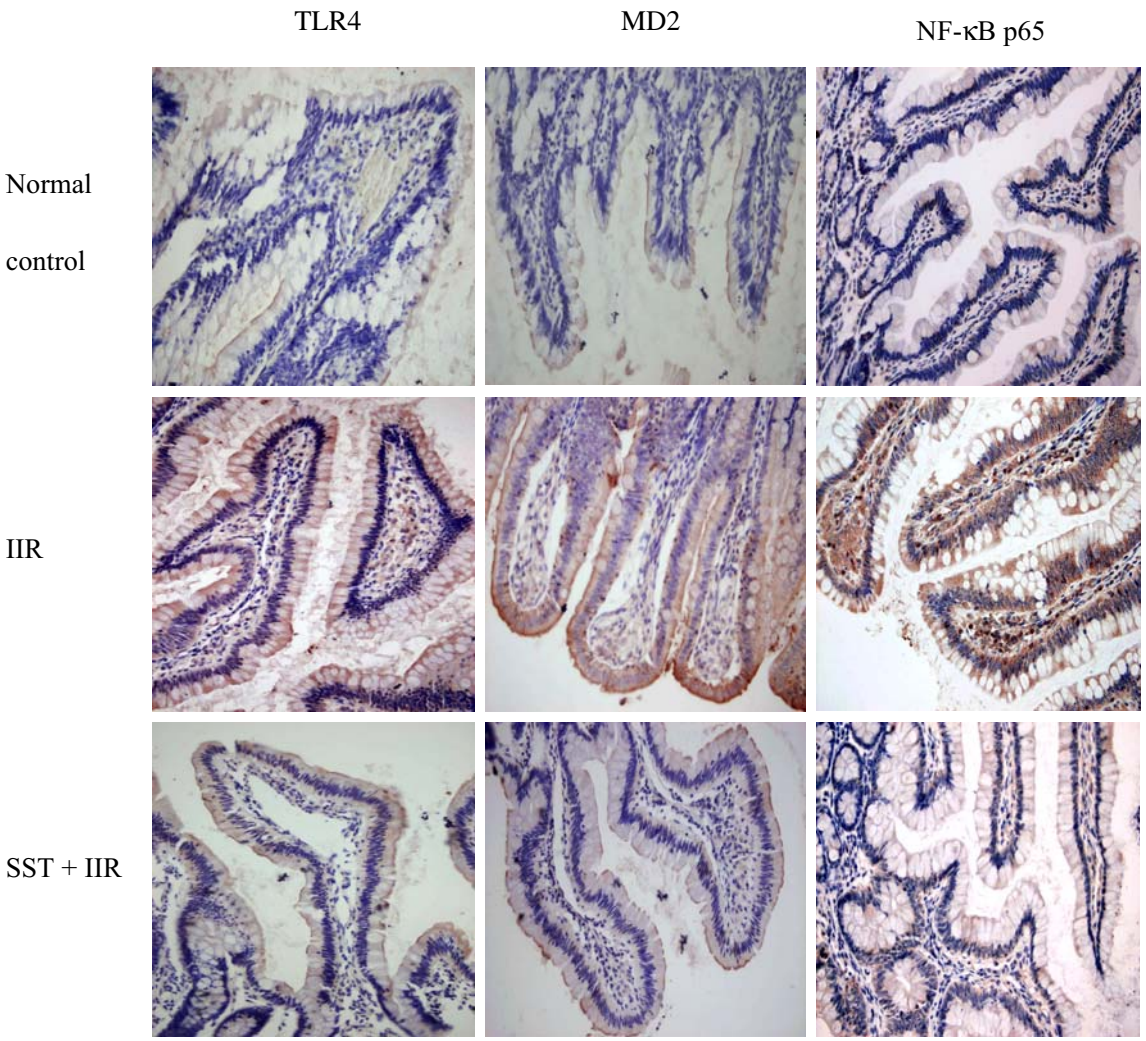

Figure 2 Expression of TLR4, MD2 and NF-κBp65 in the ileal epithelium of macaques (Immunohistochemical stain, ×400).

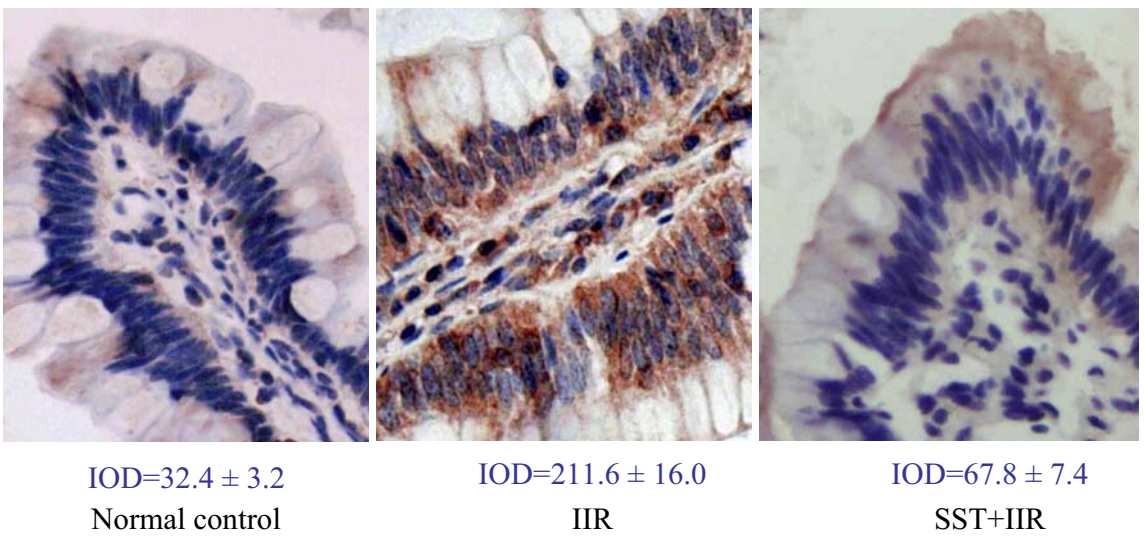

Figure 3 Visualization of NF-κBp65 in the nuclei of ileal epithelia (Immunohistochemical stain, ×800). Compared to the normal control group or SST + IIR group, much stronger positive staining for NF-kBp65 was not only showed in the cytoplasm but also visualized in the nuclei of ileal epithelia in IIR group.

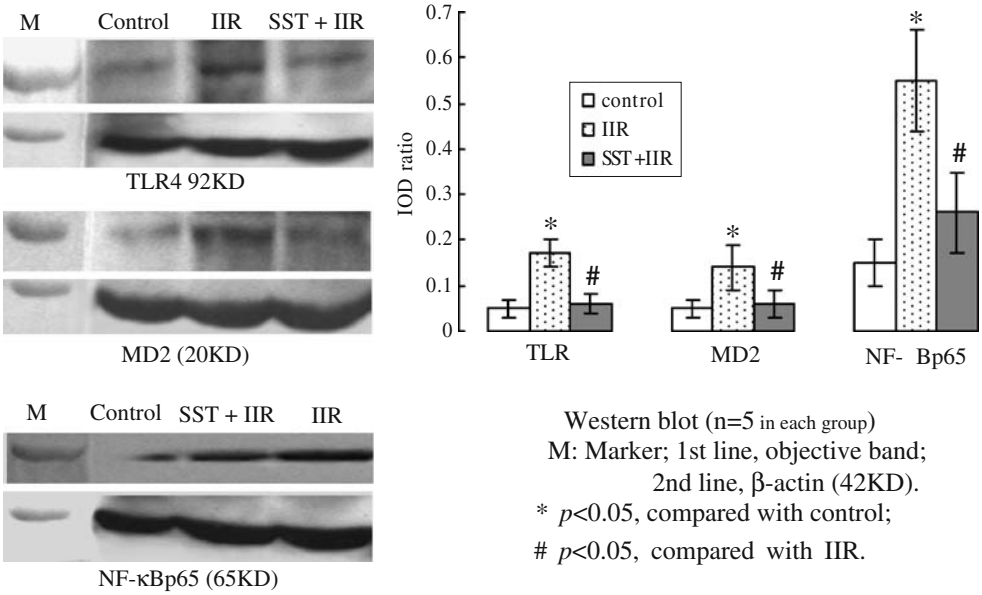

Figure 4 Expression of TLR4, MD2, and NF-κBp65 in the ileal epithelia of macaque.

In Situ Hybridization Detection of SST Receptor Subtype 2

Endogenous peroxidase was deactivated in deparaffinized sections of terminal ileum by 20% dioxogen, and 3% pepsase freshly diluted by citric acid was added to the sections before soaking in 1% paraform containing DEPC. The sections were incubated at 37°C for 4 h in prehybridization solution and covered with special coverslips for in situ hybridization, then washed in SSC at 37°C with hybridization solution and completed with confining solution. The sections were stained with biotinylated rat anti-cardiox and biotinylated peroxidase (Boshide, Wuhan, China). Color reactions were developed with DAB (Zhongshan, Beijing, China).

Radioimmunoassay for SST Levels in the Plasma and Ileal Mucosa

SST levels in the plasma and ileal mucosa of animals in each group were measured by a SST radioimmunoassay kit (Navy Radioimmunoassay Center, Beijing, China). Briefly, 2 ml of venous blood were mixed with 10% ENDA—Na_2 30 μl and aprotinin (Trasylol, 500 KIU/ml) l0 ml in the pre-cooled tubes and immediately centrifuged (4°C, 5 min, 2,500 rpm). The 0.5 ml plasma was put into 50 μl acetic acid in another tube. Two milliliters of 100% acetone precooled at 4°C was added and centrifuged (4°C, 15 min, 1,500 rpm) twice. The supernatant was collected, dried with freeze dryer, and frozen at −70°C until analyzed. The ileal specimens (0.2 g) were boiled for 3 min in 1 ml sodium chlorine, homogenized in 0.5 ml 1 N ice-cold acetic acid, left at 4°C for 1~2 h, neutralized with 0.5 ml 1 N NaOH, and then centrifuged at 4°C, 15 min, 2,500 rpm. The supernatants were lyophilized and kept at −20°C until analysis.

RIA analysis was performed as the protocol of the kit. After the supernatant was completely aspirated, the radioactivity of the pellet was counted in a gamma counter. SST level was normalized as nanogram per milliliter for plasma or nanogram per milligram protein for ileal mucosa.

Statistical Analysis

All quantitative data were presented as mean ± SD from the five animals in each group. Duplicate measurements were made for each animal and were analyzed using the Statistical Package for the Social Sciences for Windows software (SPSS, version 10.0; SPSS, Inc., Cary, NC, USA). The data were

Table 3 Quantification of the Ileal and Plasma Cytokines in the Three Groups (ELISA)

Group	TNF-α		IL-1β		IL-6	
	Ileum (pg/g protein)	Plasma (pg/ml)	Ileum (pg/g protein)	Plasma (pg/ml)	Ileum (pg/g protein)	Plasma (pg/ml)
Control	56.0±10.04	3.04±1.01	82.8±20.5	27.3±7.17	709.6±211.2	13.9±10.50
IIR	213.2±29.2*	64.8±18.7*	294.0±46.4*	79.2±14.4*	1527±160.8*	1261±297.5*
SST +IIR	97.1±32.3 **·***	19.2±10.1**	129.1±30.0**	40.0±9.9**	950.4±160 **	244.4±70.0**

n=5 in each group
*p<0.01 vs control group, **p<0.01 vs IIR group, ***p<0.05 vs control group

evaluated with ANOVA then confirmed by a post hoc test for multiple comparisons. Significance was set at $p<0.05$.

Results

Diverse Pathological Changes in the Small Intestine and not the Colon after IIR

All animals in the IIR group presented with small intestines fully inflated with gas, pale intestinal wall, multiple focus of hemorrhage, and mucosal erosion compared with the control group. No apparent changes were observed in the colon. Marked mucosal inflammatory injury of the ileum, including ablation of ileal villi, necrosis or erosion of the intestinal epithelium, hemorrhage of the intestinal mucosa, and inflammatory cell infiltration were observed under the microscope. The inflammatory lesion score in IIR group was significantly higher than that of the control group, $p<0.05$ (Table 2). In contrast, histopathological lesions observed in the right colon were minor (Fig. 1).

SST Prevented Intestinal Inflammatory Injury in Macaques with IIR In Vivo

The small intestines of macaques in the SST + IIR group were not as distended as those in IIR group. The inflammatory injuries of the intestines in SST + IIR group were obviously relieved when compared with those in IIR group (Fig. 1).The histopathological lesion score for the ileum in the SST + IIR group was significantly lower than that of the IIR group ($p<0.05$; Table 2).

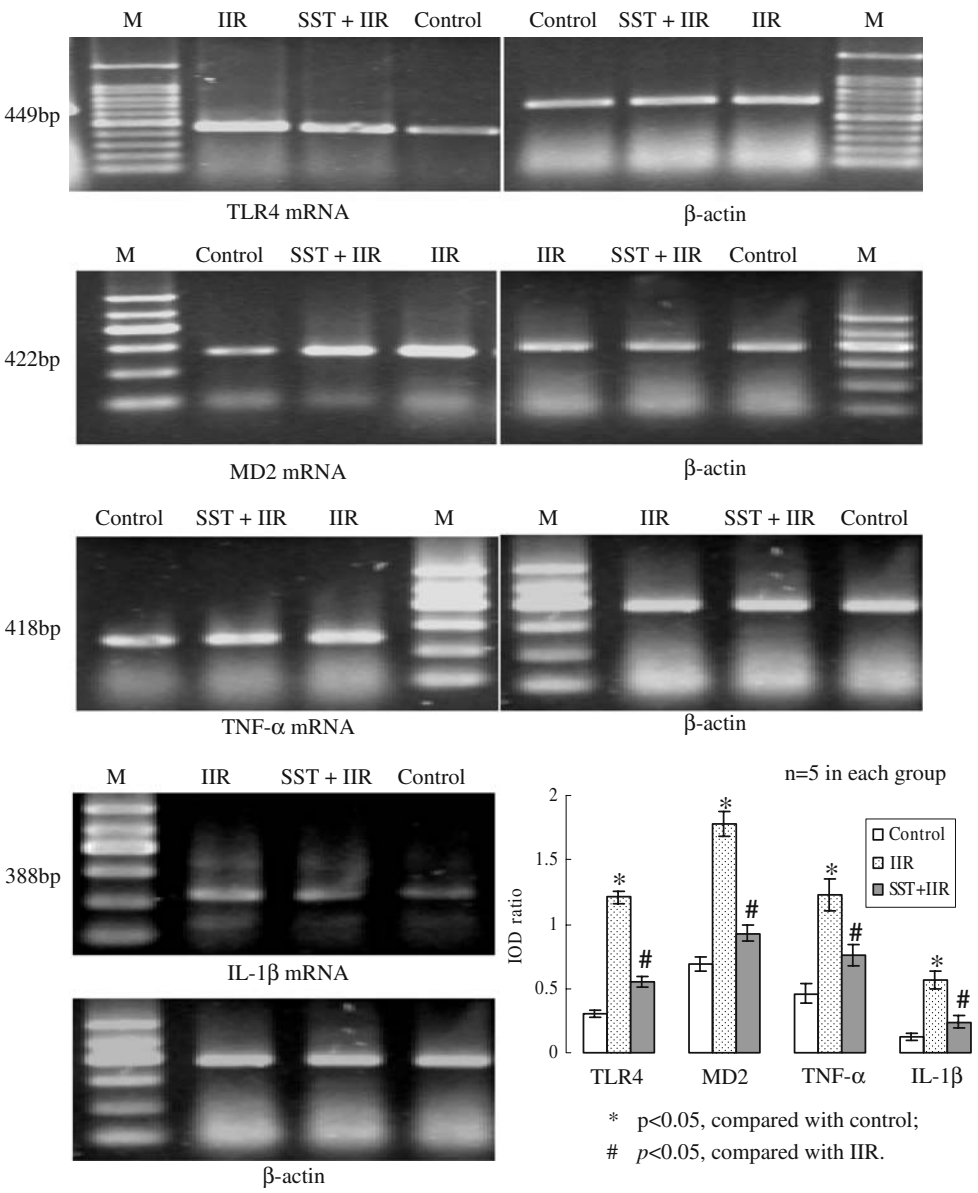

Figure 5 mRNA for TLR4, MD2, TNF-α, and IL-1β in ileal epithelia of macaque (RT-PCR).

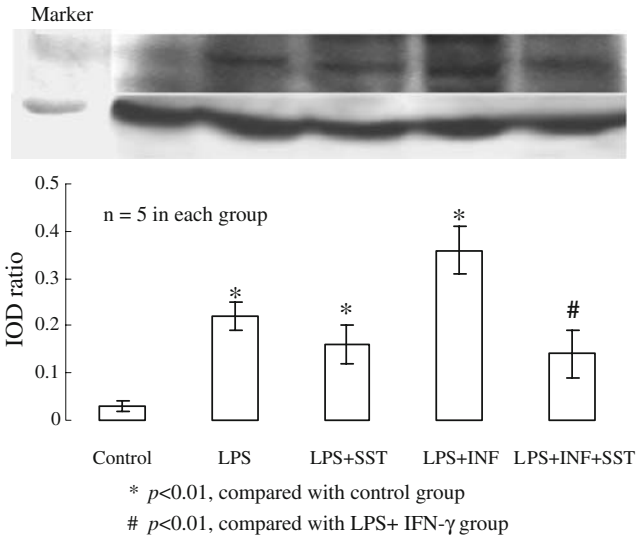

Figure 6 Effects of treatments on TLR4 expression in the ileal epithelia of macaque. Western blot: *first line*, objective bands (89 KD). *Second line*, β-actin (42 KD).

Activation of Ileal TLR4-NF-κB Cytokine Pathway and Cytokinemia after IIR

Immunohistochemistry revealed faint positive staining for TLR4, MD2, and NF-κBp65 in the ileal epithelium of the control group. After IIR, the ileal epithelium showed strong positive staining for TLR4, MD2, and NF-κBp65 (Figs. 2~3). Positive staining for TLR4 or MD2 was located in the cytoplasm and membrane of ileum epithelial cells. Strong positive staining of NF-κBp65 was visualized in the cytoplasm and nuclei of epithelial cells (Fig. 3). The nuclear expression of NF-κBp65 (IOD=211.6±16.0) in the IIR group was significantly higher than that (IOD=32.4±3.2) in the control group, $p<0.05$ (Fig. 3).

The upregulation of ileal TLR4, MD2, and NF-κBp65 after IIR, shown by immunohistochemistry, was further supported by the quantification of protein expression using Western blotting (Fig. 4). In addition, cytokine levels in the ileum of the IIR group increased significantly (Table 3). Along with the upregulation of protein expression, increased levels of ileal TLR4, MD2, and cytokine mRNA after IIR was found (Fig. 5). Moreover, the plasma cytokines increased significantly at the same time (Table 3).

SST Prevented the Activation of Ileal TLR4-NF-κB Cytokine Pathway and Cytokinemia in Macaques with IIR in vivo

Consistent with the histopathological changes, the down-regulation of ileal TLR4-NF-κB cytokine pathway after prophylactic use of SST was visualized by immunohisto-chemistry (Figs. 2 and 3) and quantified in protein and mRNA levels by Western blot, ELISA, and RT–PCR (Figs. 4~5; Table 3). Positive staining for NF-κBp65 was rare and was dramatically lower in the nuclei of epithelial cells (Fig. 3). The nuclear expression of NF-κBp65 (IOD=67.8±7.4) in the SST + IIR group was significantly lower than that (IOD=211.6±16.0) in the IIR group ($p<0.05$). In addition, plasma levels of cytokines in the SST + IIR group were significantly lower than those in the IIR group (Table 3).

Effects of LPS, IFN-γ, and SST on TLR4 Expression of Ileal Epithelium In Vitro

TLR4 expression in the isolated ileal epithelium was obviously induced by LPS. When given in combination with IFN-γ, LPS promoted more TLR4 expression than it did alone. SST significantly reduced TLR4 expression induced by LPS and notably arrested TLR4 expression promoted by LPS plus IFN-γ (Figs. 6~7; Table 4).

Effects of LPS, IFN-γ, and SST on Ileal Cytokine Levels In Vitro

The levels of IL-6, IL-1β, and TNF-α in isolated ileal epithelium were stimulated by LPS. When given in combination with IFN-γ, LPS enhanced cytokine levels more than it did alone. SST significantly reduced the levels of IL-1β and TNF-α induced by LPS and notably decreased the levels of IL-6, IL-1β, and TNF-α promoted by LPS plus IFN-γ (Table 4).

Expression of SST Receptor Subtype 2 in Ileal Epithelium of Macaques

Positive staining for SST Receptor Subtype 2 (SSTR2) was visualized in the ileal epithelium of macaques. Stronger

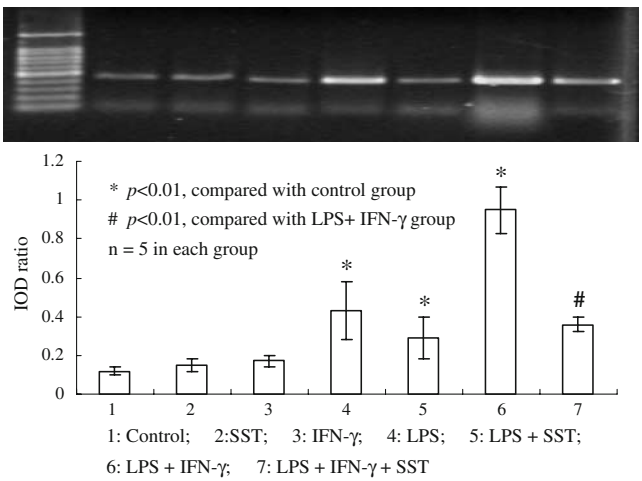

Figure 7 Effects of treatments on TLR4 mRNA expression (449 bp) in the ileal epithelia of macaque (RT-PCR).

Table 4 Effects of LPS, IFN-γ, and SST on Cytokine Levels in the Ileal Mucosa

Group	Control	LPS	SST	LPS+SST	IFN-γ	LPS+IFN-γ	LPS+IFN-γ+SST
IL-6	6.17±2.15	52.03±2.39*	8.20±1.78	43.43±11.4	9.87±3.36	156.53±33.74*	60.07±15.32*·***
IL-1β	20.63±5.79	39.07±3.07*	23.67±2.05	29.10±8.55**	26.93±5.67	68.67±11.36*	30.73±8.60*·***
TNF-α	7.57±4.00	28.13±5.99*	6.57±1.81	18.37±7.27**	13.33±2.75	68.80±7.36*	30.60±7.71*·***

n=5 in each group. The data (pg/ml) were detected by ELISA
* p<0.01 vs control group, **p<0.05 vs LPS group, ***p<0.01 *vs* LPS+ IFN-γ group

positive staining for SSTR2 was located in the epithelial crypt than in the villi epithelium (Fig. 8).

Changes of SST Levels in Plasma and Ileal Mucosa of Macaques with Different Treatments

SST levels in the plasma and ileal mucosa of macaques treated with IIR were significantly lower than those in the control group (p<0.05). Prophylactic use of SST greatly enhanced SST levels both in the plasma and ileal mucosa (Table 5).

Discussion

Gut injury because of ischemia and subsequent reperfusion events is a common pathophysiology that occurs in patients in various critical states. However, the major location of intestinal mucosal lesions has not been clearly described.[13,18] We observed that the severe inflammatory damage associated with IIR is located in the ileal mucosa of macaque monkeys after occlusion of the SMA, whereas the histopathological changes of the whole colon were slight. Because the SMA supplies the small intestine and the right colon,[19] the inflammatory lesions mainly located in the ileum cannot easily be explained by disturbances of local oxygen metabolism, oxyradical-dependent lesions, or bacteria toxin. This suggests that mechanisms other than oxidative stress might be involved. The small intestine, which is one of the major peripheral immune organs, may be more sensitive to insults during IIR than the right colon because of the initiation required for its intensive innate immune system.

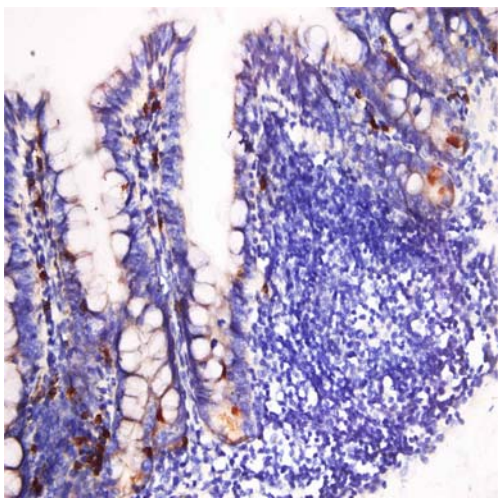

Figure 8 Expression of SSTR2 in the ileal epithelia of macaques (in situ hybridization, ×400).

As a type of pattern recognition receptor, TLRs play a pivotal role in the cellular activation of the innate immune response. Recognition of LPS by TLR4 requires mediation by MD2 and CD14 on the cell surface to form the LPS recognition compound.[20] MD2 may increase the reactivity of TLR4 to LPS.[21,22] A mutated form of MD2 can interrupt the LPS-mediated stimulation of TLR4.[23] In this study, we visualized an overexpression of TLR4 in the ileal epithelium of macaques in the IIR group, which suggests the activation of TLR4 is upregulated by the significantly increased transcription and expression of MD2.

It has been widely accepted that two signaling pathways follow the TLR4 activation, the MyD88-dependent, and the MyD88-independent pathways [24,25]. Endotoxin activation of the MyD88-dependent pathway results in rapid NF-κB activation and release of pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6, etc. Whereas the MyD88-independent pathway results in rapid activation of interferon regulatory factor 3 leading to beta interferon release and delayed NF-κB activation. NF-κB, a transcriptional factor involved in the regulation of the expression of multiple immune or inflammatory genes, usually remains inactive in the cytoplasm through association with the inhibitor IκB. As an upstream molecule, the activated TLR4 may cause the degradation of IκB that allows the translocation of NF-κB from the cytosol into the nucleus to induce the transcription of downstream gene expression.[26,27] Immunohistochemical staining in this

Table 5 SST Levels in the Plasma and Ileal Mucosa

Group	Plasma (*n*g/ml)	Ileal mucosa (*n*g/mg protein)
Control	6.09±1.29	2234. 8±301.8
IIR	3.67±0.41*	1402.3±160.0*
SST +IIR	29.3±5.97**	2975.7±354.4**

n=5 in each group
* p<0.05 vs control group, **p<0.01 vs IIR group

study revealed that a lot of NF-κB entered the nucleus of the ileal epithelial cells. Combined with the increased TNF-α, IL-1β, and IL-6, it is reasonable to deduce that the IIR-induced inflammatory injuries of the intestine are mainly related to the activation of the TLR4-MyD88-dependent pathway in macaques rather than the activation of the MyD88-independent pathway.

It is worth noting that only very faint expression of TLR4 was detected, and inflammatory injury of the ileal mucosa did not occur in the control group, although the mucosal surfaces and intestinal lumen were populated with a complex mixture of microorganisms. We hypothesized that decreased levels of endogenous SST during critical states might be involved in the expression of TLR4 after IIR. Indeed, SST levels in the plasma and ileal mucosa of macaques that underwent IIR were dramatically decreased by 40% and 37%, respectively.

Furthermore, the direct inhibitory effect of SST on the expression of TLR4 in isolated macaque intestinal epithelium was confirmed in our experiments in vitro. These experiments showed that SST was unable to affect the expression of TLR4 without the participation of LPS. In addition, SST exerted a maximum inhibitive effect on TLR4 expression when LPS coexisted with IFN-γ. Moreover, SSTR2, the molecular target for SST, was visualized in the ileal epithelium of macaques. Although the pathway between SSTR2 and TLR4 mRNA remains to be investigated, the data from this study is the first to demonstrate that SST is a direct inhibitor for the expression of TLR4 in ileal epithelium.

In vivo evidence that expression of TLR4-MD2 in the ileal epithelium of macaques was greatly decreased in the SST + IIR group further supports that SST is a strong suppressor of the expression and activation of TLR4. Consequently, the inactivated upstream molecule arrested the activation of NF-κB, which was supported by rarely observed positive staining for NF-κB in the nuclei of epithelial cells of the SST + IIR group. Along with these changes, the plasma cytokines obviously decreased. This series of events suggests that SST suppresses the TLR4-MyD88-dependent pathway in the ileal epithelium of macaques. Therefore, the shortage of SST following mesenteric ischemia reperfusion results in the loss of a vital endogenous inhibitor for inflammation and leads to massive damage of the gut mucosal barrier. The negative control of SST on the LPS/TLR4-NF-κB cytokine cascade gives us further insights into the regulation of the intestinal innate immune system in primates.

The circulatory level of SST may be a useful indicator in the clinical supervision of patients with stress or trauma. Prophylactic supplements of SST in the initial stages of IIR may maintain sufficient SST levels in plasma and the intestinal mucosa and might be a beneficial clinical strategy for the prevention of massive inflammatory injury of the intestinal mucosa in critically ill patients. Usually, IIR would follow the events such as hemorrhagic shock, infection, acute pancreatitis, and transplantation. Therefore, prophylactic supplements of SST should be given as soon as these clinical settings start other than the appearance of severe organ injury. As a therapeutic agent, SST may be too late to suppress massive inflammatory injury.

In conclusion, endogenous SST is a crucial inhibitor of massive inflammatory injury of intestinal mucosa via the direct suppression of the TLR4-NF-kB-cytokine pathway induced by LPS in ileal epithelium. IIR attacks cause shortages of endogenous SST in the plasma and intestinal mucosa of macaques. Therefore, preventive supplements of SST may limit intestinal injury of macaques with IIR.

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ORIGINAL ARTICLE

Seasoned Surgeons Assessed in a Laparoscopic Surgical Crisis

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Abstract
Objective Maintenance of certification is a relatively new concept in the United States, and there is no mandatory retirement for surgeons. Our aim was to compare technical and team performance of surgeons of different ages in a simulated laparoscopic surgical crisis and validate a potential recredentialing tool for surgeons.
Methods Using a single-blinded protocol, the performance of six "Seasoned" surgeons >55 years (mean 64, range 55–83) was compared to six "control" surgeons <55 years (mean 46, range 34–53) in a simulation. Surgical teams established pneumoperitoneum, trocar access, and managed intraabdominal hemorrhage in a simulated laparoscopic cholecystectomy while videotaped as part of an IRB protocol. Surgeons' performance was scored using validated technical and team performance scales.
Results All of the "seasoned" surgeons relegated the use of unfamiliar technology to their assistants. All control surgeons achieved intraabdominal pneumoperitoneum themselves. Mean blood loss for seasoned surgeons and control surgeons was 2,555 versus 2,725 ml (NS), respectively. After recognition of bleeding in the unstable patient, senior surgeons converted to an urgent laparotomy case after 2.4 vs. 3.3 min for control group (NS). No difference was observed in overall technical and team abilities (p=NS). On debriefing, 85% of surgeons recommended simulation for training and recertification.
Conclusions Seasoned surgeons can use their assistant surgeon well to assure a safe and effective operation. Mandatory operating room retirement based on age may be arbitrary and should be replaced by performance measures. Simulation may prove a valuable tool for self -assessment and recredentialing.

Keywords Surgical simulation · Surgical education · Patient safety · Surgeon retirement · Surgeon recredentialing

Introduction

Recently, the abilities to handle new technology by older doctors have been questioned[1]. Whether seasoned surgeons

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are as proficient at using some emerging surgical techniques as younger doctors has been placed under scrutiny. Surgeons older than 60 have been reported to have higher patient death rates in complex operations[2]. The doctor shortage is on the rise, and the percentage of working surgeons older than 65 is climbing[3]. A continuous trend toward later retirement and longer time in practice has been observed among general surgeons in the United States.[4] Consequently, surgical competence of older doctors, especially with more demand for surgery using new minimally invasive technologies, holds growing importance for patients' safety. In aviation, retirement is mandatory at age 60. Although most aging surgeons recognize limitations of their technical skills, neither recertification in specific technical surgical skills nor retirement is mandatory in surgery at any age in the US (other countries have certain cutoffs). Although peer review remains a critical element in evaluating the cognitive aptitude and performance of aging surgeons in practice, neither the American College of Surgeons nor the Joint Commission Hospital Accreditation Program provides any specific recommendations or guidelines regarding retirement. In the contemporary era of greater ethical concern for patient safety and rising intolerance for physician error and surgical complications, aging doctors might be required to prove not only their knowledge base, as is the case currently, but also their technical abilities as part of a recertification process. Since general surgery is a field with a wide scope of professional tasks, surgical competence is difficult to measure as evaluation tools do not exist for every task[5]. Outcomes achieved for a specific procedure or set of procedures have been benchmarks thus far; however, development of valid certification and recertification instruments is an important challenge that faces the medical profession and surgeons in particular.

In the past, simulators have been demonstrated to facilitate the improvement of quality and safety of surgical procedures.[6,7] Currently, the simulation movement in General Surgery is following the footsteps of Crew Resource Management (CRM) systems in aviation.[8] Technical task trainers have evolved into completely simulated operating room environments, where surgical teams can practice and perfect their technical and team skills protecting patients and themselves from possible errors encountered in during the learning curve of procedures.[9,10] At the Beth Israel Deaconess Medical Center's, Carl J. Shapiro Simulation and Skills Center (SACS), Boston, MA, USA, our team has validated a simulated scenario of intraabdominal hemorrhage complication of a routine laparoscopic cholecystectomy in an obese patient. This laparoscopic crisis scenario is played out in a mock laparoscopic operating room where the patient and procedure are simulated; however, all members of the surgical team are present, and the equipment is exactly what one would find in the operating room.[11] A novel synthetic abdomen was created with synthetic organs that allowed for simulating a laparoscopic cholecystectomy operation and simulation of intraperitoneal hemorrhage. The synthetic abdomen was connected to computerized equipment in such a way as to allow for measurement and control of physiologic parameters of the patient and to provoke realistic responses from the participants.

Using the newly developed and validated tool for training in a minimally invasive surgery crisis scenario, the aim of this study is to investigate whether age correlates with the capability of surgeons to handle new minimally invasive technologies, especially during crisis situations. We hypothesized that seasoned surgeons are as skilled as their younger controls at handling new technologies and controlling surgical crises in the simulated operating room environment. This study is the first to explore the use of a simulated endosuite environment as a potential recredentialing tool of the future.

Materials and Methods

Study Design

An Institutional Review Board approval was obtained from the Beth Israel Deaconess Medical Center (BIDMC) for a single blinded study of surgeon performance in a simulated laparoscopic operating room crisis scenario. The study took place at the Carl J. Shapiro Simulation and Skills Center. Twelve Harvard Medical School affiliated surgeons were invited to participate in the study, and stratified according to their age and experience level, and their laparoscopic technical and team communication abilities were evaluated. Face validity of the simulation as a whole was assessed. Prior to beginning the simulation, all subjects were asked to sign the IRB-approved consent form for participating in the study and being videotaped. The consent form outlined the scenario in general without disclosing the details of material tested. Demographic information was collected based on a multiple choice questionnaire.

Subjects

A standardized surgical team consisted of a circulating nurse, anesthesiologist, and an "intern" assistant, all instructed to follow scripted responses. The scrub nurse and the surgeon were the subjects of the study. Control surgeons were defined as practicing general surgeons <55 years of age, who perform over ten laparoscopic cases per month and have obtained The Fundamentals of Laparoscopic Surgery (FLS) Certification developed by the Society of American Gastrointestinal Endoscopic Surgeon (SAGES). Seasoned surgeons were defined as

practicing general surgeons >55 years of age, who perform less then ten laparoscopic cases per month and have not obtained The Fundamentals of Laparoscopic Surgery (FLS) Certification. All scrub nurses and technicians were invited to participate in the study on a voluntary basis and signed the consent forms provided. Two co-investigators acted as scripted participants, one circulating nurse, and one "intern" surgical assistant. In addition, two anesthesiologists also participated in the simulation and followed a prepared script with prompts to direct the test subjects in as required in a standardized manner.

Physical Environment and Equipment

Simulated Operating Room

The mock operating room theater contained standard equipment as found in a room designated for laparoscopy. This equipment included The Stryker Infinity System (Stryker, Kalamazoo, MI, USA) video monitors, insufflator, video light source, wall oxygen, medical air, suction, a Dreager anesthesia machine (Dräger Medical, Lübeck, Germany), and a Philips MP90 monitoring unit (Royal Philips Electronics of the Netherlands) as well as a Valleylab cautery unit (Valleylab, a division of Tyco Healthcare Group LP, USA). Cameras from the laparoscope were used to send output to the two viewing monitors in the operating room for the surgical team, and four overhead cameras stationed around the room also sent output to the control room. Standard surgical open and laparoscopic instruments were used for each case, including a Veress needle and optical trocar devices as well as surgical sponges and retractors.

Control Room and Debriefing Room

The METI HPS® (A Medical Education Technologies—Human Patient Simulator, Sarasota, FL, USA) was controlled from a desktop computer located in the control room and which was preprogrammed to reproduce the patient's vitals according to the physiological state of the patient. The vascular injury with the Veress needle was observed by the simulation leader (K.P.) who consequently triggered the adverse event in the METI HPS software, and changes in the patient's vital parameters were observed. The HPS computer also controlled the Trauma Disaster Casualty Kit (TDCK) that was used for generating intraabdominal perfusion through a six-channel umbilical hose. The TDCK used synthetic blood-like fluid that simulated bleeding from an injured splenic artery. The TDCK was programmed through the HPS's software to signal bleeding at the moment the surgeon inserts the Veress needle. Wireless headsets allowed for the communication of the simulation leader with the participating technical personnel in the control room as well as scripted participants. The recording and playback of each simulation trial occurred from DV/DVD recorders in the adjacent debriefing room. The debriefing room was used after each session for discussion and video playback of the simulation. The debriefing room houses a computer that is networked to the computer in the control room that in turn is routed to display video image onto a screen.

Simulation Device—Abdominal Model

A synthetic abdomen was created to simulate an obese human abdomen containing organs such as the liver, pancreas, small intestines, omentum, and spleen. All organs were handmade and connected to rubber tubings simulating blood vessels.[11] The synthetic model was mated with the METI HPS and draped with surgical drapes to imitate a prepped and draped patient on the operating table. Abdominal wall was a silicone-based skin look-alike which presented a surface for inserting the Veress needle and making surgical incisions. The tubing in the splenic hilum was lacerated prior to the simulation to simulate bleeding at 300 cc/min, once the TDCK was initialized through the METI software. Bleeding rate was regulated from the control room.

Simulated Laparoscopic Crisis Scenario

The simulation scenario involved an elective laparoscopic cholecystectomy on an obese patient using a closed technique abdominal entry with a Veress needle in the left upper quadrant. The subjects were initially instructed to review the simulated patient's history and physical examination in patient chart in a simulated preoperative area. The scenario was disclosed once during signing of the consent and the second time prior to the subjects entering the operating room. The limitations of the simulated environment were disclosed (e.g., inability to readjust the sterile draping).

Participants entered the simulated operating room after they had scrubbed and proceeded to gown, glove, and begin the operation. They were instructed to achieve pneumoperitoneum via the Veress needle, and CO_2 insufflation pressures were clearly visible on the monitors as the abdomen insufflated. The optical trocar was available for insertion in the supraumbilical position. The unexpected complications programmed into the scenario involved (1) no initial CO_2 flow, (2) high CO_2 intraabdominal pressures during initial insufflation, (3) intraperitoneal hemorrhage from a splenic artery puncture leading to hemodynamic instability of the patient. The bleeding was maintained from the control room until controlled by the surgical team. The simulation ended when the surgical team either failed to control the bleeding, and a cardiovascular collapse of the

patient became imminent, when bleeding was controlled laparoscopically or when the abdomen was opened and packed with laparotomy pads. Following the simulation, the surgical team was directed to the debriefing room, and a short debriefing on the team's performance was conducted. A questionnaire was given to the participants requesting their feedback on the simulation experience to establish the face validity of the simulation.

Technical Skill Evaluation

Technical skills of seasoned and control surgeons were evaluated using a previously validated technical scale.[11] Then rating scale consisted of three parts: (1) laparoscopy preparation and troubleshooting, (2) laparoscopy and management of intraabdominal hemorrhage, and (3) global operative performance individual surgeons were assessed separately, and a comparison of seasoned to control surgeon groups was undertaken. The study subjects were assessed for their technical skills and nontechnical skills, by four independent observers during a playback of a DVD from each simulation session. Objective outcomes such as time to control bleeding and blood loss were also recorded and calculated during playback of sessions on DVD.

Nontechnical Skill Evaluation

The surgeon and the scrub nurse were observed as they interacted with each other and the rest of the team in their team effort to troubleshoot during the challenges provided. Nontechnical skills were assessed using a previously described and validated, modified NOTECHS rating scale used in aviation simulations.[9,11] The scale consists of five categories for the assessment of communication and interaction skills, vigilance and situation awareness, team skills, leadership, and management and decision making in crisis. Each of the categories consists of three to five elements scaled 1 to 6 from worst to best. Four independent observers carried out the assessments independently.

Objective Outcomes Evaluation

To assess the objective outcomes of the operative team, performance time measures were recorded as follows: (1) time taken to diagnose bleeding (TD), (2) time taken to informing the team to convert to an open procedure (TT), (3) time taken to making an open incision (TC).

Data Analysis

Differences between the performance of seasoned surgeons versus control surgeons were performed using the SAS General Linear Model procedure (GLM) with Tukey–Kramer's Studentized range test (The Tukey–Kramer method was chosen because it is more powerful than the Bonferroni, Sidak, or Scheffé methods for pairwise comparisons, and it can be used for small samples of unequal cell sizes.). Statistical analysis was performed for comparisons of face validity, technical and nontechnical skills and objective outcome measures. The power of this study was calculated prospectively as follows: our previous study performed comparing expert and novice surgeons using the model described here indicated a mean blood loss of approximately 2,700 ml overall, with a SD of approximately 350 ml.[11] We prospectively considered a 25% difference on blood loss as of clinical significance. Taking a type 1 error of 0.05 and a type 2 error of 0.1 (power 90%), then $n=6$ patients are required in each group to demonstrate this difference. The inter-rater reliability (the level of agreement between the observers) and the internal consistency of the nontechnical rating scale components were determined by using Cronbach's alpha coefficient (SAS: PROC CORR). Means and SEs are reported for significant effects, with an a priori a level of 0.05.

Results

Participating surgeons ($n=12$) in the simulated laparoscopic crisis scenario were stratified into "seasoned" surgeons >55 years and performing less then ten laparoscopic cases per month; and "control" surgeons <55 years old and performing greater then ten laparoscopic cases per month (Table 1). Seasoned surgeons had a mean age of 64 and were not FLS certified. Control surgeons had a mean age of 46 and were FLS certified. The seasoned surgeons, on the average, had accumulated more than 10 years of experience in general surgery; however, they had minimal laparoscopic surgery and prior simulation training experience. In contrast, controls had performed greater then ten laparoscopic cases per month and had on average between 2 and 6 h of simulation training in their careers.

Objective Time and Blood Loss Measures of Laparoscopic Crisis Management

The objective outcome measures of the study were blood loss and time measures, obtained from the time recorded on the simulation DVD playback. The blood loss occurred at 300 cc/min and was calculated for both seasoned and control surgeons during the simulated crisis. The observed total blood loss prior to controlling hemorrhage was 2,555± 493.83 cc for Seasoned surgeons versus 2,725 cc±710.31 for control surgeons (Fig. 1a). The difference between groups in blood loss encountered did not reach statistical significance and was not clinically significant according to

Table 1 Surgeon Demographic Information

Total subjects (n=12)	Age	Years in practice (years)	Lap proc (n/month)	FLS	Team training (h)	Simulation training (h)
Controls						
1	>45 <55	>10	>10	Yes	2–6	>6
2	36–45	5–10	>10	Yes	No	No
3	36–45	2–5	>10	Yes	<2	>6
4	>45 <55	>10	>10	Yes	2–6	>6
5	>45 <55	>10	>10	Yes	2–6	2–6
6	>55	>10	>10	yes	No	No
Seasoned						
1	>55	>10	1–2	No	No	No
2	>55	>10	4–6	No	2–6	2–6
3	>55	>10	0	No	No	No
4	>55	>10	4–5	No	<2 h	No
5	>55	>10	1–2	No	>6 h	No
6	>55	>10	4–6	No	No	No

FLS Fundamentals of Laparoscopic Surgery, *Lap Exp* laparoscopic experience, *Lap Proc* laparoscopic procedures

the a priori criteria. Overall, seasoned surgeons controlled bleeding faster than controls in an open fashion, and they did not persist as long, laparoscopically, as the controls (Fig. 1b). The overall time to diagnose bleeding was 334.67 vs. 351.33 s (TD, P=0.22), time to inform the team of bleeding was 63.17 vs. 172.40 s (TT, P=0.21), time to convert to an open procedure 38.0 vs. 43.83 s (TC, P=0.22) for all seasoned surgeons versus controls, respectively. However, the differences in time measures did not reach statistical significance with clinical significance not determined a priori.

Face Validity of the Laparoscopic Team Simulation

Face validity, or realism of the simulation, was evaluated using a Likert scale-type questionnaire listed in Table 2. All surgeons found that the abdominal wall simulated the human abdomen well, and the hemorrhage encountered was realistic. The monitors did not interfere with the realism of the simulation, and the scenario overall was judged to be realistic. Overall, 83% of all participants felt that the simulation prompted realistic responses from them and from the team. Despite the lack of consensus among the surgeons, 75% of participants found it easy to treat the model as a simulated human. The highest degree of variability in the scores was found for perceiving the abdominal wall and the encountered intraabdominal hemorrhage as realistic. As demonstrated in Fig. 2, seasoned and control surgeons gave median scores of 4.23 and 5, respectively, for face validity overall. Mean scores were 4.26 and 3.67 for seasoned and control cohorts, respectively. The internal consistency of face validity questions was determined by measuring Cronbach's coefficient alpha and was 0.90 (95% lower confidence limit=0.63), indicating good scale reliability among the questions.

Use of the Model for Training and Assessment of Surgeons

Seasoned and control surgeons rated the content validity of the laparoscopic crisis endosuite scenario or the extent to

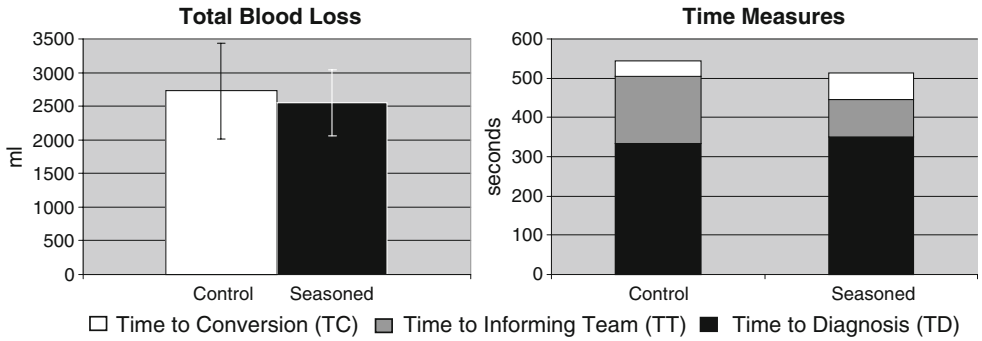

Figure 1 Laparoscopic crisis management. **a** Blood loss measured in milliliters. Data represent the mean blood loss±SD of n=6 subjects in each group p<0.05 for seasoned vs. control surgeons. **b** Time measures in seconds for *1* time taken to diagnose bleeding (TD), *2* time taken to informing the team to convert to an open procedure (TT), *3* time taken to making an open incision (TC). Data represent the mean of n=6 subjects in each group for seasoned vs. control surgeons.

Table 2 Face Validity Scored on Five-Point Likert Scales by Seasoned and Control Surgeons (n=12)

	Responses (%) (1=no, 3=somewhat, 5=yes)				
Evaluating statement	1	2	3	4	5
I found it easy to treat the model as a simulated human	1(8.3)	0	2 (16.7)	7(58.3)	2(16.7)
The abdominal wall simulated the human abdomen well	1 (8.3)	0	3(25)	5(41.7)	3 (25)
The hemorrhage encountered was realistic	1 (8.3)	0	1(8.3)	5(41.7)	5 (41.7)
The monitors functioned well as part of the simulation	1 (8.3)	0	1(8.3)	6 (50)	4(33.3)
The scenario was realistic	1 (8.3)	0	1(8.3)	5(41.7)	5(41.7)
I felt that the simulation prompted realistic responses from me	1 (8.3)	0	1(8.3)	5(41.7)	5(41.7)
The video cameras did not interfere with the simulation experience	1 (8.3)	0	1(8.3)	6(50)	4(33.3)

which the scenario would be useful for training and assessment. A five-point Likert scale type questions were used and are listed in Table 3. The majority of seasoned surgeons believed that the scenario was able to elicit the competencies required of team members to perform a laparoscopic case. Over 85% of participants considered the simulation to be appropriate for initial training in the specialty; however, only 71% believed the simulation would be a useful tool for advanced training or refresher training. Despite the variability in some responses, majority believed that the crisis simulation is a good opportunity for training and assessment of technical and team skills. Although less then 60% of participants believed that they would benefit from repeating the simulation over 85% reported, it would be useful as part of a recertification program.

Assessment of Nontechnical Skills of Seasoned Surgeons in a Laparoscopic Crisis

The modified NOTECHS rating scale was used for evaluation of team and communication skills of surgeons. The performance of seasoned and control surgeons varied within the groups; however, overall, the data showed no statistically significant differences between seasoned surgeons and controls in the total nontechnical score (Fig. 3). In looking at individual nontechnical skill categories, the lowest score for seasoned surgeons was in verbalizing their decision making during a laparoscopic crisis scenario (seasoned 59.72±9.3 vs. control 84.12±10.6 $p<0.05$). Those skills involved: (1) prompt verbal identification of the problem, (2) prompt information of the team members of the problem, (3) verbally outlining the strategy and the plan of action, (4) seeking team opinions, (5) anticipating and verbalizing potential problems. An observable difference was also noted in the surgeons "communication and interaction skills" (seasoned 74.69±6.02 vs. control 87.96±11.24 $p<0.05$). Those skills involved: (1) clear and polite instructions to assistant/scrub nurse; clear and polite, (2) awaiting acknowledgment from the assistant/scrub nurse, and (3) seeking assistance from team members.

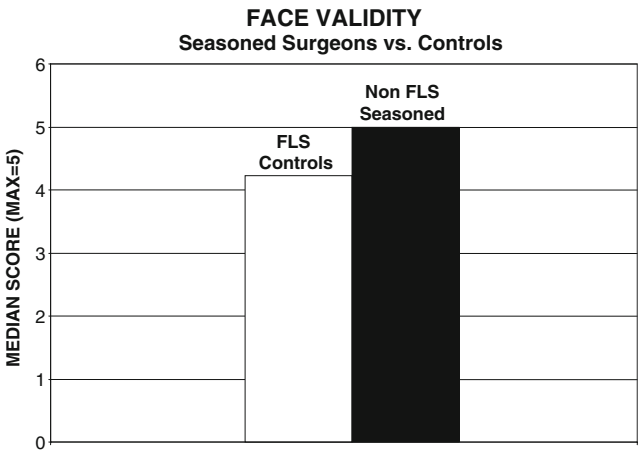

Figure 2 Face validity scored on a five-point Likert scale. Data represent the mean of n=6 per seasoned and control surgeon group.

Assessment of Technical Skills of Seasoned Surgeons in a Laparoscopic Crisis

The seasoned and control surgeons were assessed for their technical skills in three categories: (1) laparoscopy preparation and troubleshooting, (2) laparoscopy and management of intraabdominal hemorrhage, and (3) global operative performance. While all surgeons were able to adequately set up for a laparoscopic case, seasoned surgeons relegated the use of new and unfamiliar technology to their assistants, however with caution and care. When evaluated on their management of unexpected intraabdominal hemorrhage during a laparoscopic case, seasoned surgeons score was not significantly different from the controls (Fig. 4). The two technical skill categories where the difference did reach statistical differences were: (1) verbally identifying hemodynamic instability (seasoned 52%±21 vs. control 92.5%±5, $p<0.05$) and (2) efficiency of time and motion during the laparoscopic case (seasoned 68.9%±8.3 vs. control 85%±15.5 $p<0.05$). All seasoned and control surgeons chose a midline laparotomy incision for the conversion to an open case. Conversion to an open

Table 3 Use of the Model for Training and Assessment

The Median Values of the Statements Scored on Five-Point Likert Scales

		Category mean	Category median	Interquartile range	Percent in agreement
1	Initial training in my specialty	4.29	5	4.0	85.71
2	Advanced training in my specialty	4.14	5	3.5	71.43
3	Refresher training in my specialty	4.29	5	3.5	71.43
4	Part of a recertification program	4.43	5	4.0	85.71
5	The crisis simulation is a good training opportunity for training technical skills	4.71	5	4.5	100.00
6	The crisis simulation is a good training opportunity for training team skills	4.71	5	4.5	100.00
7	Use for assessment The simulation is a good method to assess my technical skills	4.14	4	4.0	85.71
8	The simulation is a good method to assess my team skills	4.71	5	4.5	100.00
9	Repeat the simulation I would benefit by repeating the simulation again	3.86	4	3.0	57.14%
10	I expect that the knowledge gained from the scenario will be helpful to me in practice	3.17	3.5	3.0	57.14
	Overall score	4.23	5.00		

procedure and control of intraabdominal hemorrhage was performed with efficient time and motion and knowledge of instruments by both groups without significant differences. In addition, there were no statistical differences between groups in their global operative performance, although a trend toward a better use of their first assistant was noted with the seasoned surgeon group compared to the controls (Fig. 5).

Discussion

In the era of ethical concerns for patient safety and introduction of new and complex surgical technologies that were not part of residency training of many surgeons of today, aging surgeons' liability risks have been questioned in the literature.[1,12–15] Some suggest that with advancing age, the surgeon's competence and ability to adopt new and improved procedures decline often to the patients detriment.[16] An analysis of examination scores from the American Board of Surgery recertification exams showed that the highest scores were achieved by the younger diplomats.[17] Further, a recent study determined that although for most procedures, surgeon age is not an important predictor of operative risk, for some complex procedures, surgeons older than 60 years, particularly those with low procedure volumes, had higher operative mortality rates than their younger counterparts.[2]

Our study assessed the technical and nontechnical expertise required to recognize and control an unexpected intraabdominal hemorrhage during a simulated laparoscopic crisis situation in a simulated operating room environment with a real operating room surgical team. Seasoned surgeons who have not been certified in The Fundamentals of Laparoscopic Surgery (FLS) program and who perform

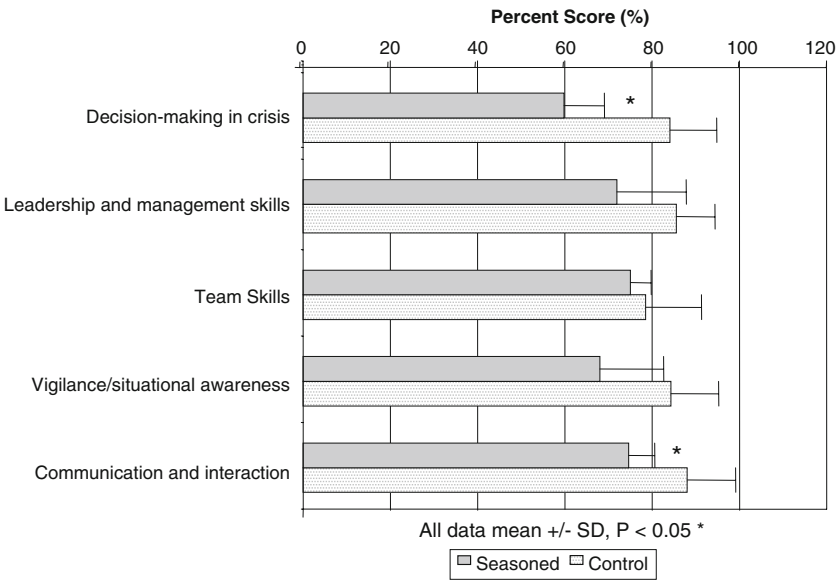

Figure 3 Nontechnical skills assessment scored on a six-point Likert scale. Data represent the mean percent score±SD of $n=6$ subjects in each group. *$p<.05$ for seasoned vs. control surgeons.

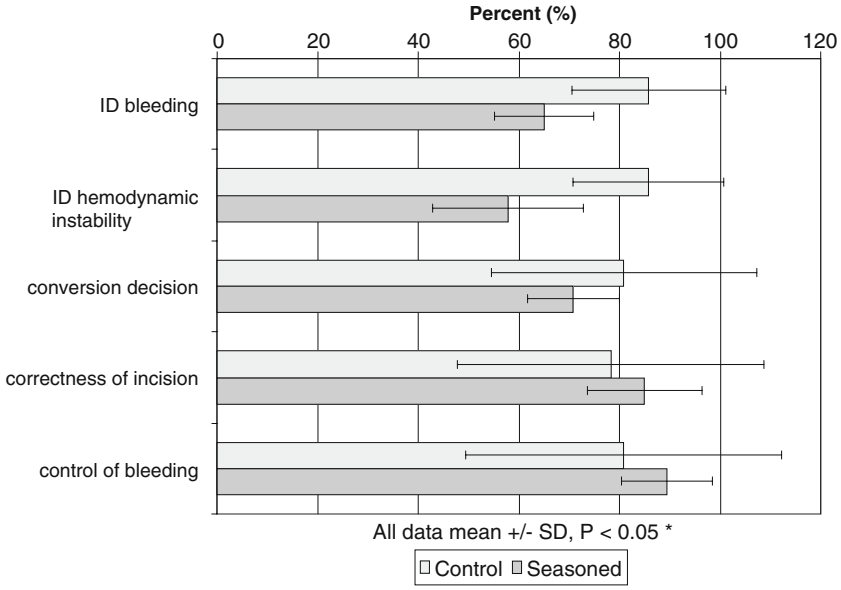

Figure 4 Laparoscopy and management of intraabdominal hemorrhage—technical skills assessment scored on a five-point Likert scale. Data represent the mean percent score±SD of $n=5$ subjects in each group. *$p<.05$ for seasoned vs. control surgeons.

low volumes of laparoscopic procedures, proved as safe overall and in their global team and leadership skills in handling a hemorrhagic crisis when compared to their younger and FLS-certified controls. Although no statistically detectable performance score differences were found overall between age groups, the individual performance of seasoned and control surgeons in our scenario varied, and some differences were observed. Most importantly, however, the a priori determined blood loss end point for clinical significance was not measured to be different between groups.

The sample size of the current study was not powered for multiple comparisons of all outcome measures, and one may stipulate that a greater number of surgeons tested in a study adequately powered would be able to detect small but clinically significant differences. However, the data presented here strongly suggest that the seasoned surgeons differed from the Controls in their ability to verbalize resuscitation plans as well as verbal communication with the team during a complex laparoscopic scenario. The reasons for these differences may be multifactorial. Other than being of younger age, the control surgeons had prior training in FLS, whereas the seasoned subjects did not. In itself, the FLS certification may not directly have influenced the results observed; however, it signifies that the control surgeons possessed basic laparoscopic skills that seasoned surgeons may not have had. Attention requirements are known to be different for laparoscopic cases compared to open procedures. Studies with cognitive loading imposed during laparoscopic drills showed that subjects performed significantly slower when they were cognitively loaded and showed greater spare cognitive capacity in surgeons with more experience[18]. The difference in attentional resources between seasoned and control surgeons or what has been termed the "attentional resource buffer" may differ due to laparoscopic experience.[19] Intense

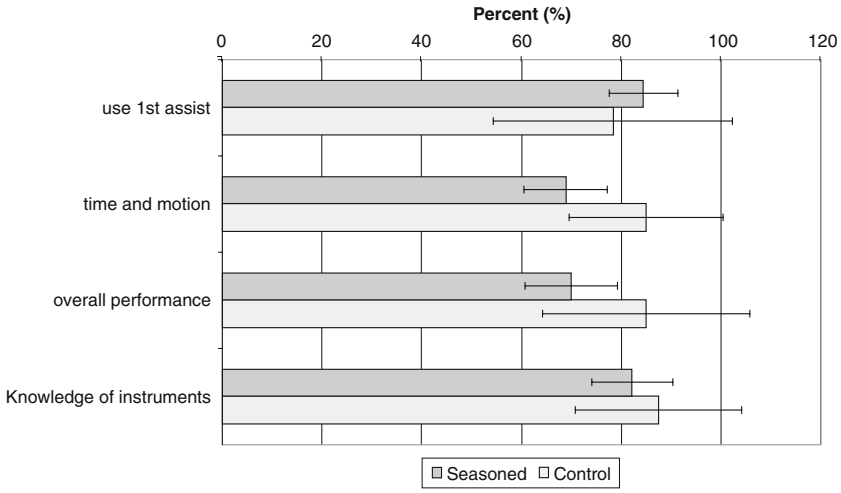

Figure 5 Global operative performance scale—technical skills assessment scored on a five-point Likert scale. Data represent the mean percent score±SD of $n=5$ subjects in each group. *$p<.05$ for seasoned vs. control surgeons.

focus on psychomotor performance, depth/spatial judgment combined with operative judgment/decision making under pressure in an unfamiliar environment by seasoned surgeons may all result in less attention devoted to verbalizing decision making to the surgical team. Despite these observable differences between seasoned and control surgeons, the two groups were able to equally maintain a positive rapport with the whole team and remain supportive of other team members. Moreover, hemorrhage control was achieved equally well by both groups.

Simulation offers a safe setting to train and assess surgical and team skills in a controlled environment and provides an alternative for testing of surgical skills. Possible bias such as healthier patient selection by seasoned surgeons, speculated as a confounding variable in other studies[15] can, as in this study, be eliminated in a simulated environment. Patients and scenarios are standardized and specific responses are observed and graded without room for selection bias. Although a certain degree of a Hawthorne effect exists with simulation, specific end points assessing the presence or absence of a particular surgical skill are possible to detect in a simulated environment. This alleviates the need for measuring surrogate end points of performance, such as patient mortality, which may be subject to a large number of confounding variables. In our study, for example, a standardized assistant, purposefully scripted for the scenario, assisted all surgeons. We were able to observe that all seasoned surgeons, when faced with unfamiliar technology of a Veress needle and an optical trocar, delegated aspects of the procedure to their assistants who were more familiar with the technology available.

Retirement for physicians and surgeons in the United States is not mandatory. Physician competence during the senior years in practice is assessed locally by practicing colleagues, hospital staff, administration, and frequently by the surgeons themselves. Factors such as the number of procedures performed and the individual surgeon's familiarity with equipment seems to play a larger role then age alone. Consequently, strategies that attempt to evaluate surgeon's performance in certain less commonly performed or more technically demanding procedures are gaining interest in the governing bodies. Although the intake questionnaire used here did not specifically request information about the types of procedures surgeons performed, the differentiating factor between the seasoned and control groups not only included age but also FLS certification. New evaluation strategies such as simulation training and testing similar to the FLS program may become mandatory as future certification and recertification standards for surgeons of all ages.

Professional registration bodies and surgical colleges worldwide have recognized the need for professional development programs and reevaluation of overall competence of surgeons at given intervals of time. Simulators and simulation are gaining a broader acceptance, finding their way into training residents and surgeons especially in laparoscopic skills. For example, the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) jointly with The American College of Surgeons have implemented using The Fundamentals of Laparoscopic Surgery (FLS) program criteria for establishing basic cognitive and technical standards in laparoscopic surgery. Recently, FLS certification became a prerequisite to practice laparoscopic procedures at BIDMC and at Cambridge Health Alliance Hospital, in Boston, MA, USA. As a patient safety initiative, the Harvard malpractice carrier, CRICO, reimbursed US$500 of premiums to all FLS-certified surgeons that they insured, a move supported by BIDMC, Brigham and Women's, Massachusetts General Hospital and Children's Hospital in Boston. Moreover, the ACS recently launched The Accreditation of Education Institutes program and is working jointly with the Association of Program Directors in Surgery (APDS) to develop a competency-based National Surgical Skills Curriculum, which uses simulation for teaching and assessment of surgical skills of residents. The laparoscopic crisis scenario presented here is one of the 12 teaching modules in the Phase Three ACS-APDS curriculum.[20]

It is conceivable that simulation-based curriculum could be implemented at regular intervals throughout a surgeon's career aimed at identifying any obvious deficiencies and aiding in recertification process with good patient outcomes as an optimum goal. One obstacle to a wider implementation of simulation curricula is costs. Maintaining a full simulation facility costs are substantial. However, we feel that the scenario presented here can be duplicated in any unoccupied operating room theater using only essential items as listed in the ACS/APDS National Skills Curriculum Phase III Team-Based Skills Laparoscopic Crisis Module.[20] The surgical equipment used for simulation can consist of discarded equipment that can simulate real laparoscopic tools and produce the same "buy in" from the participants to the reality of the scenario. The cost of such a modest simulation setup should only be a fraction of the costs associated with large-scale simulation facility.

The development of simulation instruments remains an important challenge for the medical profession and the development of specialized training centers with explicit curricula for advanced adverse event management in laparoscopic and other open procedures is the long-term goal of simulation research described here. Other laparoscopic crisis scenarios are in the process of being developed and tested in our facility. The role and implementation of simulation curricula in the recredentialing process remains beyond the principal focus of this study; nevertheless, our observations suggest that an unbiased objective assessment of technical and other skills may defy any subjective judgments of physician competence based solely on peer

review or on chronological age. This study introduces a previously validated high-fidelity simulation tool for competence training and assessment for surgeons of all ages and experience levels in model of a laparoscopic crisis scenario in a mock endosuite environment. The data presented demonstrate that the simulation model has excellent realism and maintains its face validity even among the most experienced and seasoned surgeons.

Conclusions

The physician's competence may not simply be based on chronological age. Ours is a study that correlates age and surgical performance and demonstrates that age is not a sole factor capable of discriminating individual surgeon's ability. Although seasoned surgeons relegate some parts of unfamiliar procedures to other team members, they use their assistant surgeons well to assure a safe and effective operation no less safe than their younger counterparts. As of January of 2008, The Joint Commission requires competency assessment to take place and procedure specific surgeon recredentialing to occur every 2 years. The methods of teaching and recredentialing of surgeons may need to be modified to allow for the competent and proficient use of new technologies. The learning process of aging surgeons and evaluation of surgical competence, particularly with respect to the use of complex new techniques deserves further studies. Simulation may prove a valuable tool for assessment and recredentialing in the future.

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HOW I DO IT

Modified Puestow Lateral Pancreaticojejunostomy

Eugene P. Ceppa · Theodore N. Pappas

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Abstract
Introduction There are various surgical options for the treatment of pain associated with chronic pancreatitis. The modified Puestow lateral pancreaticojejunostomy has been proven to be effective in ameliorating symptoms and expediting return to normal lifestyle while maintaining a low rate of morbidity and mortality. However, the debate regarding which surgical treatment provides the best outcomes is controversial.
Objectives The aims of this manuscript are to identify the patient population for which the Puestow benefits the most and discuss the pertinent technical aspects of the surgical procedure.

Keywords Chronic pancreatitis · Puestow · Lateral pancreaticojejunostomy

Introduction

Definitive treatment of chronic pancreatitis remains elusive. Behavioral modifications (decreased alcohol consumption and low-fat diet), pharmacologic interventions (pancreatic enzymes supplements, narcotics, and antidepressants), and endoscopic manipulation of the pancreatic duct have been recommended for amelioration of symptoms. However, surgical interventions have proven to be most effective in treating symptoms of chronic pancreatitis.[1]

In 1911, Link[2] reported treatment of chronic pancreatitis by creating a pancreotostomy as a form of external drainage. The patient's symptoms were improved only if the pancreotostomy was patent and actively draining. In the early 1950s, several notable surgeons reported their personal experiences with caudal pancreaticojejunostomy, but it was found to have mixed outcomes as treatment for chronic pancreatitis.[3–5] In 1958, Puestow and Gillesby introduced a novel approach, the lateral pancreaticojejunostomy, decompressing nearly the entire length of the pancreatic duct.[6]

Decompression surgery is generally recommended in patients with refractory pain and an obstructed, dilated main pancreatic duct. However, alternative therapies exist and are offered for treatment of chronic pancreatitis. Endoscopic pancreatic ductal stents have been used and associated with 50% of patients showing improved symptoms over 1 year.[7] Patients who have small duct disease and have failed drainage procedures are recommended resectional surgeries including pancreatic head resections (Beger or Frey procedure), pancreaticoduodenectomy (Whipple procedure), distal pancreatectomy, or total pancreatectomy. Across the numerous published studies, pancreatic resections improved pain symptoms in >50% of resected patients at 5 years following surgery.[8–10]

By most reports, the modified Puestow lateral pancreaticojejunostomy has equivalent long-term results compared to other approaches.[11–20] However, this is a controversial topic, and there are data to support all the various procedures for surgical drainage for chronic pancreatitis. Pancreatic head resections with drainage procedures (Beger, Berne, and Frey) have all been proven to be equally effective in terms of morbidity, mortality, and improvement of pain symptoms in small, randomized controlled trials.[21,22] All of these procedures have slightly higher overall improvement in long-term

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pain control when compared to the Puestow. We prefer the Puestow, since it is simple, safe by avoiding the dissection around the head of the pancreas, and is almost as effective in long-term improvement of pain symptoms. It is important to note that Puestow is used for inflammatory disease left of the gastroduodenal artery (GDA) and specifically not used as the procedure of choice for inflammatory disease of the head of the pancreas.

A consensus statement by the American Gastroenterological Association following review of studies evaluating lateral pancreaticojejunostomy for chronic pancreatitis revealed that the morbidity and mortality ranged from 0% to 5%; overall, 80% had short-term improvement of pain, and 60–70% achieved continued pain relief 2 years removed from surgery.[14,18,23–25] The lateral pancreaticojejunostomy has been shown to have a low morbidity and mortality.[26] Furthermore, patients postoperatively demonstrate subjective improvements in lifestyle, decreased narcotic consumption, and an increased return to employment.[14,18,23–25]

General Considerations

Patients seek treatment primarily for abdominal pain. Clinical symptoms of pancreatic endocrine or exocrine insufficiency are not evident unless the majority of the gland is nonfunctional. Physical examination reveals chronic mid-epigastric pain and evidence of malnutrition. Diagnostic evaluation consists of computed tomography (CT) to evaluate for pancreatic lesions, duct dilatation, or pseudocysts. In addition, either magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography (ERCP) is required to determine the size of the pancreatic duct and better define the anatomy. Various treatment options exist to address the primary symptom of pain in chronic pancreatitis.

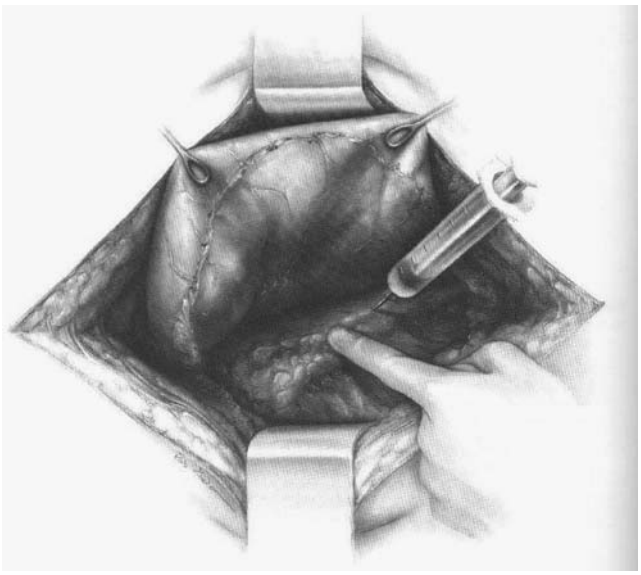

Figure 1 Location of pancreatic duct. The location of the dilated pancreatic duct is confirmed by aspiration of the duct (Figure 100-2 from Sabiston's Atlas 1994).

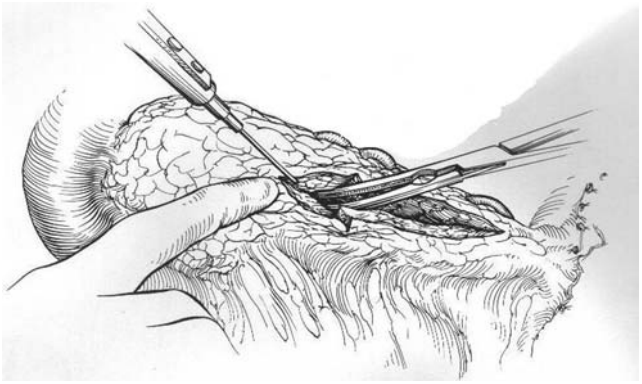

Figure 2 Opening of the pancreatic duct. The pancreatic duct is cauterized to extend the opening of the duct from the uncinate process to the distal tail of the pancreas (Figure 100-3 from Sabiston's Atlas 1994).

Celiac plexus block (CPB) is the inhibition of the celiac plexus by injection of a local anesthetic sometimes in addition with corticosteroids to provide an anesthetic and analgesic effect to the pain associated with pancreatic disease. CPB can be delivered by percutaneous approaches with US or CT or additionally with endoscopic ultrasound. There are reports on

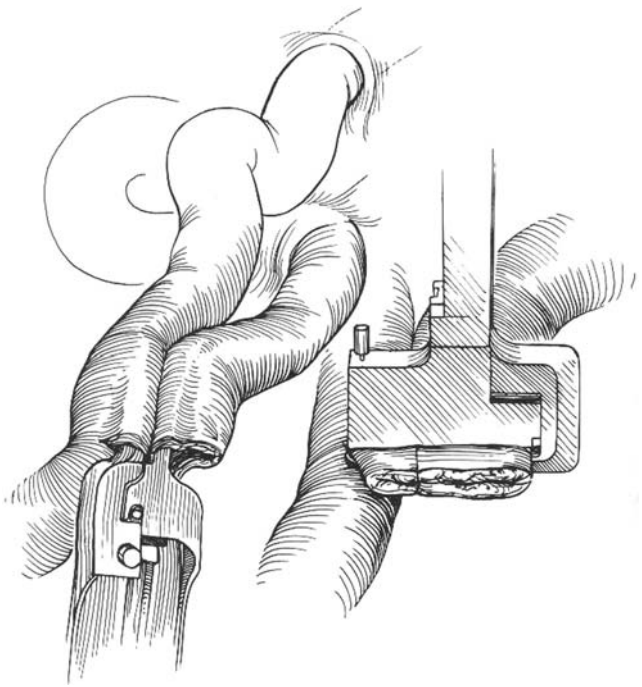

Figure 3 Roux-en-Y limb. The Roux limb is created between 40–60 cm from the ligament of Treitz by way of a side-to-side anastomosis with a linear cutting stapler and the opened ends of small bowel are closed with a linear stapler (Figure 100-5 from Sabiston's Atlas 1994).

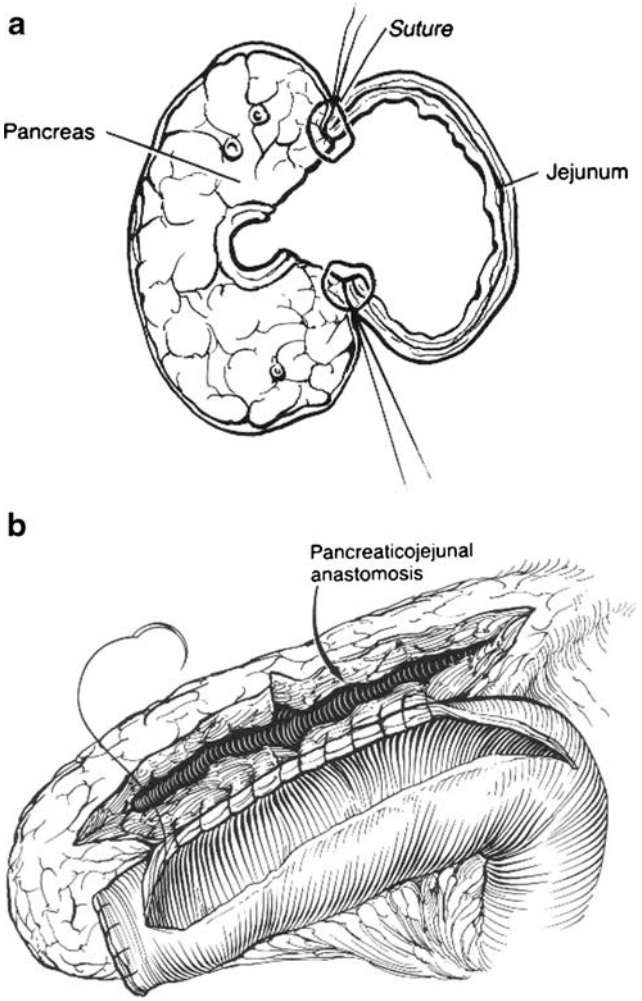

Figure 4 **a** Schematic of pancreaticojejunostomy. This cross-section of the pancreas to jejunum anastomosis reveals the suture location through the pancreatic parenchyma and the full thickness small bowel (Figure 100-7 from Sabiston's Atlas 1994). **b** Inferior suture line of pancreaticojejunostomy. A running 4-0 PDS suture anchors the anastomosis between the pancreas and small bowel (Figure 100-8 from Sabiston's Atlas 1994).

the utility of CPB for the treatment of chronic pancreatitis pain. Gress et al.[27] reported adequate early outcomes from CPB in 55% of patients at 8 weeks post procedure, while only 10% had any benefit at 24 weeks. There is no role for CPB in benign disease of the pancreas.

The decision not to manipulate the ampulla to facilitate drainage is based on several aspects. First, endoscopic treatments on the ampulla are inferior to surgical drainage procedures for the treatment of pain.[1] Secondly, the decision making involved in performing a drainage procedure is typically based on the anatomy of the pancreatic duct. Stenosis of the pancreatic duct in the head of the pancreas is better treated with resection followed by a drainage procedure (i.e., Beger, Frey). Stenosis of the body and tail of the pancreas is better treated with a drainage procedure (i.e., Puestow). A Puestow is preferred for a stenosis to the left of the GDA, which obviates the role of manipulation of the ampulla.

Surgery is more likely to relieve pain in patients with large pancreatic ducts (>4 mm). Surgical therapy is indicated for either obstruction of adjacent hollow viscera (bile duct or duodenum) or disabling pain in the setting of behavioral and diet modification as well as pharmacologic treatments. The pain is considered disabling if it interferes with daily activities or work and is refractory to high dose narcotics and supplemental pancreatic enzymes.

Puestow's description of the lateral pancreaticojejunostomy is in part different from the current modified version used by surgeons now. The original description recommended removal of the spleen following initial exposure of the pancreas upon entrance to the lesser sac. His rationale was based on the difficulty of separating the splenic vessels from the associated inflammation from the pancreas; the safer approach was to completely remove the spleen. Exposure of the duct was simply to incise the tail of the pancreas transversely until pancreatic fluid under pressure was released from the transected main duct. Puestow also described a two-layer anastomosis, although now a single-layer is commonly used. The remaining aspects of the procedure are identical and described in detail below.

Technical Considerations

Access

A bilateral subcostal incision is used to explore the abdomen. Patients with a narrow rib cage warrant an upper vertical midline incision. Self retaining retractors are placed following inspection of the abdomen.

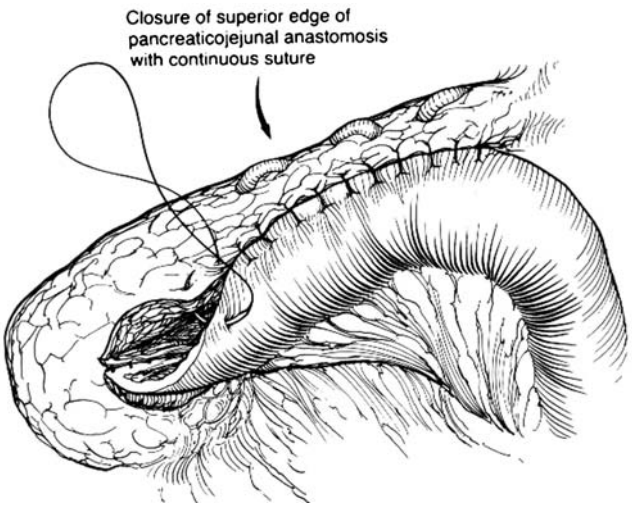

Figure 5 Superior suture line of Pancreaticojejunostomy. A running or interrupted 4-0 PDS suture completes the anastomosis between the pancreas and small bowel (Figure 100-9 from Sabiston's Atlas 1994).

Exposure of the Pancreas and Pancreatic Duct Location

The gastrocolic ligament is divided between clamps to enter the lesser sac. The stomach is retracted superiorly, while the colon is packed inferiorly into the lower abdomen. The pancreas should be visible from the uncinate process up to a few centimeters of the tail. The ventral pancreas is palpated to locate the distended pancreatic duct and for duct stones; the duct is typically superficial due to the atrophied nature of the pancreas. The dilated pancreatic duct location is confirmed by accessing the duct by aspirating a clear fluid using a 19-gauge needle with syringe (Fig. 1). The site of entry is marked using a needle-tip cautery and lengthened with a transverse opening by electrocautery. If needle aspiration is unsuccessful, then a transverse incision in the neck of the pancreas is made until the pancreatic duct is found.

Opening the Pancreatic Duct

A tonsil clamp and needle-tip electrocautery is used to make a long longitudinal opening of the duct (Fig. 2). The extent of lateral duct opening is dependent on correlating the location of duct stenosis on preoperative imaging (CT/ERCP) with the intraoperative findings of duct dilatation. If a focal stenosis is found distal to the head of the pancreas, the duct is opened beginning to the left of the GDA and extended to an area without stenosis. Duct opening to the tail is not performed routinely because it is technically tedious without any benefit postoperatively. Alternatively, the duct can be opened laterally through the body and combined with a distal pancreatectomy. If a focal stenosis extends to the right of the GDA, the GDA must be tied and divided superiorly and inferiorly with considerable distance from the lateral anastomosis to prevent the risk of massive GI bleed from an anastomotic leak.

Roux Limb Preparation

Subsequently, a 40- to 60-cm Roux-en-Y limb of small bowel is created by division of the mesentery with suture and of the bowel with a linear cutting GIA stapler. A side-to-side anastomosis of the Roux-en-Y limb is created with a linear-cutting GIA stapler. The ends of the small bowel are closed with a linear TA stapler (Fig. 3). The Roux limb is passed through the transverse mesocolon and positioned adjacent to the lateral opening of the pancreatic duct.

Pancreaticojejunostomy

The proximal Roux limb is opened longitudinally matching the length of the opened pancreatic duct. The inferior suture line consists of a single layer of a running 4-0 absorbable suture directly between the pancreatic duct and full thickness small bowel (Fig. 4a, b). When using absorbable suture, the knots can be left on the interior aspect of the posterior anastomosis for ease. Absorbable suture is preferred over non-absorbable suture due to the risk of stone formation. A sufficiently dilated duct allows for direct anastomosis to the duct. However, if the gland is adequately indurated, the anastomosis can be achieved directly to the pancreatic parenchyma without direct contact to the duct. This latter method is technically easier and equivalent in achieving adequate chronic lateral pancreatic drainage. The superior suture line is completed with a 4-0 absorbable suture, running or interrupted, suture with extra-luminal knots (Fig. 5). A single 19Fr closed suction drain is placed within the lesser sac and exteriorized through a lateral stab wound prior to closure of the fascia.

Postoperative Care

Estimated postoperative length of stay is 8 days.[28] Pancreatic leak is low (0.03–5%) in appropriate selected patients with a fibrotic gland.[26,28] The need for postoperative enteral or total parenteral nutrition is unusual.

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REVIEW ARTICLE

Physiological Effects of Pneumoperitoneum

Julia E. Grabowski · Mark A. Talamini

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Keywords Pneumoperitoneum · Laparoscopy · Insufflation

Since its inception in the early 1980s, laparoscopy has become a widely accepted surgical approach. Smaller incisions impart several clinical benefits such as improved cosmesis, decreased pain, and an earlier return to preoperative activities.[1,2] Laparoscopy, however, requires the establishment of pneumoperitoneum, which alters certain physiologic functions. We will review the physiologic effects of pneumoperitoneum (Fig. 1).

Acid/Base The most commonly used gas for insufflation is carbon dioxide. It is noncombustible, rapidly soluble in the blood, and relatively inexpensive. Because carbon dioxide is the main by-product of cellular metabolism, humans have an efficient mechanism for its elimination. A small portion of CO_2 is dissolved in blood and is delivered directly to the lungs. The majority of CO_2 combines with water in red blood cells to form carbonic acid, which then dissociates into hydrogen and bicarbonate.

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3$$

The produced hydrogen ions complex with hemoglobin, and the bicarbonate diffuses into the plasma. Carbon dioxide absorbed through the peritoneum is handled in the same manner and, ultimately, is eliminated by respiratory exchange in the lungs. Insufflation increases the delivery of CO_2 to the lungs by as much as 50%, which necessitates a compensatory increase in minute ventilation to maintain eucapnia. While under general anesthesia, minute ventilation volumes must be increased by up to 16% to maintain normocarbia.[3] Even if the increase in $PaCO_2$ is not fully compensated by hyperventilation, most healthy patients are easily able to adapt to the transient increase in end tidal CO_2 and slight decrease in pH by increasing by maximizing the use of their intracellular and plasma buffering systems and increasing the rate of CO_2 transport. Some patients, however, have less homeostatic reserve and are unable to tolerate the increased CO_2 load during insufflation. Patients particularly at risk are those with decreased pulmonary function (i.e., severe chronic obstructive pulmonary disease), reduced cardiac output, or a high metabolic and cellular respiratory rate (i.e., septic patients).[4] These patients require strict monitoring of end-tidal CO_2 and arterial blood pH to avoid significant hypercarbia and acidemia and subsequent complications.

Pulmonary Abdominal insufflation during laparoscopy affects intraoperative pulmonary mechanics. Increases in intraabdominal pressure and volume impede diaphragmatic movement resulting in decreased functional residual capacity and an increase in alveolar dead space. Postoperative pulmonary function tests reveal a significant reduction in forced expiratory volume in 1 s (FEV_1), peak expiratory flow (PEF) and forced vital capacity (FVC).[5] Additionally, there is a rise in peak airway pressures, with a concomitant decrease in pulmonary compliance.[3,4,6–8] In patients allowed to breathe spontaneously during laparoscopy, these factors can lead to hypoxemia.[9] Controlled ventilation, especially with large tidal volumes, however, decreases the risk of hypoxemia by minimizing alveolar atelectasis and the resultant ventilation/perfusion mismatch.[10] The recruit-

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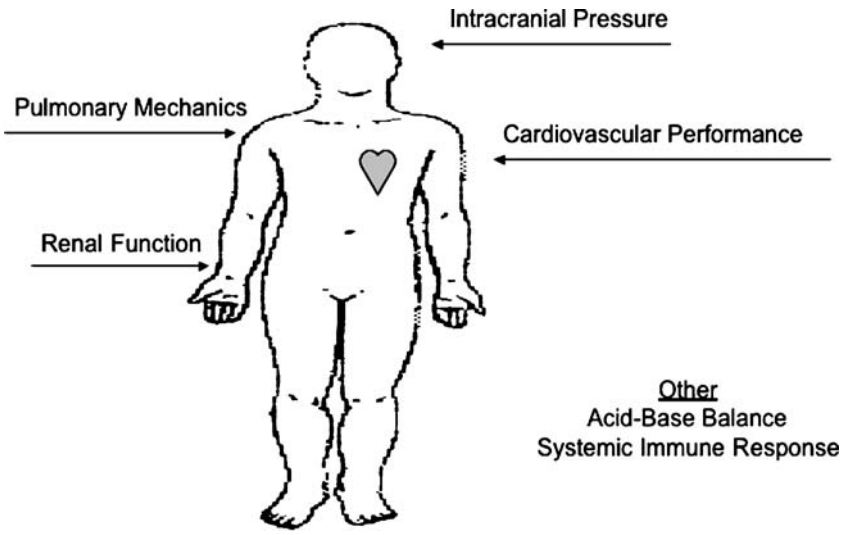

Figure 1 Pneumoperitoneum has effects on multiple organ systems.

ment of alveoli at the lung bases can be further enhanced with the addition of positive end-expiratory pressure (PEEP), though PEEP must be added with caution because of its cardiovascular effects (see below).

Though there are seemingly deleterious effects of laparoscopy to intraoperative pulmonary mechanics, these do not appear to be clinically relevant in most healthy patients.[11] Furthermore, there is abundant literature to suggest that the postoperative pulmonary status of patients is better after laparoscopy compared to after open operation. Schwenk et al.[12] evaluated pulmonary function tests (including FVC, FEV_1, and oxygen saturation) of patients before and after undergoing colon resection; either open or laparoscopically. Though all patients demonstrated depressed pulmonary mechanics postoperatively, those who had an open operation had significantly more impairment than patients in the laparoscopic group, even in light of a shorter operative time for the open operations. These changes in pulmonary function tests translated to worse outcomes. Pneumonia developed in two patients in the open group compared to none in the laparoscopic group, although this difference was not statistically significant.[12] Similar results were obtained by Hasukic et al.[5] in patients undergoing either a laparoscopic or open cholecystectomy. Patients who had an open cholecystectomy had significantly greater reduction in their FEV_1 and FVC from preoperative levels than those who had a laparoscopic cholecystectomy and had significantly more atelectasis (Table 1).[5]

Cardiac/Hemodynamic Insufflation alters cardiovascular performance because of both the effects of hypercarbia as well as the change in intraabdominal pressure. Mild hypercarbia (pCO_2 of 45–50 mmHg) has little effect on hemodynamics, whereas moderate to severe hypercarbia has both direct and indirect effects on cardiac function.[13] At a pCO_2 of 55–70 mmHg, hypercarbia and acidosis cause hemodynamic changes because of carbon dioxide's direct action on the cardiovascular system and because of its indirect effect on the autonomic system. Elevated CO_2 directly causes myocardial depression and vasodilation. These effects are counteracted by a centrally mediated sympathetic stimulation that causes tachycardia and systemic vasoconstriction. This catecholamine release effect predominates, as the overall observed effects of moderate hypercarbia include an increase in heart rate, mean arterial pressure, central venous pressure, pulmonary artery pressure, cardiac output, and stroke volume.

The hemodynamic effects of chemical hypercarbia are minimal compared to those attributable to the mechanical effect of increased intraperitoneal pressure. The degree to which increased intraabdominal pressure affects hemodynamic function is dependent on several factors, including intravascular volume, level of intraabdominal pressure, and patient position. Data from animal studies demonstrated that an increase in intraabdominal pressure to 5 mmHg increased the cardiac output in all subjects, with mean arterial pressure and caval blood flow increasing only in normovolemic subjects. Further studies showed that in-

Table 1 Changes in Pulmonary Mechanics Because of Insufflation

Respiratory factor	Change
Functional residual capacity	Decrease
Alveolar dead space	Increase
Peak airway pressures	Increase
Pulmonary compliance	Decrease
Forced expiratory volume in 1 second (FEV_1)	Decrease
Forced vital capacity	Decrease
Peak expiratory flow	Decrease

creasing the intraabdominal pressure to 40 mmHg modulates venous resistance and mean systemic pressure, although these changes depend on intravascular volume and cardiac preload.[14,15] At low right atrial pressures, the inferior vena cava compresses, causing a decrease in venous return. At high right atrial pressures, however, the vena cava resists compression, and increased intraabdominal pressures serve to augment venous return.[15,16] Additionally, an increase in intraabdominal pressure results in compression of small capacitance vessels, which also increases venous return. Overall, in hypervolemic animals, cardiac output is augmented by the elevated mean systemic pressure and consequent increase in venous return. In contrast, in hypo- and normovolemic animals, the compression of the vena cava outweighs the increased mean systemic resistance resulting in a decreased cardiac output.

Clinically, the effects of insufflation on hemodynamic function depend on a multitude of patient factors; however, the majority of studies concur that laparoscopy causes a decrease in cardiac index and that this effect appears to be dependent on the level of intraabdominal pressure. Dexter et al.[17] randomized patients to insufflation pressures of either 7 or 15 mmHg during laparoscopic cholecystectomy. Heart rate and mean arterial pressure increased in both groups, but stroke volume and cardiac output were significantly more depressed in the high-pressure group.[17] In a study by McLaughlin et al.,[18] intraabdominal pressure of 15 mmHg caused a 30% decrease in cardiac output (CO) and stroke volume (SV) and a 60% increase in mean arterial pressure (MAP) from pre-insufflation levels, and these changes were determined to be statistically significant.[18] Kraut et al.[19] demonstrated a measurable, but not significant, decrease in cardiac output and stroke volume at insufflation pressures of 15 mmHg. The addition of a 10-cm^2 PEEP, however, exaggerated these reductions to a statistically significant level. The authors, therefore, concluded that humans tolerate an intraabdominal pressure of 15 mmHg or 10 cm^2 of PEEP, but the combination should be avoided.[19]

Patients are often put in the head-up or head-down position to facilitate visualization during laparoscopy. These changes in patient position can also alter hemodynamic function. In a study by Williams and Murr,[20] dogs undergoing laparoscopy had a measurable decrease in cardiac output during insufflation. This reduction was enhanced by placing the dogs in the head-up position. In contrast, at the same level of intraabdominal pressure, dogs positioned in the head-down position had a smaller reduction in cardiac output than those in the horizontal position.[20] Joris et al.[21] measured the hemodynamic changes in patients undergoing laparoscopic cholecystectomy. Positioning the patient in the head-up position reduced the mean arterial pressure by 17% and the cardiac index by 14% compared to the horizontal position. The addition of insufflation to 14 mmHg increased the mean arterial pressure by 37%, but decreased the cardiac output an additional 18%. The combined effect of insufflation and reverse Trendelenburg positioning was a reduction of cardiac index with an unchanged mean arterial pressure. When patients are placed in the Trendelenburg position, cardiac output tends to increase, reflecting an increase in central venous pressure compared to the horizontal position that counteracts the effects on insufflation.[22]

Despite the measurable hemodynamic changes resulting from insufflation and patient position, when the standard 15-mmHg insufflation pressure is employed, these effects do not appear clinically relevant. Indeed, the European Association of Endoscopic Surgeons affirmed, in their clinical practice guidelines from 2001, that when using pressures up to 15 mmHg, the decrease in cardiac output is minimal and without clinical consequence in healthy patients.[23]

Patients with underlying cardiac disease require special consideration when undergoing laparoscopy. Increases in heart rate and afterload, in conjunction with elevated systemic vascular resistance (SVR), have the potential to increase ventricular wall tension, creating a risk of myocardial ischemia. Safran et al.[24] investigated the effects of laparoscopy on patients with severe (American Society of Anesthesiologists class III or IV) heart disease. They indeed noted significant elevations in MAP and SVR and a significant reduction of CO when patients were insufflated to an intraperitoneal pressure of 15 mmHg. In about half of the patients, this increase in intraperitoneal pressure led to a decrease in oxygen delivery accompanied by significant increases in pulmonary artery pressures. The authors concluded that, in these patients, insufflation caused a transient cardiac decompensation because of inadequate left ventricular reserve.[24] In one clinical series, hemodynamic parameters in patients with severe cardiac dysfunction were measured during laparoscopic cholecystectomy. MAP, SVR, and pulmonary artery occlusion pressure increased significantly during insufflation, and three of 17 patients required nitroglycerin to treat blood pressure alterations occurring during pneumoperitoneum.[25] In neither of these studies, however, were there any intraoperative or postoperative long-term cardiac complications, and no patients required conversion to an open procedure. Though laparoscopy does appear to be safe in patients with cardiac disease, these patients require special attention and likely require additional intraoperative monitoring (Table 2).

Renal An increase in intraabdominal pressure has long been known to affect the renal system, specifically, renal blood flow (RBF) and glomerular filtration rate (GFR). Though these effects are certainly influenced by the

Table 2 Changes in Hemodynamics Because of Insufflation with CO_2

Hemodynamic parameter	Change with hypercarbia	Change with increased intraabdominal pressure
Heart rate	Increase	Increase
Mean arterial pressure	Increase	Increase
Central venous pressure	Increase	Increase or decrease[a]
Stroke volume	Increase	Decrease
Cardiac output	Increase	Increase or decrease[a]

[a] Change depends on intravascular volume status

hemodynamic changes caused by an increase in intraperitoneal pressure, they are not entirely dependent on the decrease in cardiac output. Early studies on humans showed that an external compression of the abdomen to an intraabdominal pressure of 20 mmHg reduced both urine production and GFR.[26] Harman et al.[27] studied the effects of intraabdominal pressure by inflating intraperitoneal bags in dogs, thereby increasing their intraabdominal pressure. At a pressure of 20 mmHg, RBF and GFR were reduced to less than 25% of baseline values, with a concomitant decrease in cardiac output. When the cardiac output was returned to baseline with a volume expander, the renal effects persisted, indicating that the renal effects were independent of the hemodynamic changes.[27]

Insufflation during laparoscopy has similar effects. RBF has been evaluated in animal models with many different measurement techniques. The majority of studies indicate that RBF decreases with insufflation. Shuto et al.[28] looked at RBF in pigs undergoing laparoscopy with either helium or carbon dioxide insufflation. They demonstrated a significant decrease in RBF with an insufflation pressure of 20 mmHg, independent of the type of gas used.[28] A similar study using nitrogen as insufflant resulted in a significant decrease in RBF at pressures of 15 or 20 mmHg.[29] Though the effects of insufflation do not depend on the type of gas used, they do appear to correlate with the degree of intraabdominal pressure. Chiu et al.[30] measured the RBF in pigs undergoing insufflation at varying levels of intraabdominal pressure. They observed a gradual reduction in RBF with increasing levels of intraabdominal pressure, with a 75% reduction by 15 mmHg pressure.[30] The exact mechanism by which RBF is affected by pneumoperitoneum has not been elucidated. It does appear to be influenced by volume status, as aggressive fluid hydration can attenuate the reduction in RBF. In a study performed by London et al.,[31] pigs underwent laparoscopy with an intraabdominal pressure of 15 mmHg. They were hydrated with either maintenance fluids, bolus fluids, or hypertonic saline, and RBF was measured using a renal artery flow probe. Those pigs receiving only maintenance fluids had a 30% reduction in their RBF, which was not seen in the pigs more aggressively hydrated.[31]

In addition to decreasing RBF, insufflation affects renal function. GFR is the most accurate measure of renal function, but is difficult to measure in the acute setting.[32] Creatinine clearance, urine output, and serum creatinine have all been used as surrogate markers to assess renal function during laparoscopic procedures. Additionally, urinary *N*-acetyl-B-D-glucosaminidase (U-NAG), a sensitive marker for renal tubulular cell damage, has been measured to assess structural injury to the kidney. The majority of data from animal studies shows a transient decline in renal function during insufflation.[33–35] A study performed by Kirsch et al.,[35] for example, examined the effects on insufflation to a pressure of 5 or 10 mmHg on urine output and serum creatinine in rats. There was a significant decrease in urine output and a significant increase in serum creatinine at an intraabominal pressure of 10 mmHg. These effects, however, were temporary, as urine output returned to baseline by 22 h after desufflation and serum creatinine normalized by 2 h after desufflation.[35] Additionally, examination of kidneys procured after exposure to pneumoperitoneum has, by and large, failed to show any significant histologic damage, in both the short and long term.[36,37] Studies performed in humans corroborate the animal data. There is a measurable decrease in urine output in patients who are exposed to insufflation.[38–40] There is no clear effect on serum creatinine or U-NAG, indicating that the oliguria occurring intraoperatively has little or no postoperative significance.[38,41]

The cause of the decreased renal function seen during insufflation appears to be multifactorial. There is a clear component of vascular and parenchymal compression, but there is also evidence that vasopressin levels are increased during pneumoperitoneum.[42,43] The relative decrease in right atrial volume because of the reduced preload during insufflation induces the release of vasopressin. Vasopressin then acts on the distal tubule and collecting ducts of the kidney to promote reabsorption of water and the formation of more concentrated urine. Indeed, blocking the effects of vasopressin using an antagonist to the vasopressin receptor partially reversed the oliguria seen in rats during insufflation.[44]

RBF and renal function are affected by pneumoperitoneum, but these changes do not appear to be clinically deleterious or have long-term sequelae on kidney function or histology. Knowledge of the effects of insufflation is, however, important to effectively monitor and maintain an appropriate fluid balance for patients during laparoscopy (Table 3).

Table 3 Renal Effects of Insufflation with CO_2

Renal Parameter	Change
Urine output	Decrease
Glomerular filtration rate	Decrease
Renal blood flow	Decrease
Serum creatinine	Increase or No Change
Vasopressin	Increase

Intracranial Pressure Laparoscopy has a well-documented impact on intracranial pressure (ICP). Several animal studies have demonstrated that the induction of pneumoperitoneum provokes a measurable increase in ICP.[45,46] The rise in ICP appears to be independent of arterial pH (and therefore carbon dioxide effects), oxygenation, or mean arterial pressure.[46] The increase in ICP is seen even at low (8 mmHg) abdominal pressures and is especially pronounced in animals with baseline elevated ICP.[47] Trendelenburg position worsens the increase in ICP during insufflation, but reverse Trendelenburg does not eliminate the observed increase.[45] The exact mechanism by which intraabdominal pressure affects ICP has not been elucidated, but it appears to be multifactorial. The Monroe–Kellie doctrine states that the bony skull contains three elements: parenchymal tissue, arterial and venous blood, and cerebrospinal fluid (CSF) in a dynamic equilibrium. With a rapid change in the volume of any of these components, ICP rises. It has been proposed that increased intraabdominal and intrathoracic pressure as well as impaired CSF absorption during insufflation impedes drainage of the lumbar venous plexus and induces an increase in the vascular compartment of the sacral space causing the rise in ICP.[45,48] Additionally, hypercarbia is known to cause cerebral vasodilation, which causes an increased ICP. The peritoneal absorption of carbon dioxide may induce such a vasodilation, exacerbating intracerebral hypertension. In most healthy patients without preexisting intracranial disease, the increase in ICP is without clinical consequence. However, laparoscopy is being considered and used more frequently in critically ill and traumatized patients. Until these effects have been more completely described, caution is in order.

Immune System The trauma of surgery stimulates the systemic immune and inflammatory responses. These responses appear to be different, however, depending on whether the surgical approach is open or laparoscopic. Originally, the immune modification seen with laparoscopy was attributed entirely to the smaller size of the incisions, with a proportionally reduced degree of trauma. There is also compelling data to indicate that insufflation, and, specifically, carbon dioxide insufflation, plays a role.

Acute-Phase Reaction Acute-phase proteins are produced in response to tissue injury. C-reactive protein (CRP) is one of the most thoroughly studied markers of the acute-phase response to surgery. It rises 4 to 12 h after surgery, peaks at 24–72 h, and remains elevated for about 2 weeks.[49] Many studies have shown that the CRP does not reach the same elevated levels after laparoscopic procedures compared to open surgery.[49] Whether this is because of incision size or carbon dioxide insufflation was investigated by Sietses et al.[50] in 2002. They examined patients undergoing cholecystectomy, either with carbon dioxide insufflation, helium insufflation, or with an abdominal wall lifting technique. They noted that CRP levels were significantly higher in the helium and abdominal wall lifting groups, indicating that incision size alone was not responsible for the altered CRP response.[50] Similar findings were seen in an animal model when the rat acute-phase proteins α2-macroglobulin and β-fibrinogen were evaluated in response to abdominal sepsis.[51] Rats underwent cecal ligation and puncture either open or laparoscopically using either carbon dioxide or helium insufflation. The expression of the genes for α2-macroglobulin and β-fibrinogen were significantly lower in the rats with carbon dioxide insufflation compared to those with laparotomy or helium insufflation. These and other studies demonstrate that carbon dioxide insufflation is a key component to the attenuated inflammatory response after laparoscopy.

Cytokines The cytokine response to laparoscopy has been thoroughly investigated. Interleukin 6 (IL-6) is the major cytokine responsible for the acute-phase protein response. It is an early marker of tissue damage and its levels rise in proportion to tissue trauma. Like CRP, IL-6 levels do not reach levels as high in patients undergoing laparoscopic procedures compared to open procedures.[49] In a prospective trial, patients undergoing laparoscopic cholecystectomy had significantly lower IL-6 response than those who had a conventional, open cholecystectomy up to 2 days postoperatively.[52] Similar responses were seen after colon resection, with patients undergoing laparoscopic colectomy exhibiting a significantly reduced IL-6 release when compared with those undergoing an open colectomy.[27] The reduction in IL-6 response appears to be influenced specifically by CO_2 insufflation. Ure et al.[53] showed that pigs insufflated with carbon dioxide had a significantly lower release of IL-6 compared to those insufflated with air.

Further studies have shown that other cytokines are also influenced by the carbon dioxide environment of laparoscopy. West et al.,[54] investigated the release of the pro-inflammatory cytokines tumor necrosis factor alpha (TNF-α) and IL-1 in macrophages incubated in different environments and stimulated with lipopolysaccharide (LPS). The release of these cytokines was significantly

lower in those cells incubated in carbon dioxide as compared to helium or air.[54] Similar results were seen in an in vivo experiment in which rats stimulated with intravenous LPS were either not insufflated or insufflated with helium or carbon dioxide. Those animals exposed to CO_2 pneumoperitoneum had a significantly lower level of TNF-α than the control animals. Furthermore, those animals insufflated with carbon dioxide had an even lower level of TNF-α than those insufflated with helium.[55] These results all suggest that there is a modulation of the pro-inflammatory response with carbon dioxide insufflation.

Bacterial Clearance There is continued debate over whether there is an increased occurrence of infectious complications and tumor spread with laparoscopic procedures compared to open laparotomy. Because of this debate, there has been active investigation of the phagocytic capability and immune response of intraperitoneal cells to carbon dioxide pneumoperitoneum with no clear consensus yet reached. Watson et al.[56] examined the phagocytic activity of murine peritoneal macrophages during laparotomy or laparoscopy with either air or carbon dioxide and found the macrophages from mice insufflated with carbon dioxide had significantly better phagocytic capacity than the other groups.[56] Gutt et al.,[57] however, had different results. They studied the function of the mononuclear phagocyte system (MPS) during open fundoplication, laparoscopic fundoplication using carbon dioxide, or gasless laparoscopic fundoplication in rats. They evaluated the MPS function using a carbon clearance test and noted the best carbon clearance in the gasless laparoscopy group and the worst carbon clearance in the carbon dioxide laparoscopy group.[57] Finally, in a randomized trial in human patients undergoing upper gastrointestinal laparoscopic surgery with either helium or air, type of insufflation gas did not affect macrophage phagocytosis.[58] Thus, this is still an important open question.

Overall, the effects of carbon dioxide insufflation on the stress response continue to be discovered. It seems to be one of a blunted inflammatory response compared to open procedures. There are divergent data on the effect of carbon dioxide on other peritoneal macrophage immune functions and no convincing evidence that insufflation increases the incidence of or protects from postoperative infections. The clinical consequences of the immune alterations seen during laparoscopy continue to be investigated (Fig. 2).

Conclusion

As surgeons, we are exposing millions of patients each year to operations that involve the placement of gas (usually CO_2) under pressure in various, and sometimes multiple, body cavities. General clinical experience suggests that there are no obvious dire or hugely beneficial effects of this. However, we owe it to our patients to understand the biology of this dramatic change in our mode of surgery. This is particularly true, as laparoscopic operations become longer, more complex, and take place in less healthy patients. We have reviewed some of the key laboratory findings to date in this important emerging field.

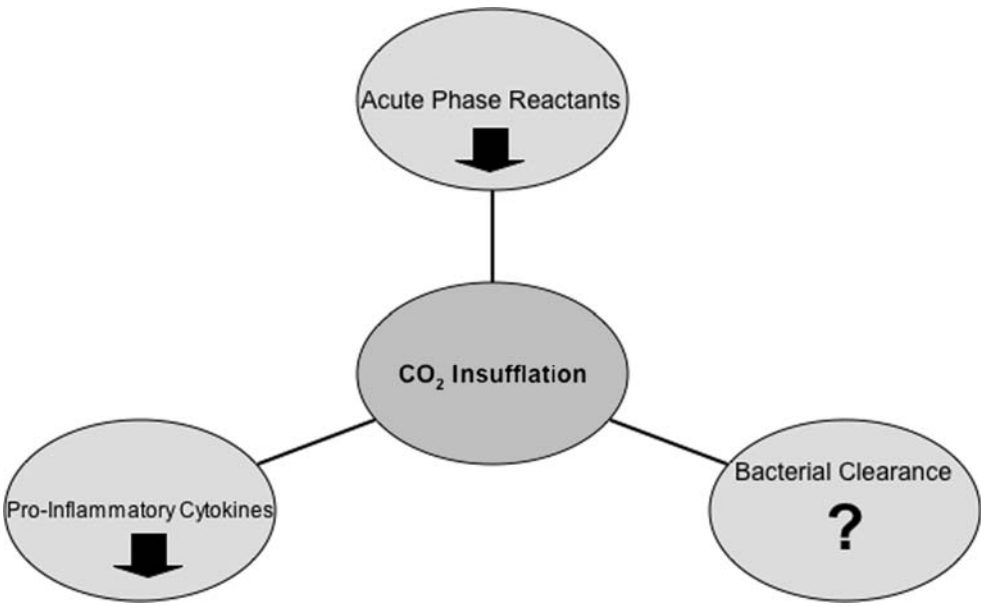

Figure 2 The proposed effect of carbon dioxide insufflation on the systemic inflammatory response compared to either open operation or laparoscopy using helium, air, or abdominal wall lifting technique.

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GI IMAGE

CT Findings in Diffuse Rectosigmoid Cavernous Heamangioma. A Case Report

Aijaz Ahmad Hakeem · Hakim Shafi · Tariq Gojwari · Feroze Shaheen · Manjeet Singh · Muneer Wani · Shubana Rasool

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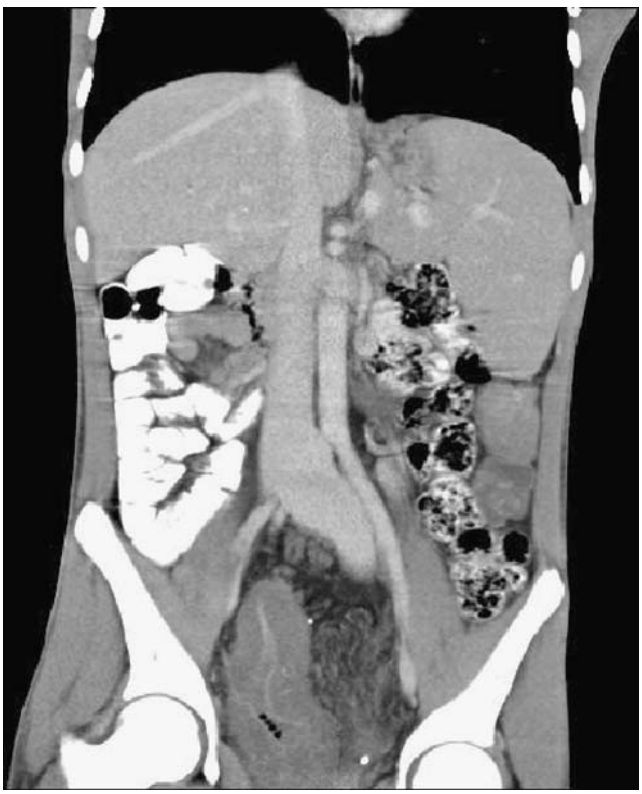
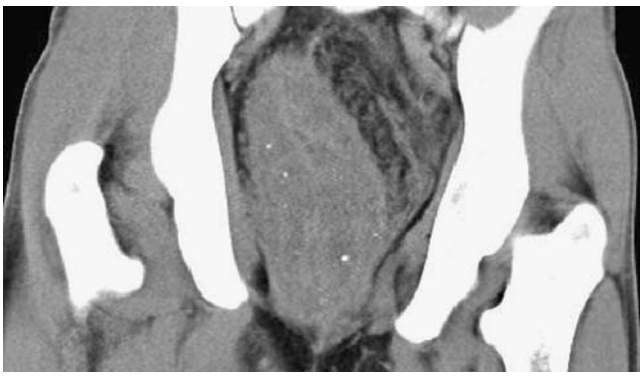
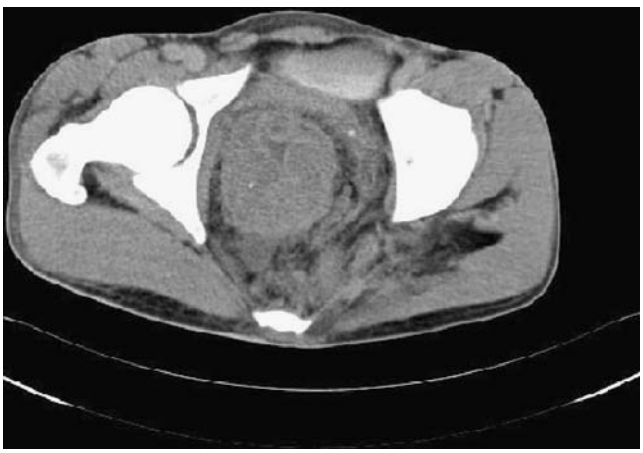
Case Report

A 15-year-old boy presented with long-standing bleeding of the rectum to the department of gastroenterology. Per rectal digital examination and proctoscopy did not reveal any definite local cause of bleeding. The patient was sent to the department of radiology for computed tomography (CT) scan. CT was done on 64 multislice CT scan, which shows marked rectosigmoid wall thickening as a result of varices and vascular malformations and phleboliths of the rectosigmoid colon. The patient was subjected to abdominal surgery in which a sphincter-saving procedure was done. Postoperative course in the hospital was uneventful.







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Discussion

Vascular malformations of the gastrointestinal tract causing hemorrhage were first described by Philip in 1829.[1] The pathogenesis of these tumors is not well defined. However, they are generally congenital, with their origin in embryologic sequestrations of mesodermal tissue. Enlargement occurs by projection of budding endothelial cells. Whether these growths are neoplastic or congenital is a matter of some controversy. Malignant transformations are rare.[2] The results of ligation and embolization of the mesenteric vessels are not successful, although abdominoperineal resection was the most often recommended procedure. In recent years, sphincter-saving procedures have become popular if hemorrhage can be controlled and there is no evidence of malignant change.[3] Cavernous hemangioma of the rectosigmoid colon is a rare disease, with no more than 200 cases reported in the literature. The rectosigmoid is the most common site of this disease in the gastrointestinal tract.[4] The patients' ages range from 5 to 25 years and the principal presenting complaint is painless, massive rectal bleeding.[5] Colonoscopy is, without doubt, the diagnostic technique of choice, and it allows establishing the localization, morphology, and total extension of the lesion; its characteristic image is a red-purplish nodule with great vascular congestion. According to the opinion of most authors, biopsy is not advisable during colonoscopy since imaging techniques are sufficient for an accurate diagnosis and the risk of bleeding while manipulating this lesion is not negligible.

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LETTER TO THE EDITORS

The Effect of Vasopressors on Perfusion of Gastric Graft after Esophagectomy

Marc Buise · Jasper van Bommel · Diederik Gommers

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Dear editor,

We read with interest the article on gastric graft perfusion by Theodorou and co-workers.[1] The article describes the negative effect of norepinefrin in gastric graft microcirculation. Gastric microvascular blood flow following esophagectomy is a difficult area for research at which we recently tried to contribute and we encourage every research in this specific field.[2,3]

However, we have some remarks on this study. First, the use of a hemorrhage model is not a good analog of the clinical situation. The use of vasopressors in case of hemorrhage will affect microcirculation. Hypotension during surgery and especially the hemodynamic effect of epidural analgesia, as mentioned in the conclusion, have other physiological mechanisms. Recently, the positive effect of epinephrine on gastric tube perfusion, in combination with epidural analgesia has been described.[4] Second, in humans, the gastric tube is fashioned along the greater curvature of the stomach, and the blood supply is mainly based on the right gastricepiploic artery. In the model used, blood supply of the gastric graft was also based on the right gastroepiploic artery. In pigs, however, the main characteristic of vascular anatomy was a dominant left gastroepiploic artery, sometimes combined with well-defined short gastric arteries.[5] Third, fluid management is of great importance in such a study, but no additional information is given. We wonder why blood pressure was so low at the end of the hemorrhage; in a pig of 30 kg, the loss of 200 ml blood is normally not accompanied by a decrease in pressure. We miss the information of central venous pressure and cardiac output. Animal number 5 is not recovering from the shock, and blood pressure is extremely low during steps 3 and 4. Is this animal still representative for the study? According to the protocol, the blood pressure should be increased from 80 to 90 mm Hg. Figure 1, in their article, shows this goal was never reached. Is this perhaps an effect of hypovolemia?

Finally, in our opinion, the use of paired *t* test in this study design is not appropriate. Analysis of variance would be more correct for repeated measurements.

Yours sincerely,

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LETTER TO THE EDITORS

The Effect of Vasopressors on Perfusion of Gastric Graft after Esophagectomy—Reply to Buise et al.

Stylianos Katsaragakis · Andreas Larentzakis · Panagiotis Drimousis · Dimitrios Theodorou

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Dear Editor,

We appreciate the comments of Dr. Buise and his team that have extensively studied and published on the effects of several pharmacological agents on splanchnic perfusion.

In our hospital, we use epidural analgesia but especially avoid the use of local anesthetics perioperatively in order to avoid the hypotension that these agents provoke. Regarding the effects of epinephrine on splanchnic perfusion, we have to bear in mind that epinephrine is not only a pure vasoconstrictor but also has a positive inotropic cardiac effect, which increases the cardiac output. As epinephrine is rarely used in the perioperative period, due to several side effects that it has (i.e., tachycardia, coronary artery vasoconstriction), we elected not to study this medication.

It is known that the left gastroepiploic artery is the main vessel in the pigs' gastric greater curvature anatomy. We did preserve the vascular arcade, we used the same technique in all animals, and finally, we had baseline measurements in order to maintain the comparability of our results.

Further measurements and details of the protocol are available but were not found necessary to be included in the presented data.

Yours sincerely

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