J Gastrointest Surg (2009) 13:2095–2103
DOI 10.1007/s11605-009-1049-6

2009 SSAT PLENARY PRESENTATION

Multiple Preoperative Endoscopic Interventions Are Associated with Worse Outcomes After Laparoscopic Heller Myotomy for Achalasia

Christopher W. Snyder · Ryan C. Burton · Lindsay E. Brown · Manasi S. Kakade · Kelly R. Finan · Mary T. Hawn

Received: 29 May 2009 / Accepted: 11 September 2009 / Published online: 30 September 2009

Abstract
Background The effect of preoperative pneumatic dilation or botulinum toxin injection on outcomes after laparoscopic Heller myotomy (LHM) for achalasia is unclear. We compared outcomes in patients with and without multiple preoperative endoscopic interventions.
Methods This cohort study categorized achalasia patients undergoing first-time LHM by the number of preoperative endoscopic interventions: zero or one intervention vs. two or more interventions. Outcomes of interest included surgical failure (defined as the need for re-intervention), gastrointestinal symptoms, and health-related quality of life. Logistic regression modeling was performed to determine the independent effect of multiple preoperative endoscopic interventions on the likelihood of surgical failure.
Results One hundred thirty-four patients were included; 88 (66%) had zero to one preoperative intervention, and 46 (34%) had multiple (more than one) interventions. The incidence of surgical failure was 7% in the zero to one intervention group and 28% in the more than one intervention group ($p<0.01$). Greater improvements in gastrointestinal symptoms and health-related quality of life were seen in the zero to one intervention group. On logistic regression modeling, the likelihood of surgical failure was significantly higher in the more than one intervention group (odds ratio=5.1, 95% confidence interval 1.6–15.8, $p=0.005$).
Conclusions Multiple endoscopic treatments are associated with poorer outcomes and should be limited to achalasia patients who fail surgical therapy.

Grant Support: Dr. Snyder receives salary support under an educational grant from Olympus America, Inc.

Presented at the 50th Annual Meeting of the Society for Surgery of the Alimentary Tract, June 1, 2009, Chicago, IL.

C. W. Snyder
Department of Surgery, University of Alabama at Birmingham, Birmingham, AL, USA

R. C. Burton · L. E. Brown
School of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA

M. S. Kakade · M. T. Hawn (✉)
Section of Gastrointestinal Surgery, Department of Surgery, University of Alabama at Birmingham, 1922 7th Avenue South, KB 428, Birmingham, AL 35294-0016, USA
e-mail: mhawn@uab.edu

K. R. Finan
Barnes-Jewish Medical Center, St. Louis, MO, USA

M. T. Hawn
Center For Surgical, Medical Acute Care Research and Transitions, Birmingham Veterans Affairs Medical Center, Birmingham, AL, USA

Keywords Achalasia · Pneumatic dilation · Botulinum toxin · Myotomy · Treatment failure · Outcomes

Introduction

Laparoscopic Heller myotomy (LHM) is safe, effective, and the most definitive treatment for the symptoms of achalasia.[1–5] Endoscopic pneumatic balloon dilations or botulinum toxin (Botox, Allergan) injections at the lower esophageal sphincter (LES) are effective but less durable.[6,7] The optimal treatment strategy for newly diagnosed achalasia remains controversial. Some authors advocate endoscopic treatments as a cheaper and less invasive initial approach, with LHM as a rescue therapy if symptoms recur.[8–11] Others contend that endoscopic interventions cause inflammation and scarring at the LES, compromising future surgical treatment.[12,13] Studies evaluating the association of preoperative endoscopic interventions with surgical outcomes have yielded conflicting results, with some showing worse outcomes among those treated endoscopically[14–17] and others showing no difference.[18–21]

The association between preoperative endoscopic treatments and surgical outcomes is further clouded by varying definitions of surgical failure based on postoperative symptoms. Postoperative dysphagia may arise from recurrence or persistence of achalasia, possibly due to endoscopic LES trauma, inadequate myotomy, or a different subtype or severity of achalasia.[3,22,23] Postoperative gastrointestinal (GI) symptoms may also arise due to separate conditions, such as gastroesophageal reflux disease (GERD) or gastroparesis.

Based on the proven effectiveness of LHM and evidence suggesting that preoperative endoscopic treatments worsen surgical outcomes, some have argued that endoscopic interventions should have no role among surgical candidates.[16] However, a single endoscopic dilation or Botox injection may be useful as a bridge to surgery, and response to Botox injection may provide valuable information in cases where the diagnosis is unclear.[24,25]

The present study evaluated a group of achalasia patients treated with LHM, comparing those with zero or one preoperative endoscopic intervention to those with multiple interventions with respect to clinical outcomes, symptom profiles, and health-related quality of life (HRQOL).

Methods

This cohort study included all patients undergoing first-time laparoscopic Heller myotomy for achalasia at the University of Alabama at Birmingham (UAB) between November 2001 and January 2008. Patients who had previously undergone transabdominal or transthoracic esophagomyotomy were excluded. Operations were performed by two surgeons with minimally invasive surgery fellowship training, using standard techniques for myotomy and Dor fundoplication.[26] Approval for the study was obtained from the UAB Institutional Review Board.

Chart review was used to quantify preoperative pneumatic dilations and Botox injections. Bougie dilations (e.g., Maloney or Savary-Guillard) were not counted as endoscopic interventions. Patients were classified into two groups based on the total number of preoperative endoscopic interventions performed: zero or one intervention vs. two or more interventions.

Demographics, medical history, operative details, and clinical outcomes were obtained by chart review. Preoperative GI symptom profiles and HRQOL were assessed with the GERD Symptom Assessment Scale (GSAS) and Short Form-36 (SF-36, RAND Corporation, Santa Monica, CA, USA), respectively. The GSAS is a validated questionnaire used to quantify the frequency, severity, and distress of 15 GERD-related GI symptoms that often overlap with achalasia symptoms.[27] Symptom distress scores range from zero for not at all distressing to three for extremely distressing. The SF-36 is a questionnaire used to assess generic HRQOL; it has been used in several recent studies of achalasia patients.[28,29]

At a median of 22 months postoperatively, three questionnaires were mailed to all patients: an achalasia-specific outcome questionnaire, a GSAS, and an SF-36. The achalasia-specific outcome questionnaire inquired about overall symptom improvement, satisfaction, current medication use for GI symptoms, weight changes, dietary restrictions, and any additional postsurgical therapy.

Surgical failure, the primary outcome of interest, was defined as requiring postoperative Botox injection, pneumatic dilation, or repeat surgical myotomy. A patient was classified as a surgical failure if the need for additional intervention was documented in the chart or reported by the patient on the survey.

Secondary outcomes of interest included gastroparesis, changes in GI symptoms, and changes in HRQOL. Symptomatic gastroparesis was defined as chronic nausea, vomiting, early satiety, or abdominal bloating, in association with either delayed gastric emptying on upper GI contrast or nuclear medicine study, or gastric bezoar on endoscopy. Norm-based scores for the eight SF-36 domains, Physical Component Score (PCS), and Mental Component Score (MCS) were calculated using 1998 US population norms.

Patient characteristics, outcomes, baseline GSAS symptoms, and baseline HRQOL scores were compared for the two groups using Wilcoxon rank-sum and chi-square tests for continuous and categorical variables, respectively. To confirm the appropriateness of classifying patients into zero to one vs. more than one intervention groups, alternate

patient classification schemes were also explored. Logistic regression modeling was performed to evaluate the following potential predictors of surgical failure: preoperative treatment category (zero to one vs. more than one endoscopic interventions), age, sex, body mass index (BMI), duration of symptoms, American Society of Anesthesiologists (ASA) class, chronic narcotic use, and vigorous achalasia or esophageal tortuosity on barium swallow. Since the median duration of follow-up for the overall cohort was relatively short, the modeling process was repeated using only a subset of patients with longer follow-up. This subset consisted of all patients who had both survey and chart outcome data. Statistical analysis was performed using SAS 9.1.3 (SAS Institute, Cary, NC, USA).

Patient-reported outcomes were compared between groups using chi-square and Wilcoxon rank-sum tests. Baseline GSAS symptom profiles and SF-36 HRQOL scores were compared between groups. Pre- to postoperative changes in GSAS symptom presence and distress level and SF-36 HRQOL scores were evaluated for significant departure from baseline using chi-square and Student's *t* tests.

Results

One hundred and thirty-four patients met inclusion criteria; 88 (66%) patients were in the zero to one intervention group and 46 (34%) in the more than one intervention group. Group characteristics and clinical outcomes are shown in Table 1. Patients in the more than one intervention group were slightly older (median age 51 vs. 47, $p=0.05$), had longer durations of symptoms (median 36 vs. 24 months, $p=0.003$), and had higher ASA classifications (41% vs. 18% ASA 3–4, $p=0.004$). There were no significant differences between groups with respect to intraoperative vagus nerve injury, gastric or esophageal mucosal tears, operative time, or estimated blood loss. No postoperative leaks or deaths occurred in either group. Median length of hospital stay

Table 1 Study Population Characteristics and Outcomes, Stratified by Number of Preoperative Endoscopic Interventions

	0–1 (*N*=88)	>1 (*N*=46)	*p*
Preoperative			
Age, median (range)	47 (17–76)	51 (18–77)	0.05
Female sex, %	43	46	0.78
BMI, median (range)	26 (17–49)	27 (17–49)	0.43
Symptom duration in months, median (range)	24 (3–240)	36 (5–300)	<0.01
Diabetes mellitus, %	15	11	0.53
Current smoker, %	17	24	0.31
Chronic narcotic user, %	6	11	0.31
ASA class, %			
1–2	81	59	<0.01
3–4	18	41	
Prior abdominal surgery, %	40	41	0.86
Prior cardiothoracic surgery, %	3	11	0.12
Esophageal tortuosity on barium swallow, %	4	9	0.49
Vigorous achalasia, %	9	15	0.53
Intraoperative			
Dor fundoplication, %	80	84	0.49
Vagus nerve injury, %	1	4	0.27
Esophageal/gastric mucosal tear, %	17	15	0.79
Operation time in minutes, median (range)	95 (53–192)	96 (63–203)	0.38
Estimated blood loss in mL, median (range)	25 (5–200)	25 (10–100)	0.92
Postoperative			
Leak, %	0	0	–
Length of stay in days, median (range)	1 (1–12)	1 (1–4)	0.15
Surgical failure[a], %	7	28	<0.01
Time to surgical failure in mos., median (range)	3.5 (2–30)	3.0 (1.8–41)	0.95
Symptomatic gastroparesis[b], %	2	7	0.35
Length of follow-up in months, median (range)	10 (1–62)	12 (1–65)	0.87
Survey response rate, %	52	59	0.48

[a] Defined as requirement for additional intervention: Botox injection, pneumatic dilation, or repeat surgical myotomy

[b] Symptoms of gastroparesis (abdominal bloating, nausea, vomiting), in association with delayed gastric emptying on radiographic imaging, or bezoar on endoscopy

was 1 day for both groups. The overall median duration of follow-up was 11.2 months (interquartile range (IQR), 1.4–24.6 months), and the survey response rate was 54%; follow-up time and survey response rates were similar for the two groups.

Overall, 19 patients (14%) required additional interventions and were classified as surgical failures. The proportion of patients experiencing surgical failure was significantly higher in the >1 intervention group (28% vs. 7%, $p=0.001$). Two patients in the zero to one intervention group (2%) and three in the more than one intervention group (7%) were diagnosed with symptomatic gastroparesis postoperatively.

Table 2 summarizes surgical failure rates by number and type of preoperative endoscopic interventions. Failure rates in the groups with zero interventions and one intervention were similar (6.7% vs. 7.1%, $p=0.93$), but both of these rates significantly differed from the failure rate of 28.3% in the multiple intervention group ($p=0.003$ for zero vs. multiple, $p=0.03$ for single vs. multiple). Failure rates were statistically similar for patients with exactly two interventions vs. more than two interventions and for those treated with Botox vs. dilation.

Initial logistic regression modeling revealed that sex, BMI, chronic narcotic use, esophageal tortuosity, and vigorous achalasia did not approach significance as predictors of surgical failure ($p>0.08$). After exclusion of these variables, the final model contained preoperative endoscopic intervention category (zero to one vs. more than one interventions), age, duration of symptoms, and ASA classification. After adjustment for covariates, having multiple preoperative endoscopic interventions was a significant predictor of surgical failure (odds ratio (OR) 5.1, 95% confidence interval (CI) 1.6–15.8, $p=0.005$). Age, duration of symptoms, and ASA class were not significant predictors ($p>0.25$). Forcing vigorous achalasia and esophageal tortuosity into the regression model resulted in a poorer-fitting model and did not substantially alter the results.

Seventy-three patients (54%) returned the postoperative questionnaires. Forty-six (63%) were in the zero to one intervention group and 27 (37%) were in the more than one group. Median follow-up in this subset of patients was 23.1 months (IQR, 13.8–33.8 months). Fifteen patients (20.5%) in the subset experienced surgical failure (i.e., required subsequent intervention). Kaplan–Meier estimates of the overall 1- and 5-year cumulative failure rates were 13% and 35%, respectively. The estimated 5-year failure rate was significantly higher in the more than one intervention group (57% vs. 14%, $p=0.002$, log-rank test). When limited to the subset with longer duration of follow-up, logistic regression modeling of surgical failure produced very similar results to those obtained when modeling the entire cohort. Multiple preoperative endoscopic interventions remained the only significant predictor of surgical failure (OR 6.1, 95% CI 1.5–23.9, $p=0.01$).

Achalasia outcome questionnaire responses are shown in Table 3. Overall, 65 patients (89%) reported resolution or improvement of their achalasia symptoms. Those in the zero to one intervention group were more likely to choose surgery again (100% vs. 89%, $p=0.05$), more likely to be free from dietary restrictions (74% vs. 48%, $p=0.04$), and less likely to be taking daily proton-pump inhibitor medication (24% vs. 52%, $p=0.02$). There was a trend toward more complete symptom resolution among the zero to one group (83% vs. 59% resolved, $p=0.06$).

Fifty-five of the 73 patients who returned postoperative surveys had also completed a preoperative baseline GSAS questionnaire, allowing calculation of the prevalence of

Table 2 Surgical Failure Rates by Number and Type of Preoperative Intervention

	Number in group	*N* (%) failures	p[a]
Number of preoperative endoscopic interventions			
0	60	4 (7)	<0.01
1	28	2 (7)	
2	22	7 (32)	
>2	24	6 (25)	
Single intervention			
Single Botox	11	0 (0)	0.51
Single dilation	17	2 (12)	
Multiple interventions			
Multiple Botox alone	9	2 (22)	0.33
Multiple dilations alone	17	7 (41)	
Botox and dilation	20	4 (20)	
Intervention type			
Any Botox injection, but no dilation	20	2 (10)	0.18
Any dilation, but no Botox	34	9 (26)	

[a] Fisher's exact test

Table 3 Patient-Reported Outcomes in the Zero to One (N=46) and More Than One Intervention Groups (N=27)

	0–1	>1	p
Achalasia symptoms after surgery, %			
Resolved	83	59	0.06
Improved	11	26	
Unchanged	4	15	
Worse	2	0	
Would choose to have surgery again, %	100	89	0.05
No dietary restrictions, %	74	48	0.04
Weight change in kg, median (range)	0.68 (−10.4–30.4)	1.4 (−33.4–28.6)	0.70
Taking daily medication for GI symptoms, %			
Proton pump inhibitor	24	52	0.02
H_2 blocker	2	11	0.14
Metoclopramide	2	0	1.0

various GI symptoms at baseline and follow-up (Table 4). Preoperative symptom profiles were generally similar between the groups, except that the zero to one intervention group reported more baseline hoarseness (31% vs. 5%, p=0.04). Postoperatively, the predominant symptoms of achalasia, difficulty swallowing and regurgitation, decreased significantly in both groups. The prevalence of lump in the throat, acid taste in the mouth, and coughing decreased significantly in the zero to one group but remained unchanged in the more than one group.

Pre- to postoperative changes in symptom distress level are shown in Fig. 1. Distress scores for swallowing difficulty decreased significantly among both groups. Patients in the zero to one group also reported significant decreases in distress from regurgitation, lump in throat, acid taste, and coughing, whereas decreases in distress from

Table 4 GSAS Preoperative and Postoperative Symptom Profiles of the Zero to One (N=35) and More Than One Intervention Groups (N=20)

Symptom	Preoperative symptom prevalence			Postoperative symptom prevalence (change in prevalence[b])			
	0–1	>1	p[a]	0–1	p[c]	>1	p[c]
Achalasia							
Difficulty swallowing	91	80	0.22	32 (−59)	<0.01	35 (−45)	<0.01
Regurgitation	83	75	0.50	32 (−51)	<0.01	45 (−30)	0.05
Pressure or lump in throat	66	47	0.19	18 (−48)	<0.01	40 (−7)	0.64
Chest pain after eating	34	40	0.67	21 (−13)	0.23	20 (−20)	0.17
Reflux							
Heartburn	46	30	0.25	49 (+3)	0.81	55 (+25)	0.11
Acid or sour taste in mouth	57	50	0.61	26 (−31)	<0.01	26 (−24)	0.13
Hoarse voice	31	5	0.04	24 (−7)	0.46	15 (+10)	0.29
Belching	57	50	0.61	47 (−10)	0.40	30 (−20)	0.20
Gastroparesis							
Early satiety	56	55	0.95	35 (−21)	0.09	40 (−15)	0.34
Abdominal bloating	32	45	0.35	41 (−9)	0.45	28 (−17)	0.27
Nonspecific							
Excess flatulence	46	55	0.51	53 (−7)	0.55	35 (−20)	0.20
Shortness of breath	31	35	0.79	26 (−5)	0.65	25 (−10)	0.49
Coughing	64	50	0.33	24 (−40)	<0.01	25 (−25)	0.10
Gurgling in stomach	46	40	0.68	32 (−14)	0.26	25 (−15)	0.31
Pressure in chest	46	55	0.51	29 (−17)	0.16	30 (−25)	0.11

[a] Chi-square test for difference in baseline prevalence between groups

[b] Postoperative prevalence minus preoperative prevalence; negative values indicate symptom resolution

[c] Chi-square test for difference between preoperative and postoperative prevalence within group

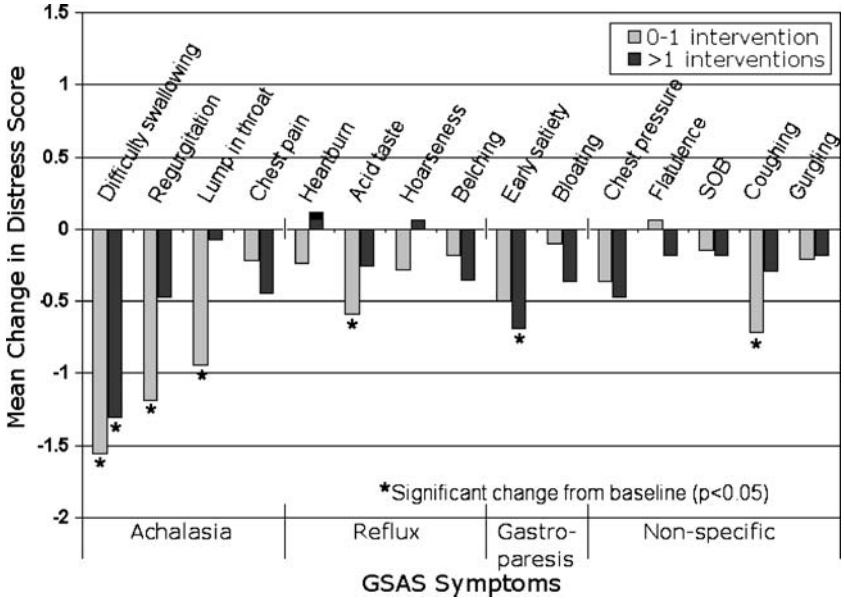


Figure 1 Postoperative changes in GSAS symptom distress level in the zero to one (N=35) and more than one intervention groups (N=20).

these symptoms in the more than one group did not reach significance. Patients in the more than one group reported a significant decrease in early satiety, whereas those in the zero to one group did not reach significance (p=0.07). Distress from other GI symptoms did not change significantly in either group.

Fifty of the 73 patients with postoperative surveys had also completed a preoperative SF-36. Norm-based baseline HRQOL scores and postoperative changes for the two groups are provided in Table 5. Baseline scores were similar for both groups; however, patients in the zero to one group demonstrated significant postoperative improvements in physical function, bodily pain, general health, vitality, social function, and summary physical component scores, whereas those in the more than one group did not improve significantly in any domains.

Discussion

Our study demonstrated that achalasia patients who underwent multiple endoscopic interventions prior to LHM had poorer outcomes than patients with a single intervention or no interventions. After adjustment for relevant covariates, the odds of surgical failure were five times higher among those with multiple interventions.

Table 5 SF-36 Health-Related Quality of Life Preoperative Scores and Postoperative Score Changes for the Zero to One (N=32) and More Than One Intervention Groups (N=18)

SF-36 subscale	Preoperative score, median (range)			Change in score[b], mean (SD)			
	0–1	>1	p[a]	0–1	p[c]	>1	p[c]
Physical function	53 (15–57)	55 (17–57)	0.69	+4.4 (11.9)	0.04	+0.4 (8.3)	0.86
Role limitations—physical	53 (28–56)	56 (28–56)	0.47	+3.2 (15.7)	0.26	0 (11.4)	0.99
Bodily pain	51 (20–63)	46 (30–63)	0.86	+4.8 (10.2)	0.01	+2.1 (12.6)	0.49
General health	47 (22–64)	49 (31–60)	0.63	+3.7 (9.3)	0.03	+0.8 (6.1)	0.58
Vitality	47 (28–68)	48 (28–66)	0.63	+4.1 (9.8)	0.03	+3.7 (9.2)	0.10
Social function	44 (14–57)	49 (35–57)	0.11	+8.0 (14.8)	<0.01	0.6 (10.2)	0.80
Role limitations—emotional	55 (24–55)	55 (24–55)	0.66	+1.7 (13.9)	0.50	+1.8 (12.6)	0.56
Mental health	50 (10–64)	53 (35–64)	0.43	+2.3 (9.6)	0.20	+1.1 (9.3)	0.63
PCS	50 (18–59)	52 (25–59)	0.58	+5.2 (11.4)	0.02	−0.1 (8.5)	0.95
MCS	49 (20–66)	50 (29–60)	0.44	+2.9 (11.7)	0.18	+2.1 (9.1)	0.36

[a] Rank-sum test for difference in baseline scores between groups

[b] Postoperative score minus baseline score; positive values indicate improvement in HRQOL

[c] Student's t test for significance of postoperative change from baseline (i.e., whether mean score change equals zero)

While GI symptoms tended to improve for both groups, patients with multiple interventions reported resolution of fewer symptoms and had smaller decreases in symptom distress. Health-related quality of life improved significantly for patients with zero to one intervention, but remained unchanged among those with multiple interventions.

Our findings agree with those of Smith et al.,[16] who found that the risk of failure after LHM (defined by a symptom score) was nearly twice as high among patients who had undergone preoperative endoscopic intervention. Our results are also in accordance with reports of lower postoperative satisfaction among achalasia patients who were initially treated endoscopically.[15] However, our findings appear inconsistent with several previous studies, including an earlier work from our own institution, which found no difference in outcomes.[18–21]

Such apparent inconsistencies are possibly explained by our approach to patient categorization. Previous studies have compared patients with any preoperative endoscopic treatment to those receiving no prior treatment. If single endoscopic interventions do not adversely affect outcomes and the endoscopically treated cohort consists predominantly of patients with a single prior intervention, then the adverse effects of multiple treatments will be diluted out and the overall effect will be insignificant. Thus, the greater the proportion of multiply treated patients in the endoscopically treated group, the greater is the likelihood of seeing an overall effect. This explanation is supported by the observation that in positive studies of this question, half or more of the endoscopically treated group received multiple treatments.[14,16] Conversely, only about one third of the endoscopically treated group in a recent negative study could be definitely categorized as having received multiple treatments.[21]

The overall failure rates reported in this study may appear high, but one must keep in mind that we defined surgical failure as the need for subsequent intervention. Most previous studies have defined it as failure to relieve symptoms. If surgical success is defined as symptom relief, then our overall success rate was 89% at a median of 23 months, similar to reported success rates of 77–96% in other series.[4] Our overall cumulative failure rate (i.e., re-intervention rate) was 21% at a median 23-month follow-up, with estimated 1- and 5-year cumulative rates of 13% and 35%, respectively. These findings are consistent with a recent large population-based study demonstrating post-myotomy re-intervention rates of 16% at 1 year and 30% at 5 years.[30]

Since gastroparesis after LHM has not been previously reported, it is unclear how our five cases (4%) compare to other institutional experiences. Gastroparesis after LHM may represent a manifestation of advanced achalasia, a preexisting condition unmasked by LES decompression, or a complication caused by endoscopic or surgical trauma. It is biologically plausible that gastroparesis could represent progression of the neurodegenerative achalasia disease process,[31] and gastroparesis has been reported after Botox injection for achalasia.[32] We found no significant effect of multiple endoscopic treatments on gastroparesis risk, although it is interesting that three of the five patients who developed gastroparesis had received preoperative Botox injections.

The reasons underlying the association between multiple preoperative endoscopic interventions and poorer outcomes are unclear. While repeated endoscopic interventions could have caused traumatic changes that compromised surgical therapy, it is also possible that multiple interventions are simply a marker for a refractory disease subtype or additional unmeasured comorbidities. Even though causation cannot be established in this retrospective study, the recognition of multiple endoscopic interventions as a risk factor for suboptimal outcomes is important for prognostication and preoperative patient counseling.

Our findings must be interpreted in the context of several limitations. Follow-up time in the overall cohort was relatively short (median 11 months), so it is likely that the true surgical failure rate was higher than what was observed. However, the patient-reported outcomes, GI symptom, and HRQOL analyses involved a subset of patients with longer follow-up time (median 23 months). When we performed logistic regression within this subset, the results were similar to those obtained by modeling the entire cohort, strengthening our conclusion that surgical failure risk is higher among patients with multiple interventions.

Survey bias may have skewed the patient-reported outcomes, but since follow-up time and survey response rate were evenly distributed between groups, the bias should also be evenly distributed and therefore unlikely to change the results. Diminishing sample size limited the power of the GI symptom and HRQOL analyses and may have disproportionately affected the results for the more than one intervention group, which was smaller. However, the effect sizes for postoperative GI symptom and HRQOL improvement were considerably larger in the zero to one group, so the lack of significant changes in the more than one group cannot be attributed solely to a lack of power.

Conclusion

Our study supports the use of laparoscopic Heller myotomy as the preferred first-line treatment for achalasia. A single preoperative endoscopic intervention as a diagnostic maneuver or bridge to surgery may be appropriate, but multiple interventions are associated with poorer surgical outcomes and should be avoided. Advances in surgical and

anesthetic technique have made operative treatment safe and feasible for most patients with a reasonable life expectancy. Further investigation is needed to elucidate the relationships between endoscopic interventions, treatment failure, symptom patterns, and gastroparesis in patients with achalasia.

References

1. Costantini M, Zaninotto G, Guirroli E, Rizzetto C, Portale G, Ruol A, Nicoletti L, Ancona E. The laparoscopic Heller–Dor operation remains an effective treatment for esophageal achalasia at a minimum 6-year follow-up. Surg Endosc 2005;19:345–351.
2. Frantzides CT, Moore RE, Carlson MA, Madan AK, Zografakis JG, Keshavarzian A, Smith C. Minimally invasive surgery for achalasia: a 10-year experience. J Gastrointest Surg 2004;8:18–23.
3. Patti MG, Molena D, Fisichella PM, Whang K, Yamada H, Perretta S, Way LW. Laparoscopic Heller myotomy and Dor fundoplication for achalasia: analysis of successes and failures. Arch Surg 2001;136:870–877.
4. Williams VA, Peters JH. Achalasia of the esophagus: a surgical disease. J Am Coll Surg 2009;208:151–162.
5. Zaninotto G, Costantini M, Rizzetto C, Zanatta L, Guirroli E, Portale G, Nicoletti L, Cavallin F, Battaglia G, Ruol A, Ancona E. Four hundred laparoscopic myotomies for esophageal achalasia: a single centre experience. Ann Surg 2008;248:986–993.
6. Kostic S, Kjellin A, Ruth M, Lonroth H, Johnsson E, Andersson M, Lundell L. Pneumatic dilatation or laparoscopic cardiomyotomy in the management of newly diagnosed idiopathic achalasia. Results of a randomized controlled trial. World J Surg 2007;31:470–478.
7. Zaninotto G, Annese V, Costantini M, Del Genio A, Costantino M, Epifani M, Gatto G, D'Onofrio V, Benini L, Contini S, Molena D, Battaglia G, Tardio B, Andriulli A, Ancona E. Randomized controlled trial of botulinum toxin versus laparoscopic Heller myotomy for esophageal achalasia. Ann Surg 2004;239:364–370.
8. Eckardt VF, Gockel I, Bernhard G. Pneumatic dilation for achalasia: late results of a prospective follow up investigation. Gut 2004;53:629–633.
9. Richter JE. Update on the management of achalasia: balloons, surgery and drugs. Expert Rev Gastroenterol Hepatol 2008;2:435–445.
10. Urbach DR, Hansen PD, Khajanchee YS, Swanstrom LL. A decision analysis of the optimal initial approach to achalasia: laparoscopic Heller myotomy with partial fundoplication, thoracoscopic Heller myotomy, pneumatic dilatation, or botulinum toxin injection. J Gastrointest Surg 2001;5:192–205.
11. Rosemurgy A, Villadolid D, Thometz D, Kalipersad C, Rakita S, Albrink M, Johnson M, Boyce W. Laparoscopic Heller myotomy provides durable relief from achalasia and salvages failures after Botox or dilation. Ann Surg 2005;241:725–733. discussion 733–5.
12. Richardson WS, Willis GW, Smith JW. Evaluation of scar formation after botulinum toxin injection or forced balloon dilation to the lower esophageal sphincter. Surg Endosc 2003;17:696–698.
13. Horgan S, Hudda K, Eubanks T, McAllister J, Pellegrini CA. Does botulinum toxin injection make esophagomyotomy a more difficult operation? Surg Endosc 1999;13:576–579.
14. Patti MG, Feo CV, Arcerito M, De Pinto M, Tamburini A, Diener U, Gantert W, Way LW. Effects of previous treatment on results of laparoscopic Heller myotomy for achalasia. Dig Dis Sci 1999;44:2270–2276.
15. Peillon C, Fromont G, Auvray S, Siriser F. Achalasia: the case for primary laparoscopic treatment. Surg Laparosc Endosc Percutan Tech 2001;11:71–75.
16. Smith CD, Stival A, Howell DL, Swafford V. Endoscopic therapy for achalasia before Heller myotomy results in worse outcomes than Heller myotomy alone. Ann Surg 2006;243:579–584. discussion 584–6.
17. Portale G, Costantini M, Rizzetto C, Guirroli E, Ceolin M, Salvador R, Ancona E, Zaninotto G. Long-term outcome of laparoscopic Heller–Dor surgery for esophageal achalasia: possible detrimental role of previous endoscopic treatment. J Gastrointest Surg 2005;9:1332–1339.
18. Bonavina L, Incarbone R, Reitano M, Antoniazzi L, Peracchia A. Does previous endoscopic treatment affect the outcome of laparoscopic Heller myotomy? Ann Chir 2000;125:45–49.
19. Deb S, Deschamps C, Allen MS, Nichols FC 3rd, Cassivi SD, Crownhart BS, Pairolero PC. Laparoscopic esophageal myotomy for achalasia: factors affecting functional results. Ann Thorac Surg 2005;80:1191–1194. discussion 1194–5.
20. Finan KR, Renton D, Vick CC, Hawn MT. Prevention of postoperative leak following laparoscopic Heller myotomy. J Gastrointest Surg 2008;13:200–205.
21. Cowgill SM, Villadolid DV, Al-Saadi S, Rosemurgy AS. Difficult myotomy is not determined by preoperative therapy and does not impact outcome. JSLS 2007;11:336–343.
22. Zaninotto G, Costantini M, Portale G, Battaglia G, Molena D, Carta A, Costantino M, Nicoletti L, Ancona E. Etiology, diagnosis, and treatment of failures after laparoscopic Heller myotomy for achalasia. Ann Surg 2002;235:186–192.
23. Pandolfino JE, Kwiatek MA, Nealis T, Bulsiewicz W, Post J, Kahrilas PJ. Achalasia: a new clinically relevant classification by high-resolution manometry. Gastroenterology 2008;135:1526–1533.
24. Katzka DA, Castell DO. Use of botulinum toxin as a diagnostic/therapeutic trial to help clarify an indication for definitive therapy in patients with achalasia. Am J Gastroenterol 1999;94:637–642.
25. Vittal H, Pasricha PF. Botulinum toxin for gastrointestinal disorders: therapy and mechanisms. Neurotox Res 2006;9:149–159.
26. Patti MG, Fisichella PM. Laparoscopic Heller myotomy and Dor fundoplication for esophageal achalasia. How I do it. J Gastrointest Surg 2008;12:764–766.
27. Rothman M, Farup C, Stewart W, Helbers L, Zeldis J. Symptoms associated with gastroesophageal reflux disease: development of a questionnaire for use in clinical trials. Dig Dis Sci 2001;46:1540–1549.
28. Harnish JL, Darling GE, Diamant NE, Kortan PP, Tomlinson GA, Deitel W, Laporte A, Urbach DR. Patient-centered measures for achalasia. Surg Endosc 2007;22:1290–1293.
29. Huffmanm LC, Pandalai PK, Boulton BJ, James L, Starnes SL, Reed MF, Howington JA, Nussbaum MS. Robotic Heller myotomy: a safe operation with higher postoperative quality-of-life indices. Surgery 2007;142:613–618. discussion 618–20.
30. Lopushinsky SR, Urbach DR. Pneumatic dilatation and surgical myotomy for achalasia. JAMA 2006;296:2227–2233.
31. Csendes A, Smok G, Braghetto I, Gonzalez P, Henriquez A, Csendes P, Pizurno D. Histological studies of Auerbach's plexuses of the oesophagus, stomach, jejunum, and colon in patients with achalasia of the oesophagus: correlation with gastric acid secretion, presence of parietal cells and gastric emptying of solids. Gut 1992;33:150–154.
32. Gutierrez-Galiana E, Botoman VA, Bech H. Symptomatic gastroparesis in a patient with achalasia. J Clin Gastroenterol 1998;27:166–168.

Discussant

Dr. John G. Hunter (Portland, OR): Over a decade ago, John Dent, a gastroenterologist and an acknowledged "dean" of evidence-based esophagology stated: "...For the

otherwise healthy patient, the PRIMARY treatment of choice for achalasia should be laparoscopic Heller myotomy and partial fundoplication," and yet we continue to see patients who have had several endoscopic treatments before surgical referral. This observational study concludes that Heller outcomes are dramatically worse in patients who have had multiple previous treatments, yet the operation itself is not that much more difficult in patients following endoscopic therapy. Is it possible that:

1. Patients who are symptomatic failures of balloon and/or Botox are more likely to remain symptomatic after any therapy (including Heller) than their counterparts who achieve symptomatic success after primary treatment? Said another way, are unhappy patients likely to stay unhappy, no matter what you do to them? I would suggest that your quality of life data would support this hypothesis.
2. While not statistically significant on univariate analysis and therefore not entered into the regression modeling, it appears that there was more anatomically advanced or functionally atypical disease in group 2. Lumped together, might it be suggested that patients with more advanced or atypical disease at presentation might do worse?
3. And what about gastroparesis? Pan GI motility disorders can be seen in Chaga's disease, but has not commonly associated with "idiopathic" achalasia. What is the cause? Should we start looking for this in all our achalasia patients?

In closing, I would like to return to the primary finding of this paper: Not only is it more expensive to treat achalasia patients inadequately before surgical referral, it appears that outcome will be MUCH improved if they are referred for surgery immediately after diagnosis. Congratulations Drs. Snyder, Hawn, and team. This paper is a great contribution, and, oh yes, the manuscript is excellent. Read it in JOGS or on the Springer website soon.

Closing Discussant

Dr. Christopher W. Snyder (Birmingham, AL): Thank you very much, Dr. Hunter, for your insightful questions and for taking the time to review our manuscript. Regarding your first question, it is certainly possible that selection bias and unmeasured confounders affected our results.

But I think two things suggest that is not the only thing going on.

One is that these groups were similar preoperatively in terms of quality of life, and two, we saw differences both in subjective outcomes and in the objective outcome of re-intervention. We do not re-intervene just because a patient is unhappy; there has to be objective evidence of recurrent or persistent achalasia.

Two, regarding possible confounding effects of vigorous achalasia and esophageal dilation: We tried forcing those variables back into our regression models even though they did not reach significance, and including them did not change the overall results.

In terms of gastroparesis, I think the answer is unknown. Some histologic studies have shown progression of the neurodegenerative process onto the stomach in achalasia patients, so gastroparesis may just be a progression of disease. It could also be an unrelated comorbidity that is unmasked when you decompress the lower esophageal sphincter, or it could be an iatrogenic byproduct of surgical or endoscopic trauma. We really do not know and it is an interesting hypothesis for further study.

Discussant

Dr. Mario Costantini (University of Padua): I have a question. Did you try and split the group of patients with multiple endoscopic treatments between patients who received Botox and those who underwent dilatations? Are there any difference between the two groups? This is because, in our own experience, the dilatations do not really matter, but Botox does.

Closing Discussant

Dr. Christopher W. Snyder (Birmingham, AL): We would have preferred to stratify our analysis by Botox and dilation. Unfortunately, when we tried, our group sizes got so small that we did not have the statistical power to do a meaningful analysis.

Discussant

Dr. Selwyn M. Vickers (Minneapolis, MN): In your preparation of the manuscript after the study, what is the persistence in the GI literature that supports the interventions that you see by our colleagues with these multiple diseases before pursuing surgery?

Closing Discussant

Dr. Christopher W. Snyder (Birmingham, AL): There are several studies in the GI literature that advocate endoscopic interventions as an initial treatment. One of them was a cost-effectiveness study that compared endoscopic interventions vs. immediate surgery, and they found that overall costs were lower among those that got endoscopic treatments.

J Gastrointest Surg (2009) 13:2104–2112
DOI 10.1007/s11605-009-1053-x

2009 SSAT PLENARY PRESENTATION

Transoral Endoscopic Inner Layer Esophagectomy: Management of High-Grade Dysplasia and Superficial Cancer with Organ Preservation

Bart P. L. Witteman · Tyler J. Foxwell · Sandy Monsheimer · Andres Gelrud · George M. Eid · Alejandro Nieponice · Robert W. O'Rourke · Toshitaka Hoppo · Nicole D. Bouvy · Stephen F. Badylak · Blair A. Jobe

Received: 1 June 2009 / Accepted: 16 September 2009 / Published online: 14 October 2009

Abstract
Introduction Limitations of endoscopic therapies for Barrett's esophagus and superficial cancer include a compromised histological assessment, the need for surveillance, subsequent procedures, and stricture formation. Circumferential en bloc resection of the mucosa–submucosa complex followed by deployment of a biologic scaffold onto the remaining muscularis propria may address these concerns. The objective of this study was to determine technical feasibility of transoral resection of the esophageal lining.
Materials and Methods Transoral endoscopic inner layer esophagectomy was performed in ten swine. Endpoints included procedure duration, hemorrhage, number of perforations, and adequacy of resection length and depth.
Results Procedures were successfully completed in all animals without perioperative mortality. Procedure times averaged 179 min (range 125–320). No perforations were found, and a mean of 1.7 (0–4) interventions for hemorrhage was required. Complete longitudinal resection was achieved in nine of ten animals. Resection depth included all mucosal layers in 100% of tissue sections, the submucosal layers, SM1 in 100%, and SM2 in 96%. A portion of SM3 was adherent to the muscularis propria in 70%.
Conclusion Transoral endoscopic resection of the inner esophageal layers was feasible and reproducible. This technique may facilitate a single-step definitive treatment and staging tool for early neoplastic lesions, obviating the need for esophagectomy.

Keywords Endoscopy · Esophagus · Barrett's esophagus · High-grade dysplasia · Esophagectomy · Cancer · Transoral · Incisionless

Abbreviations
TEE Transoral endoscopic inner layer esophagectomy
MSC Mucosa–submucosa complex

Introduction

Esophageal resection is the standard treatment for Barrett's esophagus with high-grade dysplasia (HGD) and invasive malignancy.[1,2] Despite a significant reduction in mortality rate reported by experienced centers, esophagectomy is associated with substantial morbidity rates.[3–5] As a result,

This work was presented at the annual meeting of the Society of Surgeons of the Alimentary Tract, during the Digestive Disease Week, May 30th–June 4th 2009, McCormick Place, Chicago, IL, USA.

Electronic supplementary material The online version of this article (doi:10.1007/s11605-009-1053-x) contains supplementary material, which is available to authorized users.

B. P. L. Witteman · T. J. Foxwell · S. Monsheimer · T. Hoppo · B. A. Jobe
Division of Thoracic and Foregut Surgery, Heart, Lung and Esophageal Surgery Institute, University of Pittsburgh, Pittsburgh, PA, USA

A. Gelrud
Department of Medicine, Division of Gastroenterology, University of Pittsburgh, Pittsburgh, PA, USA

there has been an impetus to move toward esophageal preservation in patients with intramucosal neoplastic lesions in which lymphatic involvement is unlikely.[6–8]

The introduction of endoscopic approaches such as endoscopic mucosal resection and radiofrequency ablation has resulted in a public demand for definitive endoscopic treatments which ultimately preserve the esophagus. The primary limitation of current techniques resides in an incomplete and inconsistent histological assessment of the entire affected luminal surface area. As such, patients require life-long surveillance and subsequent interventions for undetected synchronous or metachronous lesions.[9,10] While endoscopic submucosal dissection provides larger specimens, this technique is highly operator dependent, limited by existing technology, and has a high risk of perforation.[11–13] Finally, with all techniques aimed at esophageal preservation, there is a risk for stricture formation, particularly when resection involves the complete circumference, if ablation depth travels into the submucosal layer or if the defect is over 30 mm in length.[14–16]

In an attempt to overcome these limitations, we started a research project, which is focused on obtaining an intact sleeve of the mucosa–submucosa complex (MSC) over the entire length of the diseased esophagus, while preventing stricture formation with the colocalization of porcine bladder-derived extracellular matrix in the remaining muscularis propria tube. The purpose of this study was to evaluate the technical feasibility of transoral endoscopic inner layer esophagectomy (TEE) and determine adequacy of resection length and depth in an animal model.

Materials and Methods

All experiments were conducted in accordance with the 1996 Guide for the Care and Use of Laboratory Animals after approval by the Institutional Animal Care and Use Committee at the University of Pittsburgh.

Procedure Development and Description

Under general anesthesia using intramuscular injections of ketamine (20 mg/kg) and xylazine (0.1 mg/kg) for induction and 2% isoflurane with endotracheal intubation for maintenance, ten adult female swine (Yorkshire cross) weighing 40–50 kg underwent percutaneous endoscopic gastrostomy placement. The distance from the dental arch to the esophagogastric junction was measured and recorded. In order to access the plane between the MSC and muscularis propria, the procedure was initiated with circumferential "suck-and-cut" endoscopic mucosal resection starting at 25 cm from the dental arch (Fig. 1; Video 1). Using a flexible double channel therapeutic endoscope (GIF-2T160, Olympus America, Center Valley, PA, USA), a circumferential cuff of MSC was developed over a 2 cm length, with submucosal dissection using cap dissection, cautery dissection (insulated tip electrosurgical knife, Olympus, Japan), or hydrodissection with an irrigation catheter (Olympus America, Center Valley, PA, USA). A vein stripper was then passed retrograde through the gastrostomy tube, retrieved endoscopically, and exited orally. A 60-cm trailing suture was tied to the vein stripper at the oral end and a 9.5-mm olive-shaped cap was attached. Subsequently, the stripper was pulled back into the esophagus and secured to the MSC using an endoloop (Olympus America, Center Valley, PA, USA). Drawing back on the vein stripper at the site of the gastrostomy facilitated inversion of a sleeve of the MSC. With this maneuver, a submucosal dissection plane was acquired and tension was distributed evenly throughout the circumference of the submucosa–muscularis propria interface. By withdrawing the trailing suture orally or pulling the vein stripper caudally, additional exposure and counter traction was facilitated along the dissection plane. The dissection was continued across the anatomic esophagogastric junction until the entire sleeve of MSC was inverted into the stomach (Fig. 2; Video 2). The sleeve was subsequently penetrated below the level of the esophagogastric junction using an endoscopic needle knife, and the opening was balloon-dilated until it was large enough to facilitate passage of the endoscope into the gastric lumen.

G. M. Eid · A. Nieponice · S. F. Badylak
Department of Surgery, University of Pittsburgh,
Pittsburgh, PA, USA

A. Nieponice · S. F. Badylak
McGowan Institute for Regenerative Medicine,
University of Pittsburgh,
Pittsburgh, PA, USA

R. W. O'Rourke
Department of Surgery, Oregon Health & Science University,
Portland, OR, USA

N. D. Bouvy
Department of Surgery,
Maastricht University Medical Centre,
Maastricht, The Netherlands

B. A. Jobe (✉)
Shadyside Medical Center,
5200 Centre Avenue, Suite 715,
Pittsburgh, PA 15232, USA
e-mail: jobeba@upmc.edu

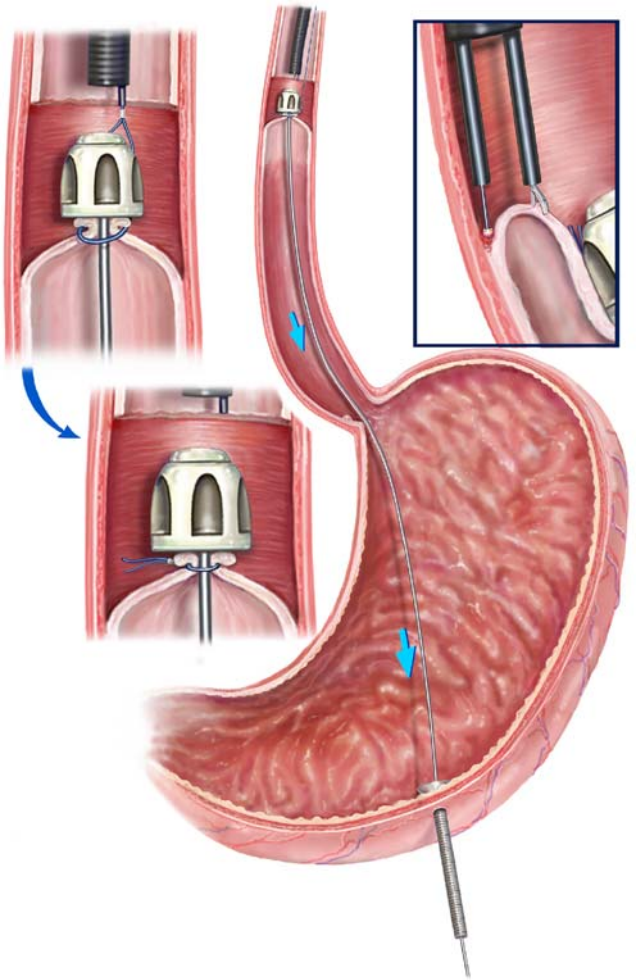


Figure 1 After initial circumferential resection of the mucosa–submucosa complex, a vein stripper is secured to a cuff of MSC. By drawing back on the vein stripper, the MSC sleeve is inverted to facilitate submucosal dissection.

Circumferential transection of the MSC was performed with the endoscope on a retroflexed position (Fig. 3; Video 3). Prior to transoral removal of the MSC, the specimen was turned "outside in" by drawing proximally on the trailing suture; conceptually, the purpose of this maneuver is to eliminate exposure of the muscularis propria to malignant cells within the mucosal surface of the specimen (Fig. 4). Hemorrhage within the muscularis propria tube was controlled and the endoscope was removed. All animals were euthanized and en bloc removal of the remaining esophagus and stomach was performed.

Technical Evaluation

All procedures were recorded and reviewed to establish the following endpoints: procedure duration (minutes), number of endoscopic resections required to achieve circumferential MSC removal at the proximal cuff site, qualitative assessment of techniques used for submucosal dissection during proximal cuff creation, number of hemorrhage episodes requiring suction and intervention, and number of perforations within each MSC sleeve and muscularis propria tube.

Gross Morphology Examination

The entire lengths of MSC and muscularis propria were examined for perforation using pressurized intraluminal infusion of saline solution (Fig. 5a, b). Adequacy of resection length was evaluated by comparing MSC with the corresponding muscularis propria tube that was opened longitudinally after leak testing was performed (Fig. 5c). The specimen length in centimeters from proximal to distal resection margin was measured within the length of muscularis propria. Incomplete resection length was defined as any residual MSC adherent to the muscularis

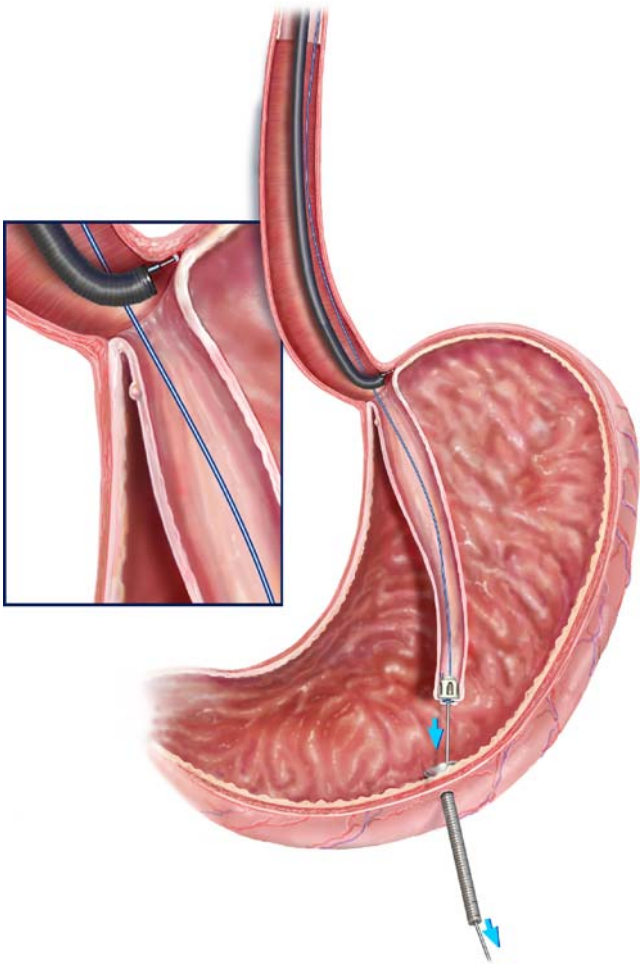


Figure 2 The diseased part of mucosa–submucosa complex is dissected away from the muscularis propria and inverted into the stomach.

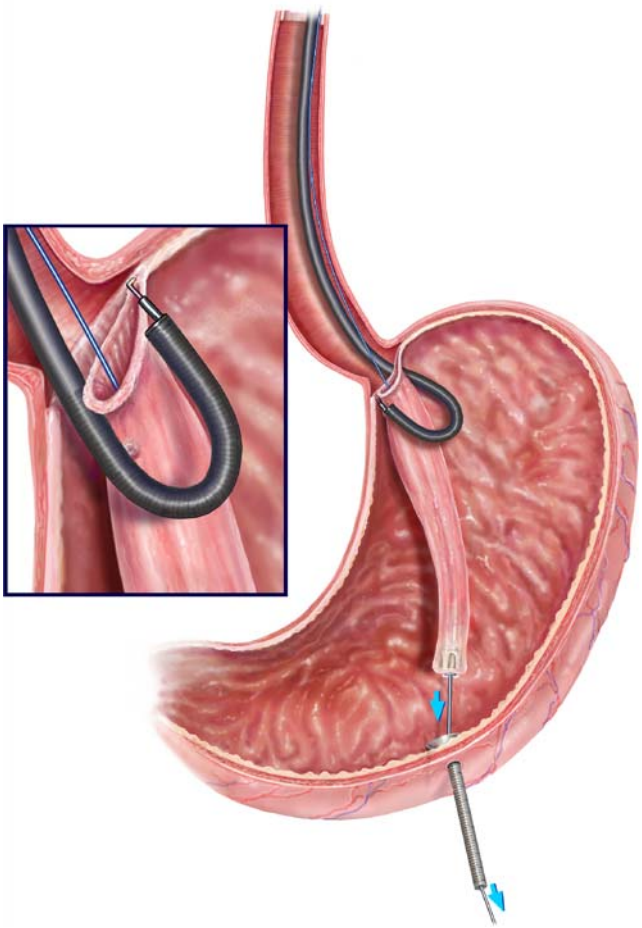


Figure 3 Transection of the sleeve of mucosa–submucosa complex was performed from within the gastric lumen in a retroflexed position using electrocautery.

propria proximal to the anatomic esophagogastric junction, defined as the point at which the esophagus "flared" into the proximal stomach.

Histology Analysis

To determine adequacy of resection depth, MSC and muscularis propria sleeves were cross-sectioned into five tissue samples along the entire length of the esophagus and processed in paired fashion for each animal. Specimens were then placed in buffered formalin solution and subsequently stained with hematoxylin–eosin for histological exanimation. At each level, five sections of each tissue sample were examined. Evaluation of resection depth was categorized based on established histopathological classification of tumor invasion depth in the gastrointestinal tract, wherein the mucosa is subdivided into epithelium, lamina propria, and muscularis mucosa (M1–3) and the submucosal layer is subdivided into thirds (SM1–3).[17–19] Resection depth was defined adequate as sections contained all mucosal layers and at least the complete SM1 layer.

Results

Technical Evaluation

In an acute survival model, TEE was successfully completed without perioperative mortality in all animals over a mean length of 32.2 cm (range 20–55). Procedure time averaged 179 min (range 125–320). The mean number of cap resections required to reach a circumferential plane to initiate proximal cuff submucosal dissection was 2.6 (range 1–6); in six animals, a single 360° circumferential endoscopic resection of the MSC was accomplished by applying suction within the center of the esophageal lumen.

For creation of the 2 cm proximal cuff of MSC, we relied primarily on established techniques for submucosal dissection, which included tapered cap dissection between

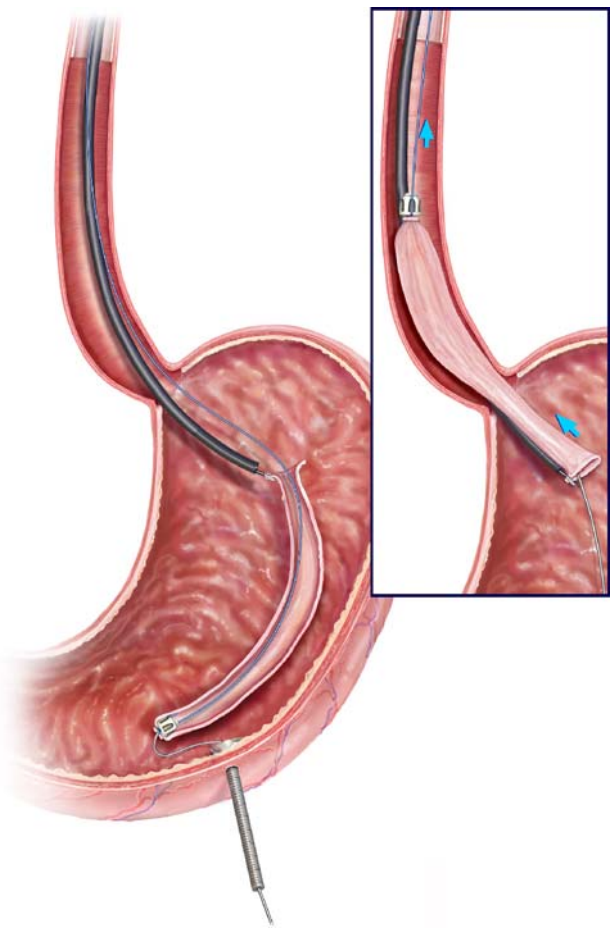


Figure 4 Before oral retrieval, spillage of tumor cells on to the muscularis propria is prevented by turning the sleeve of MSC "outside-in" by drawing the trailing suture cranially.

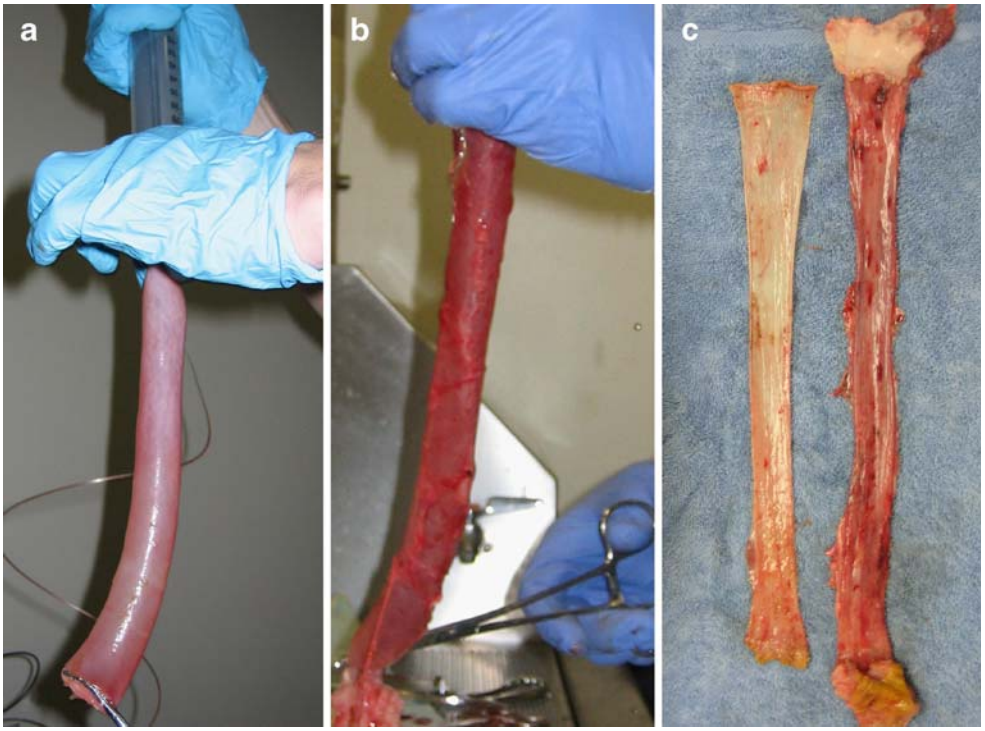


Figure 5 Evaluation of integrity of the mucosa–submucosa complex sleeve (**a**) and muscularis propria tube (**b**) at necropsy using pressurized intraluminal infusion of saline solution. Resection length was evaluated macroscopically by comparing the specimen with the corresponding muscularis propria tube (**c**).

the MSC and muscularis propria aided with needle knife cautery dissection after saline submucosal "lift". The use of sodium hyaluronate solution, which is isotonic and provides long-lasting submucosal elevation away from the muscularis propria, was not employed in this study secondary to cost. Hydrodissection was difficult to control with precision and was abandoned.

Once secured to the proximal cuff, dissection of the MSC away from the muscularis propria was accomplished by drawing back on the vein stripper at the site of the gastrostomy thereby leading to inversion of the MSC. Electrocautery aided the dissection by dividing fibrous attachments and controlling bleeding as the stripping was stepwise carried distally. It was essential to carry the MSC inversion on to the proximal stomach to ensure there was no remaining tissue within the esophagus after distal transection of the MSC sleeve. Hemorrhage events were encountered in a mean of 1.7 (range 0–4) and were best controlled with endoscopic coagulation forceps. No perforations were identified during the procedure and no other complications occurred.

Gross Morphology Examination

There were no perforations identified along the length of the MSC or muscularis propria. In nine of ten animals, the entire length of MSC was completely resected leaving an intact muscularis propria tube in situ. Adequate resection length was not achieved in one animal in which a 3-cm-long and 0.5-cm-wide segment of MSC remained adherent to the muscularis propria at the level of the esophagogastric junction.

Histology Analysis

Histological assessment demonstrated that resection depth included all mucosal layers and the SM1 layer in 100% of sections. The entire SM2 layer was included in 96% of sections, and a complete SM3 layer was present in only 30% of sections, as in 70% of sections, the lower half of SM3 was found to be adhered to the muscularis propria (Fig. 6).

Discussion

The incidence of Barrett's esophagus and esophageal adenocarcinoma is dramatically rising, and esophageal cancer has become the world's sixth leading cause of cancer death.[20,21] Overall morbidity and mortality rates associated with esophagectomy are substantial, and esophageal resection has been challenged as a treatment for HGD and intramucosal cancer since lymph node involvement is unlikely (<5%).[6–8] However, early lesions have the potential to be lethal and are only curable if completely removed. Since surveillance programs have increased the number of patients detected within early stage disease,[22,23] interest in less invasive endoscopic treatments has grown.

Currently available endoscopic techniques, however, have significant limitations. Photodynamic therapy initially demonstrated promising results, but has been abandoned by

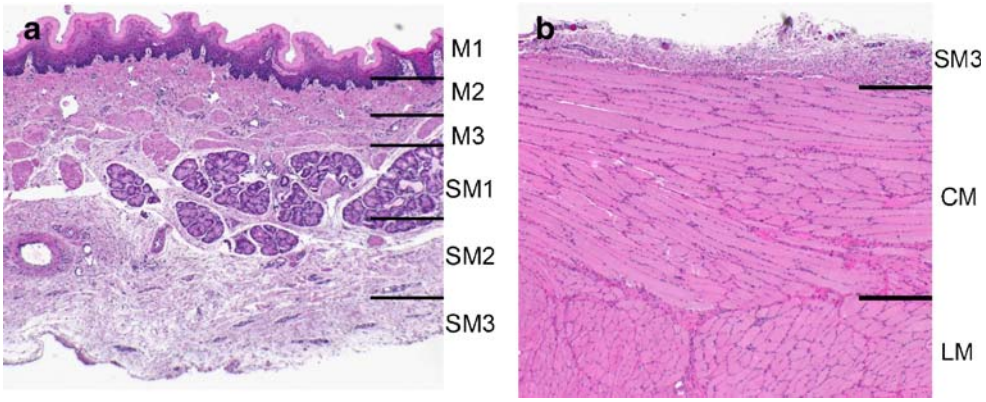


Figure 6 **a**, **b** Histological image showing the resection depth of TEE was mainly through the SM3 layer in 96% of specimens. A small portion of the SM3 layer was found attached to the muscularis propria after resection in 70% of specimens; *M1–3* mucosal layers (epithelium, lamina propria, muscularis mucosae), *SM1–3* submucosal layers, *CM* circular muscle layer, *LM* longitudinal muscle layer.

many centers due to photosensitivity-related side effects, recurrent disease, uncontrolled depth of ablation, and stricture formation.[24,25] Early results of radiofrequency ablation in the treatment of dysplasia have been encouraging, but as in photodynamic therapy, there is no specimen available for histopathological examination and the depth of ablation is limited to 500 μm, thereby preventing its use in the treatment of invasive cancer. In addition, although recent data suggest that radiofrequency ablation may reduce the occurrence of subsquamous intestinal metaplasia when compared to prevalent pretreatment cases, patients are committed to a lifetime of surveillance endoscopy and the need for subsequent interventions.[2,25,26] The use of endoscopic mucosal resection has generated excellent results in treatment of high-grade dysplasia and early adenocarcinoma with an extrapolated 5-year survival rate of 98% in highly selected patients.[4] However, it is important to note that disease recurrence secondary to synchronous or metachronous cancers is common and requires frequent surveillance endoscopies with the need for subsequent endoscopic resection and combination therapy with radiofrequency ablation.[27,28] Furthermore, currently used cap or snare endoscopic resection techniques limit the lesion resection size to 20 mm, requiring piecemeal resections of larger lesions with a compromised histological assessment of radial resection margins. In addition, the thermal destruction of lateral edges makes this even more challenging. Finally, long lesions will require a stepwise approach to prevent stricture formation with the need for multiple procedures and an exhaustive follow-up.

Recent reports describe successful endoscopic en bloc dissection of larger esophageal MSC specimens in patients using endoscopic submucosal dissection. This technique was shown to be superior to endoscopic mucosal resection as an effective staging procedure as well as a curative treatment in a small series of patients with superficial adenocarcinoma at the esophagogastric junction. However, this technique is highly operator dependent and limited by existing technology resulting in a risk of perforation and stricture formation.[11–13,29] To overcome these limitations, we designed transoral endoscopic inner layer esophagectomy for resection of a sleeve of the mucosa–submucosa complex, leaving the intact muscularis propria in situ.

Submucosal dissection was demonstrated to be feasible in the swine model in earlier studies.[30,31] These findings in combination with the inversion concept, which was first described for the entire esophagus by Akiyama et al. formed the basis for the TEE concept.[32] In the present study, inversion provided equally distributed circumferential counter traction that facilitated separation along the plane between the submucosal and muscular layer. As opposed to endoscopic submucosal dissection, which is known to have a high risk of perforation and the potential for intra- and perioperative hemorrhage, with TEE, there was minimal blood loss and an unobstructed plane of dissection without perforation. Hemorrhage was easily controlled by following the groove between the MSC and muscle during the stripping process and coagulating with forceps or needle knife.

The resection length and depth were found to be both accurate and reproducible. It appears as if the path of least resistance during stripping is located within the outermost aspect of SM3 as 70% of animals had a small portion adherent to the muscularis propria. Assuming reproducibility in humans, TEE could be a reliable staging tool and/or treatment for patients with long segment multifocal dysplasia and intramucosal cancer, thereby providing the pathologist a complete specimen that can be assessed for tumor invasion depth (T status), grade of differentiation (G status), involvement of lymphatic vessels and veins and the presence of metachronous lesions, and completeness of resection (R status). This robust information will better guide clinicians in their efforts to balance procedural risk (i.e., esophagectomy) with the risk for lymphatic involvement in the face of esophageal preservation. While lymph node involvement is infrequent in T1a-stage adenocarcinoma of the esophagus, it is increased by nearly 10-fold when there is submucosal involvement (T1b stage).[6,8,33] There-

fore, TEE will not be suitable as definitive treatment in patients with T1b lesions, and surgical candidates should undergo esophagectomy.

Limitations of the present study are the swine model and the swine's healthy esophagus. It can be anticipated that the "stripping" with inversion technique will be more difficult and require the assistance of submucosal electrocautery dissection in the diseased human esophagus in the presence of inflammation or fibrous attachments caused by many years of progressing disease. Another concern for clinical application in patients with esophageal cancer is the potential risk of seeding the gastrostomy side with shed malignant mucosal cells. This risk could be minimized by using percutaneous fluoroscopic placement instead of an endoscopic approach and also by initiating the resection 2–3 cm above the lesion to prevent contact of the gastrostomy tube with diseased esophageal tissue after inversion.

Circumferential endoscopic mucosal resection has resulted in significant stricture formation if performed in a single setting and therefore is expected to be a major concern related to TEE.[14] The use of extracellular matrix scaffolds, derived from porcine urinary bladder, are known to promote site-specific tissue remodeling. Recently, this technique has been demonstrated to prevent stricture formation in the canine esophagus after short segment (5 cm) circumferential endoscopic mucosal resection.[34,35] In further experiments, we plan to evaluate prevention of stricture formation after TEE with extracellular matrix scaffold deployment over the entire length of the esophagus in a survival model.

Conclusion

Transoral endoscopic inner layer esophagectomy was feasible and reproducible and resulted in intact, en bloc specimens over the entire esophageal length. The inversion technique provided a blunt dissection with an equally distributed circumferential counter traction and this prevented perforation. This technique may lead to a single step staging and/or therapeutic approach with esophageal preservation for BE and early stage malignancy that avoids the morbidity of traditional esophagectomy. Future work will need to focus on stricture prevention after TEE with the use of a xenograft biologic scaffold.

Conflict of Interest The authors report that there are no disclosures relevant to this publication.

Funding This study was supported by the Robert Anthony McHugh Research Fund for the Prevention and Early Detection of Esophageal Cancer, an American Surgical Association Foundation Fellowship Award (RWO), and National Institutes of Health grants K23 DK066165-01 (BAJ) and K08 DK074397 (RWO).

References

1. DeMeester SR. New options for the therapy of Barrett's high-grade dysplasia and intramucosal adenocarcinoma: endoscopic mucosal resection and ablation versus vagal-sparing esophagectomy. Ann Thorac Surg 2008;85:S747–750.
2. Shaheen NJ, Sharma P, Overholt BF, Wolfsen HC, Sampliner RE, Wang KK, Galanko JA, Bronner MP, Goldblum JR, Bennett AE, Jobe BA, Eisen GM, Fennerty MB, Hunter JG, Fleischer DE, Sharma VK, Hawes RH, Hoffman BJ, Rothstein RI, Gordon SR, Mashimo H, Chang KJ, Muthusamy VR, Edmundowicz SA, Spechler SJ, Siddiqui AA, Souza RF, Infantolino A, Falk GW, Kimmey MB, Madanick RD, Chak A, Lightdale CJ. Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med 2009;360:2277–2288.
3. Thomas P, Doddoli C, Neville P, Pons J, Lienne P, Giudicelli R, Giovannini M, Seitz JF, Fuentes P. Esophageal cancer resection in the elderly. Eur J Cardiothorac Surg 1996;10:941–946.
4. Ell C, May A, Pech O, Gossner L, Guenter E, Behrens A, Nachbar L, Huijsmans J, Vieth M, Stolte M. Curative endoscopic resection of early esophageal adenocarcinomas (Barrett's cancer). Gastrointest Endosc 2007;65:3–10.
5. Holscher AH, Bollschweiler E, Schneider PM, Siewert JR. Early adenocarcinoma in Barrett's oesophagus. Br J Surg 1997;84:1470–1473.
6. Oh DS, Hagen JA, Chandrasoma PT, Dunst CM, Demeester SR, Alavi M, Bremner CG, Lipham J, Rizzetto C, Cote R, Demeester TR. Clinical biology and surgical therapy of intramucosal adenocarcinoma of the esophagus. J Am Coll Surg 2006;203:152–161.
7. Rice TW, Blackstone EH, Adelstein DJ, Zuccaro G Jr., Vargo JJ, Goldblum JR, Murthy SC, DeCamp MM, Rybicki LA. Role of clinically determined depth of tumor invasion in the treatment of esophageal carcinoma. J Thorac Cardiovasc Surg 2003;125:1091–1102.
8. Rice TW, Zuccaro G Jr., Adelstein DJ, Rybicki LA, Blackstone EH, Goldblum JR. Esophageal carcinoma: depth of tumor invasion is predictive of regional lymph node status. Ann Thorac Surg 1998;65:787–792.
9. Farrell JJ, Lauwers GY, Brugge WR. Endoscopic mucosal resection using a cap-fitted endoscope improves tissue resection and pathology interpretation: an animal study. Gastric Cancer 2006;9:3–8.
10. Ahmadi A, Draganov P. Endoscopic mucosal resection in the upper gastrointestinal tract. World J Gastroenterol 2008;14:1984–1989.
11. Kakushima N, Yahagi N, Fujishiro M, Kodashima S, Nakamura M, Omata M. Efficacy and safety of endoscopic submucosal dissection for tumors of the esophagogastric junction. Endoscopy 2006;38:170–174.
12. Yoshinaga S, Gotoda T, Kusano C, Oda I, Nakamura K, Takayanagi R. Clinical impact of endoscopic submucosal dissection for superficial adenocarcinoma located at the esophagogastric junction. Gastrointest Endosc 2008;67:202–209.
13. Oyama T, Tomori A, Hotta K, Morita S, Kominato K, Tanaka M, Miyata Y. Endoscopic submucosal dissection of early esophageal cancer. Clin Gastroenterol Hepatol 2005;3:S67–70.
14. Kamler JP, Borsatto R, Binmoeller KF. Circumferential endoscopic mucosal resection in the swine esophagus assisted by a cap attachment. Gastrointest Endosc 2002;55:923–928.
15. Katada C, Muto M, Manabe T, Boku N, Ohtsu A, Yoshida S. Esophageal stenosis after endoscopic mucosal resection of superficial esophageal lesions. Gastrointest Endosc 2003;57:165–169.

16. Conio M, Sorbi D, Batts KP, Gostout CJ. Endoscopic circumferential esophageal mucosectomy in a porcine model: an assessment of technical feasibility, safety, and outcome. Endoscopy 2001;33:791–794.
17. Kudo S. Endoscopic mucosal resection of flat and depressed types of early colorectal cancer. Endoscopy 1993;25:455–461.
18. Ono H, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D, Hosokawa K, Shimoda T, Yoshida S. Endoscopic mucosal resection for treatment of early gastric cancer. Gut 2001;48:225–229.
19. Endo M, Yoshino K, Kawano T, Nagai K, Inoue H. Clinicopathologic analysis of lymph node metastasis in surgically resected superficial cancer of the thoracic esophagus. Dis Esophagus 2000;13:125–129.
20. Ries LA, Wingo PA, Miller DS, Howe HL, Weir HK, Rosenberg HM, Vernon SW, Cronin K, Edwards BK. The annual report to the nation on the status of cancer, 1973–1997, with a special section on colorectal cancer. Cancer 2000;88:2398–2424.
21. Enzinger PC, Mayer RJ. Esophageal cancer. N Engl J Med 2003;349:2241–2252.
22. Fitzgerald RC, Saeed IT, Khoo D, Farthing MJ, Burnham WR. Rigorous surveillance protocol increases detection of curable cancers associated with Barrett's esophagus. Dig Dis Sci 2001;46:1892–1898.
23. van Sandick JW, van Lanschot JJ, Kuiken BW, Tytgat GN, Offerhaus GJ, Obertop H. Impact of endoscopic biopsy surveillance of Barrett's oesophagus on pathological stage and clinical outcome of Barrett's carcinoma. Gut 1998;43:216–222.
24. Overholt BF, Panjehpour M, Halberg DL. Photodynamic therapy for Barrett's esophagus with dysplasia and/or early stage carcinoma: long-term results. Gastrointest Endosc 2003;58:183–188.
25. Prasad GA, Wang KK, Buttar NS, Wongkeesong LM, Krishnadath KK, Nichols FC 3rd, Lutzke LS, Borkenhagen LS. Long-term survival following endoscopic and surgical treatment of high-grade dysplasia in Barrett's esophagus. Gastroenterology 2007;132:1226–1233.
26. Ganz RA, Overholt BF, Sharma VK, Fleischer DE, Shaheen NJ, Lightdale CJ, Freeman SR, Pruitt RE, Urayama SM, Gress F, Pavey DA, Branch MS, Savides TJ, Chang KJ, Muthusamy VR, Bohorfoush AG, Pace SC, DeMeester SR, Eysselein VE, Panjehpour M, Triadafilopoulos G. Circumferential ablation of Barrett's esophagus that contains high-grade dysplasia: a U.S. multicenter registry. Gastrointest Endosc 2008;68:35–40.
27. Giovannini M, Bories E, Pesenti C, Moutardier V, Monges G, Danisi C, Lelong B, Delpero JR. Circumferential endoscopic mucosal resection in Barrett's esophagus with high-grade intraepithelial neoplasia or mucosal cancer. Preliminary results in 21 patients. Endoscopy 2004;36:782–787.
28. Lopes CV, Hela M, Pesenti C, Bories E, Caillol F, Monges G, Giovannini M. Circumferential endoscopic resection of Barrett's esophagus with high-grade dysplasia or early adenocarcinoma. Surg Endosc 2007;21:820–824.
29. Ishihara R, Iishi H, Uedo N, Takeuchi Y, Yamamoto S, Yamada T, Masuda E, Higashino K, Kato M, Narahara H, Tatsuta M. Comparison of EMR and endoscopic submucosal dissection for en bloc resection of early esophageal cancers in Japan. Gastrointest Endosc 2008;68:1066–1072.
30. von Delius S, Feussner H, Henke J, Schneider A, Hollweck R, Rosch T, Prinz C, Schmid RM, Frimberger E. Submucosal endoscopy: a novel approach to en bloc endoscopic mucosal resection (with videos). Gastrointest Endosc 2007;66:753–756.
31. Willingham FF, Gee DW, Sylla P, Lauwers GY, Rattner DW, Brugge WR. En bloc esophageal mucosectomy for concentric circumferential mucosal resection (with video). Gastrointest Endosc 2009;69:147–151.
32. Akiyama H, Tsurumaru M, Ono Y, Udagawa H, Kajiyama Y. Esophagectomy without thoracotomy with vagal preservation. J Am Coll Surg 1994;178:83–85.
33. Nigro JJ, Hagen JA, DeMeester TR, DeMeester SR, Peters JH, Oberg S, Theisen J, Kiyabu M, Crookes PF, Bremner CG. Prevalence and location of nodal metastases in distal esophageal adenocarcinoma confined to the wall: implications for therapy. J Thorac Cardiovasc Surg 1999;117:16–23. discussion 23–15.
34. Nieponice A, Gilbert TW, Badylak SF. Reinforcement of esophageal anastomoses with an extracellular matrix scaffold in a canine model. Ann Thorac Surg 2006;82:2050–2058.
35. Nieponice A, McGrath K, Qureshi I, Beckman EJ, Luketich JD, Gilbert TW, Badylak SF. An extracellular matrix scaffold for esophageal stricture prevention after circumferential EMR. Gastrointest Endosc 2008;69:289–296.

Discussant

Dr. Lee Swanstrom (Portland, OR): Thank you for inviting me to discuss this very interesting paper and congratulations to Dr. Witteman, Jobe, and their team for doing this very innovative and I think thought-provoking study. Also thank you for sending the very nicely written manuscript.

I think we are looking at the future of GI surgery here; it certainly represents a developing trend toward local treatment of early cancers. This is a porcine model of en bloc esophageal mucosal resection, not quite esophagectomy yet. Your title is a little challenging in this regard but I think, as you point out, this is just step one in an ongoing study.

As you also mention, it is not a totally new concept. It has obviously always been desirable to not excise the whole en bloc esophagus for early cancer or for benign disease; Akiyama and DeMeester described this over 20 years ago, as you mentioned, as a treatment in humans for benign disease: stripping the mucosa out with a vein stripper and for diseases like end-stage achalasia to do a subsequent pull-up through the muscularis tube. So it has been around for awhile. But obviously, what is novel here is that you are applying it to cancer, and I think that is a very important stage because it really goes hand in hand with some of the things like Barrett's ablation that are increasingly popular.

I just want to point out to the audience some of the points that need to be emphasized. The first is that this is an extension, a surgical extension of those technologies like Barrett's ablation of early cancers that I think is probably going to eliminate traditional esophagectomy for premalignant mucosa and early stage malignancies. This approach is superior to ablation in that it provides us with a pathology specimen, so margin determination and better staging are possible. There is no doubt in my mind that this is the way things are obviously going to go.

I think the other thing to stress is that this was totally an endoscopic procedure. Unlike traditional mucosal stripping

techniques which require open or laparoscopic access, this is essentially done with no incisions other than a peg tube. So it is an important and "NOTES"-like development in patient friendly care. I would also emphasize the fact that this is a bunch of surgeons doing a very complex interventional endoscopic procedure and use this as a chance to soap box that surgeons need to be involved in flexile endoscopy and especially interventional endoscopy.

Then, as you mentioned with your teaser at the end of the presentation and in your previous publications, this is a platform for future development in tissue engineering for stricture prevention and maybe someday for esophageal replacement and that has a very exciting future. So my questions to you are: Please enlarge a little bit more on what you see are the differences between doing this in the porcine model and in humans who have a very different esophageal physiology. If you work with pigs, you are aware that the mucosa is pretty slippery on the submucosa, but is it the same in humans, and what do you forecast the difficulties being along that line? Will there be more bleeding? And will the split on the same plain that nice deep submuscularis in a human or will it split in a more superficial plain?

You mentioned the possibility of fibrosis. These experiments were done in a normal esophagus. How are you going to investigate looking at a diseased esophagus whether it is ulcerated, fibrotic, or with Barrett's? What impact will that have? How are you going to investigate that before this technique goes into widespread human use?

A couple of technical questions: The procedure took 3 h, even though the video made it look like 10 min. What steps actually used up most of that time? It sounds like the early experience with getting that proximal mucosectomy is a little bit difficult, and I see that one of your video clips shows a very elegant one-stage technique. Maybe you can enlarge on that just briefly.

How much of this was really dissection versus stripping? Or maybe this is a more relevant question in a human; how much do you think is actually going to be dissection under direct vision to get a good clean layer versus just tying a strip to it by yanking real hard, which makes the endoscope only needed for mopping up the bleeding? Bleeding control in humans is a real problem with endoscopic submucosal (ESD) kind of techniques. How do you control bleeding? Did you use clips?

Finally, the last question: I think you tease us a bit with this tissue regeneration thing. I think we all know that that is probably a way out there before it is widely available. Do you see an intermediate use of this technique of massive en bloc lengths of Barrett's being stripped out, i.e., could you do a pull-up through muscular tube potentially to combine this with maybe a minimally invasive tubularization of the stomach and a pull-up? Can you perhaps comment on that?

Closing Discussant

Dr. Bart P. Witteman (Pittsburgh, PA): Thank you Dr. Swanstrom for your very interesting remarks and questions. The first question was on the expected difference in performing this technique in humans instead of in the swine model. We expect that this dissection will be more challenging in the human esophagus. In the patient I showed, we used submucosal dissection techniques, which were spearheaded by the Japanese. I expect that these techniques will be very useful not only to access the initial submucosal plain but also to assist the inversion process, once the vein stripper is secured. I think during a stepwise procedure in which the assistant carefully draws back on the vein stripper and strips portions of the submucosal complex down the esophagus, the surgeon can use submucosal dissection tools endoluminally to control hemorrhage and dissect adhesions between the submucosa and muscular layer. That brings me to the second question, which was on how to perform TEE in a diseased esophagus. I think the submucosal dissection techniques will also be very helpful in this area, as many years of progressing disease can cause more adherence of the submucosal layer to the muscularis propria. In our procedures, the creation of an initial 2–3-cm cuff was most time-consuming as for this step we tried different techniques. We used hydrodissection techniques to lift the submucosa from the muscularis propria and also blunt dissection, using the transparent cap of the EMR kit at the tip of the endoscope for dissection, but these were time-consuming and insufficient for tight adhesions. Therefore, we relayed on the mentioned submucosal dissection techniques.

The third question was how to control bleeding. We used an endoscopic forceps with cautery in the swine model, which will probably be very useful in humans too. With the inversion technique, vessels become nicely visible and are easily grabbed with the forceps during a stepwise dissection.

The fourth question was on how we think about the use of a biologic scaffold for controlling stricture formation and if there is a role for gastric pull-up in the resected area instead. The use of an extracellular matrix scaffold has been very promising in the canine model after circumferential EMR and showed site-specific tissue remodeling. We now perform a study to explore the effects of a bioscaffold on stricture formation after TEE in the swine model. We also have future plans to perform a study in patients with en bloc resection and bioscaffold substitution for treatment of Barrett's esophagus with high-grade dysplasia. I think the technique of a gastric pull-up in the muscularis tube will be a less attractive option as the laparoscopic part will add invasiveness to the procedure. Especially after the experience in our first patient, we would like to explore the use of TEE technique, the endoscopic circumferential stripping of the mucosa–submucosa complex, followed by placement of the extracellular matrix scaffold to control postoperative stricture formation.

J Gastrointest Surg (2009) 13:2113–2120
DOI 10.1007/s11605-009-1042-0

2009 SSAT POSTER PRESENTATION

The Value of High-Resolution Manometry in the Assessment of the Resting Characteristics of the Lower Esophageal Sphincter

Shahin Ayazi · Jeffrey A. Hagen · Joerg Zehetner · Oliver Ross · Calvin Wu · Arzu Oezcelik · Emmanuele Abate · Helen J. Sohn · Farzaneh Banki · John C. Lipham · Steven R. DeMeester · Tom R. DeMeester

Received: 10 June 2009 / Accepted: 2 September 2009 / Published online: 25 September 2009

Abstract
Introduction High-resolution manometry (HRM) is faster and easier to perform than conventional water perfused manometry. There is general acceptance of its usefulness in evaluating upper esophageal sphincter and esophageal body. There has been less emphasis on the use of HRM to evaluate the lower esophageal sphincter (LES) resting pressure and length, both factors important in LES barrier function. The aim of this study was to compare the resting characteristics of the LES determined by HRM and conventional manometry in the same patients.
Methods We performed both HRM and conventional manometry including a slow motorized pull-through technique in 55 patients with foregut symptoms. The characteristics of the LES analyzed were: resting pressure, total length, and abdominal length. Four available modes of HRM analysis were used to assess resting characteristics of the LES: spatiotemporal mode using both abrupt color change and isobaric contour, line tracing, and pressure profile. The values obtained from these four HRM modes were then compared to the conventional manometry measurements.
Results High-resolution manometry and conventional manometry did not differ in their measurement of LES resting pressure. LES overall and abdominal length were consistently overestimated by HRM. A variability up to 4 cm in overall length was observed and was greatest in patients with hiatal hernia (1.8 vs. 0.9 cm, $p=0.027$).
Conclusion The current construction of the catheter and software analysis used in high-resolution manometry do not allow precise measurement of LES length. Errors in the identification of the upper border of the sphincter may compromise accurate positioning of a pH probe.

Keywords Motility · Esophagus · High-resolution manometry · Pull-through technique · Lower esophageal sphincter · Gastroesophageal reflux disease (GERD)

Introduction

Recent advances in catheter and transducer design coupled with improved image processing and display techniques have yielded significant upgrades in technology, cumulating in the development of high-resolution manometry (HRM). The technical advantages of HRM lie in its high density of recording sites, advanced solid-state sensor technology, and intuitive spatiotemporal representation of the data. High-resolution manometry is also faster and easier to perform than conventional water-perfused manometry and has been reported to be superior in the assessment of the upper esophageal sphincter (UES) and esophageal body.[1] However, high-resolution manometry has not been compared to conventional "pull-through" manometry in the assessment of the lower esophageal sphincter (LES). The aim of this

This work has been designated as poster of distinction at the Digestive Diseases Week, June 2009, Chicago, IL.

S. Ayazi · J. A. Hagen (✉) · J. Zehetner · O. Ross · C. Wu · A. Oezcelik · E. Abate · H. J. Sohn · F. Banki · J. C. Lipham · S. R. DeMeester · T. R. DeMeester
Division of Thoracic and Foregut Surgery, Department of Surgery, Keck School of Medicine, University of Southern California, 1510 San Pablo Street, Suite 514, Los Angeles, CA, USA
e-mail: hagen@surgery.usc.edu

study was to compare the resting characteristics of the LES measured by HRM and those measured by a slow motorized pull-through technique (MPT) of conventional manometry in the same group of patients.

Materials and Methods

Prior to using HRM in our clinical practice, we prospectively evaluated this new technology by comparing it to conventional manometry. Since HRM software allows analysis of esophageal body function in an identical manner to conventional manometry, we focused the evaluation on the resting characteristics of the LES since HRM does not include a traditional pull-through technique.

The study population consisted of 55 consecutive patients with foregut symptoms who had both HRM and conventional manometry performed. All of these patients had a video-esophagram to assess for the presence of a hiatal hernia. This study was approved by the University of Southern California Institutional Review Board.

Conventional Manometry

Conventional manometry was performed in the supine position using a 12 French eight-channel water-perfused catheter (Arndorfer Medical Specialties, Greendale, WI, USA). The stationary pull-through technique was performed by withdrawing the catheter through the sphincter in 1 cm increments. The upper and lower borders of the LES were identified using the classic definition of 2 mmHg constant rise from the gastric baseline pressure. Values obtained from five individual tracings were averaged.

A slow motorized pull-through technique was also performed for detailed assessment of the LES.[2,3] Motorized pull-through technique was performed in the same setting with the same catheter; a separate intubation was not required. Four radially placed sensors at the same level were used in MPT. The radial sensors were positioned just below the LES, and a mechanical puller was used to withdraw the catheter at a rate of 1 mm/s through the sphincter while the patient breathed normally. If the patient swallowed during this time, the procedure was repeated. The recording was analyzed using the Polygram® software program (version 5.22 Upper GI Edition, Gastrosoft, Medtronic Medical) to determine LES resting pressure, overall length, and abdominal length using the end expiratory gastric pressure as a reference. The lower border of the LES was defined as a persistent rise in pressure ≥2 mmHg above the gastric baseline. The upper border of the LES was defined as the point where the pressure dropped below the gastric baseline. The respiratory inversion point (RIP) was defined as the location where the positive deflections with inspiration recorded in the abdomen changed to negative deflections recorded in the chest. The resting pressure of the sphincter was measured at the RIP during the middle of the respiratory cycle. The overall length was defined as the distance in centimeters between the upper and the lower borders of the LES and the abdominal length as the distance in centimeters between the lower border and the RIP. The values obtained from the four radial channels were averaged.

High-Resolution Manometry

High-resolution manometry was performed during the same visit in the supine position 30 min after finishing the conventional manometry. A solid-state manometry catheter with 36 circumferential pressure sensors spaced at 1-cm intervals was used (Sierra Scientific Instruments; Los Angeles, CA). The catheter was positioned so that at least four sensors were in the stomach to optimize recording of intragastric pressure. The sensors measured pressure over a length of 0.25 cm, and in the remaining 0.75 cm of space between the sensor recording area, the data was interpolated using an algorithm to generate a pseudo-3-dimensional topographic plot. A 25-s period of recording documented the resting status of the esophagus and determined the location and resting pressure profile of the upper and lower esophageal sphincters. This was followed by ten swallows of 5 cc of water at 20-s intervals to assess upper esophageal sphincter function, esophageal body function, and LES relaxation.

Overall and abdominal lengths of the LES were assessed using ManoView® analysis software (Sierra Scientific Instruments, Los Angeles, CA). The data were first corrected for thermal sensitivity according to the manufacturer's instructions. All pressures were referenced to gastric baseline pressure. The LES reading were analyzed using all four available modes:

1. Spatiotemporal mode using abrupt color change
2. Spatiotemporal mode using isobaric contour=2 mmHg
3. Line tracing mode using constant rise ≥2 mmHg
4. Pressure profile mode

In the spatiotemporal mode, the lower border of LES was defined by a distinct color change from blue (i.e., gastric pressure) to green (i.e., high-pressure zone in distal esophagus).The upper border of the LES was defined by a change back from green to blue (Fig. 1a). In the same mode, the upper and lower borders of the LES were determined using an isobaric contour tool that defined a pressure domain of ≥2 mmHg above gastric pressure (Fig. 1b).

In the line tracing mode, channels can be selected by the user to display tracings in the stomach, the entire gastroesophageal junction, and the distal esophagus. In this display, the most distal line tracing with a constant pressure ≥2 mmHg above gastric baseline represents the lower

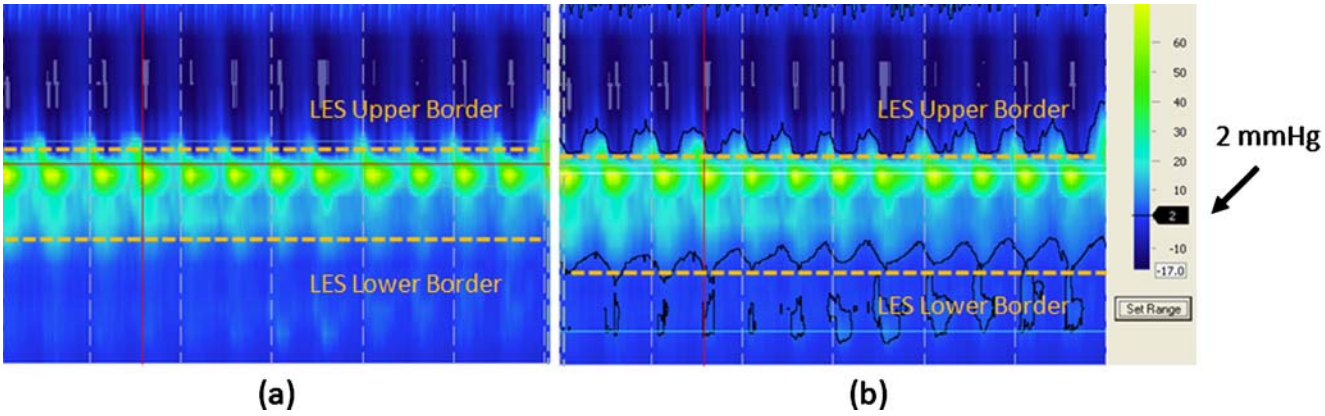


Figure 1 **a** Analysis of the LES in the spatiotemporal mode using abrupt color change. The color changes at the mid respiratory points are identified visually and marked with *horizontal lines* to identify the upper and lower borders of the LES. The software calculates the overall length of the LES as the distance in centimeters between these lines. **b** Analysis of the LES in the spatiotemporal mode using isobaric contour. The user selects a pressure threshold, and the software draws a contour line at this pressure. The upper and lower borders are marked with *horizontal lines* at the mid respiratory point of these contour lines. The software calculates the overall length of the LES as the distance in centimeters between these lines.

border of the LES. The most proximal tracing with a constant pressure ≥2 mmHg above gastric baseline pressure represents the upper border of the LES (Fig. 2).

In the pressure profile mode, the data from the 36 sensors are used to construct a dynamic graph that is shown in the analysis software (Fig. 3). This graph represents the pressure profile along the entire esophagus relative to gastric baseline pressure at any given time during the study. The borders of the LES were defined by the points where the pressure profile line crosses the gastric baseline.

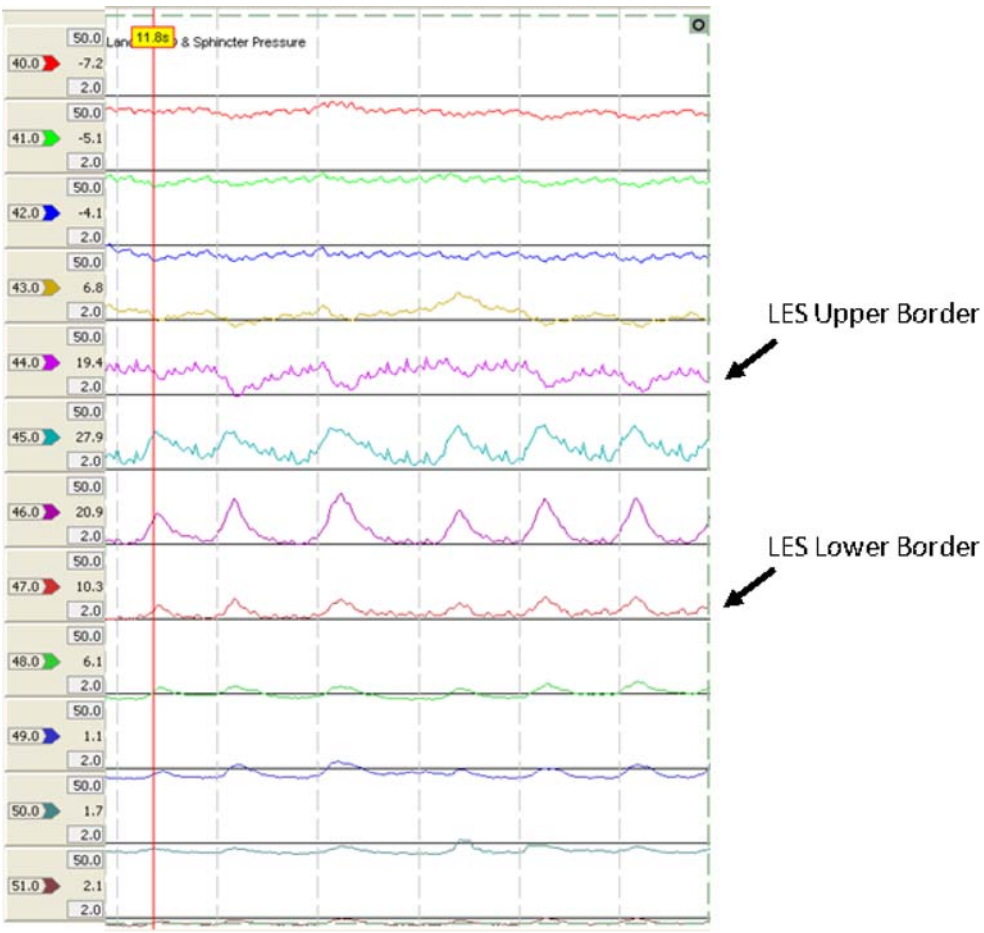


Figure 2 Analysis of the LES in the line tracing mode. The most distal line tracing with a constant pressure ≥2 mmHg above gastric baseline represents the lower border of the LES. The most proximal tracing with a constant pressure ≥2 mmHg above gastric baseline pressure represents the upper border of the LES. The distance between these sensors is recorded as the overall length of the LES.

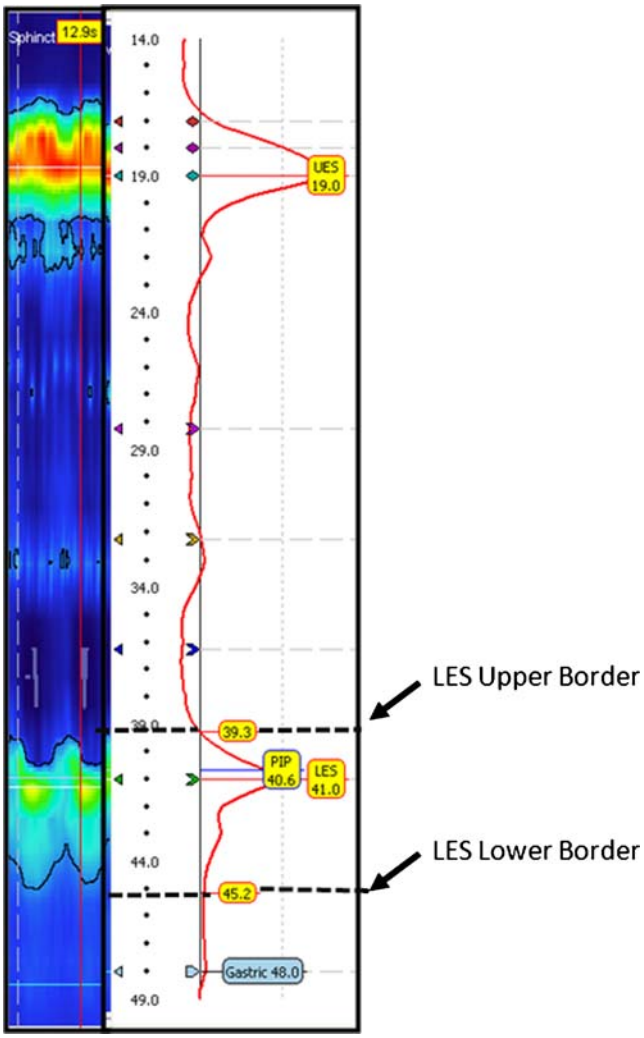


Figure 3 Analysis of the LES in the pressure profile mode. The pressure profile is displayed for a representative location in the LES at the mid respiratory point. The user places *horizontal lines* where the pressure profile crosses the gastric baseline. The software calculates the overall length of the LES as the distance in centimeters between these lines.

The respiratory inversion point was identified using the pressure inversion point tool provided in the software. The location of the RIP was used to determine the upper extent of the abdominal portion of the LES in order to calculate the abdominal length of the LES in all four modes.

The resting pressure of the LES was determined in two ways. In the spatiotemporal mode, with the upper and lower borders of the LES marked as described above, the E-Sleeve software tool identifies the highest pressure point in the LES. The resting pressure of the LES was also determined by positioning the smart mouse cursor included in the software at the level of RIP at the mid respiratory point to measure the pressure at this location.

Statistical Analysis

Values are reported as median and interquartile range (IQR). The Wilcoxon signed rank test was used to compare continuous variables. The Spearman test was used to assess correlation between variables reported as the correlation coefficient R with 95% confidence intervals (CI). A p value less than 0.05 was considered statistically significant. The analysis was performed using Prism 4 statistical software (Graphpad, San Diego, CA, USA).

Results

There were 29 male and 26 female patients with a median age of 53 years (IQR 45–65). The resting characteristics of the LES measured by the conventional stationary pull-through technique are compared to those obtained by the motorized pull-through technique in Table 1. The LES resting characteristics were similar between these two methods.

Overall lengths of the LES as measured by MPT and the four modes of HRM are compared in Table 2. Overall lengths measured by all modes of HRM were significantly longer compared to the MPT measurements, with the exception of the line-tracing mode. Likewise, the abdominal lengths of the LES measured by HRM were significantly longer than those measured by MPT with the exception of the line tracing mode (Table 3).

The Spearman correlation analyses of overall and abdominal lengths measured by MPT and HRM are shown in Table 4. No correlation was found between overall lengths as measured by MPT and any of the HRM modes. There was a weak correlation between the abdominal length measured by MPT and the pressure profile and spatiotemporal (color change) modes of HRM.

The overall length of the LES was overestimated by all four modes of HRM. This overestimation was maximal for the spatiotemporal mode using color change in which 82% of patients had a longer overall length compared to MPT. The corresponding percentages for other HRM modes

Table 1 Comparison Between Stationary Pull-through (SPT) and Motorized Pull-through (MPT) Techniques of Conventional Manometry Assessment of the LES Resting Characteristics

	SPT	MPT	p value
Overall length (cm)	3.0 (2.2–3.4)	2.8 (2.2–3.8)	0.55
Abdominal length (cm)	1.8 (1.1–2.2)	1.9 (1–2.9)	0.19
Resting pressure (mmHg)	13.5 (8–20.2)	12.8 (8.1–19.5)	0.69

Values expressed as median (IQR)

Table 2 Comparison of Overall Lengths of the LES Measured by MPT and the Four Modes of HRM, Values Expressed as Median (IQR)

	Conventional manometry	High-resolution manometry			
	Motorized pull-through	Pressure profile	Spatiotemporal (color change)	Spatiotemporal (isobaric=2mmHg)	Line tracing
Overall length (cm)	2.8 (2.2–3.8)	4.7 (3.3–5.3)	3.5 (2.7–4.1)	4.4 (3.4–5.3)	3 (2–4)
p value[a]	–	<0.0001	0.0114	<0.0001	0.94

[a] For comparison to MPT values using Wilcoxon signed rank test

Table 3 Comparison of Abdominal Lengths of the LES Measured by MPT and the Four Modes of HRM, Values Expressed as Median (IQR)

	Conventional manometry	High-resolution manometry			
	Motorized pull-through	Pressure profile	Spatiotemporal (color change)	Spatiotemporal (isobaric=2 mmHg)	Line tracing
Abdominal length (cm)	1.9 (1.0–2.9)	3.7 (2.6–4.6)	3.0 (2.1–3.6)	3.8 (2.7–4.5)	3 (2–4)
p value[a]	–	<0.0001	<0.0001	<0.0001	0.094

[a] For comparison to MPT values using Wilcoxon signed rank test

Table 4 Correlation Between Overall and Abdominal Lengths of the LES Measured by the Four Modes of HRM and the MPT Technique of Conventional Manometry*

	Pressure profile	Spatiotemporal (color change)	Spatiotemporal (isobaric=2mmHg)	HRM Line tracing
Overall length	n.s	n.s	n.s	n.s
Abdominal length	0.31 (0.04–0.53)	0.40 (0.14–0.61)	n.s	n.s

*$p<0.05$, Spearman coefficient (95% CI) reported for analyses

n.s. not significant

Table 5 Comparison of Overall and Abdominal Lengths Measured by MPT and the Spatiotemporal Isobaric Contour and Line Tracing Modes of HRM using a Threshold of 5 mmHg, Values expressed as median (IQR)

	Motorized pull-through	Spatiotemporal (isobaric=5 mmHg)	HRM Line tracing (5 mmHg)
Overall length (cm)	2.8 (2.2–3.8)	3.7 (2.7–4.1)*	2 (1–3)
Abdominal length (cm)	1.9 (1.0–2.9)	3.5 (2.5–4.3)*	2 (1–3)

*$p<0.05$ vs. MPT

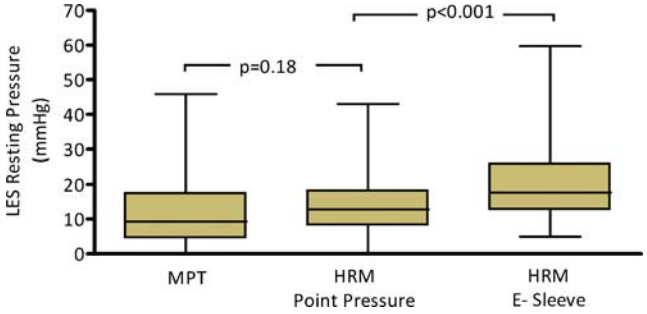


Figure 4 Comparison of the resting pressure of the LES measured by MPT and two techniques by HRM.

were: 76% for the pressure profile, 60% for the spatiotemporal mode using isobaric contour of 2 mmHg, and 49% for the line tracing using the cut point of 2 mmHg.

We reanalyzed the HRM data using a threshold of 5 mmHg for the isobaric contour in the spatiotemporal mode and a constant rise ≥5 mmHg above gastric pressure in the line tracing mode. Using this higher pressure threshold, the overall and abdominal lengths measured by spatiotemporal mode (using isobaric contour) were shorter but remained significantly different from the values obtained by MPT. With the higher pressure threshold, the lengths measured by the line tracing mode were similar to MPT (Table 5).

Figure 4 compares the resting pressure of the LES measured by MPT and HRM. The pressure measured by the E-sleeve was significantly higher than the MPT pressure. There was no difference between the pressure at the RIP measured by HRM using the smart mouse and the resting pressure measured by MPT.

The location of the upper border of the LES was determined by stationary pull-through during conventional manometry and in the spatiotemporal mode using color change. There was a modest correlation between these measurements with discrepancies as large as 3.4 cm in individual patients (Fig. 5).

Radiologic evidence of a hiatal hernia was present in 38 patients (70%). The presence of a hernia was associated with a greater variability in overall lengths of the LES measured by MPT and the spatiotemporal mode using color change [1.8 cm (1–2.5) vs. 0.9 cm (0.3–2.1), $p=0.027$].

Discussion

High-resolution manometry has grown in popularity since its introduction in 2000.[4] This has occurred for a number of reasons. It is faster to perform which makes it attractive to both patients and to foregut diagnostic laboratories performing the test. The presence of simultaneous recording channels from the pharynx to the stomach eliminates the need to move the catheter during the study which simplifies the conduct of the procedure and makes it more tolerable for the patients. The solid state catheter eliminates the need for a water perfusion system, which makes the exam technically easier to perform. The sophisticated software package also simplifies the conduct of the study and its analysis. This is especially true when the spatiotemporal mode is used. All of these factors combine to make this HRM popular especially in community-based centers.

High-resolution manometry has been shown to be useful and accurate in the assessment of motor function of the UES[5,6] and esophageal body,[7,8] and it may offer unique insights into assessment of esophageal function particularly in evaluating bolus transport.[9] To date, no studies have assessed the use of HRM in measuring the resting characteristics of the lower esophageal sphincter. In particular, the impact of the elimination of the "pull-through" component of LES analysis has not been studied. We hypothesized that the interpolated data points over the short segment that is the LES may lead to under- or overestimation of the true length of the sphincter by HRM since the pressure sensors are placed at 1 cm intervals.

We have shown that there are significant differences in all measurements of the resting characteristics of the LES between the results obtained using high-resolution manometry and those obtained by the motorized pull-through technique of conventional manometry. We analyzed all four available HRM techniques for assessing the LES using two different pressure thresholds and found that the overall and abdominal lengths of the LES were consistently overestimated. The resting pressure of the LES was also overestimated when the E-sleeve was used as recommended by the manufacturer.

In clinical practice, the spatiotemporal mode of HRM using color change is the most common method used to assess the status of the LES. We have shown that the degree of overestimation of the resting characteristics of the LES was greatest for this mode of analysis. In fact, 82% of

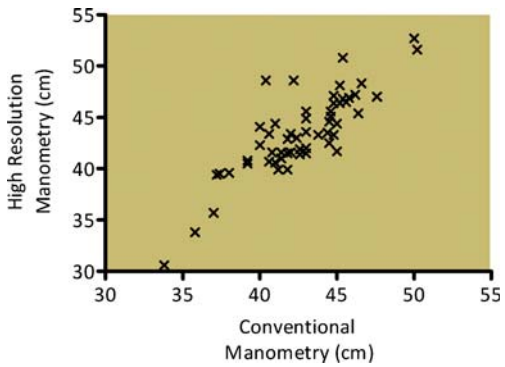


Figure 5 Correlation between the upper border of the LES determined by conventional manometry and the spatiotemporal mode of HRM using color change ($R^2=0.45$, $p<0.001$).

patients had overestimation of the LES length of up to 4 cm. There are several factors which may explain this discrepancy. First, there is subjectivity in identifying the exact location of the color change to localize the upper and lower borders of the sphincter. Second, the high-pressure zone marked by this method of analysis includes not only the intrinsic sphincter but the impression of the crural diaphragm. As a result, the true length of the LES is overestimated when a hernia is present, which we have also shown. Finally, as a consequence of catheter design, there is the inherent inaccuracy created by mathematical interpolation of the pressure values in the 0.75 cm between recording segments.

Analyses of the LES in the other three modes result in measurements that differ less from those obtained by conventional manometry. This is especially true for the line tracing mode. These methods of analyzing the LES require more experience and considerable adjustment of the software settings, which increases the demands on the technician performing the study. These requirements tend to negate many of the benefits to the diagnostic laboratory performing HRM.

The location of the upper border of the LES is an important landmark for placement of a pH catheter.[10,11] The location of the upper border of the LES determined by HRM was variable when compared to the results of conventional manometry. Overall, there was only a moderate correlation between the two measurements with variation of as much as 3.4 cm noted. This degree of variation in positioning the probe may lead to inconsistencies in pH measurements, given the gradient of acid exposure in the distal esophagus that has been documented in both patients with GERD[12] and in normal subjects.[13] This inconsistency in pH probe placement can affect clinical management by reporting false positive and false negative pH monitoring.

The differences that we have observed between high-resolution manometry and the motorized pull-through technique highlight limitations in the high-resolution technology. Elimination of the pull-through combined with mathematical interpolation of the pressure values between recording segments limits the precision of the length measurements of the LES to 1 cm. It is anticipated that future versions of the analytical software and pending modifications to catheter design will overcome many of the sources of inaccuracy in assessing the LES. In the next generation of HRM currently under development, referred to as high-definition manometry (Sierra Scientific Instruments Inc, Los Angeles, CA), the pressure sensors are more closely spaced such that 128 individual pressure recordings can be made over a distance of 4.8 cm.[14] With this modification, a 3-dimensional representation of the sphincter can be constructed in a manner similar to the sphincter pressure vector volume technique in assessment of LES that we have shown has advantages over conventional manometry in assessing sphincter incompetence.[15]

Conclusion

For more than half a century, the "pull-through" technique has been the standard means of assessing the resting characteristics of the LES.[16] High-resolution manometry eliminates this procedure and is associated with consistent overestimation of the resting characteristics of the LES and errors in the identification of the upper border of the sphincter and pH probe positioning. It appears that this simplification in the conduct and analysis of esophageal manometry has come at the detriment of accuracy in LES assessment.

References

1. Kahrilas PJ, Sifrim D. High-resolution manometry and impedance-pH/manometry: valuable tools in clinical and investigational esophagology. Gastroenterology 2008;135(3):756–769.
2. Campos GM, Oberg S, Gastal O, et al. Manometry of the lower esophageal sphincter: inter- and intraindividual variability of slow motorized pull-through versus station pull-through manometry. Dig Dis Sci 2003;48(6):1057–1061.
3. Ayazi S, Hagen JA, Chan LS, et al. Obesity and gastroesophageal reflux: quantifying the association between body mass index, esophageal acid exposure, and lower esophageal sphincter status in a large series of patients with reflux symptoms. J Gastrointest Surg 2009;13(8):1440–1447.
4. Clouse RE, Staiano A, Alrakawi A, Haroian L. Application of topographical methods to clinical esophageal manometry. Am J Gastroenterol 2000;95(10):2720–2730.
5. Takasaki K, Umeki H, Enatsu K, et al. Investigation of pharyngeal swallowing function using high-resolution manometry. Laryngoscope 2008;118(10):1729–1732.
6. Ghosh SK, Pandolfino JE, Zhang Q, et al. Deglutitive upper esophageal sphincter relaxation: a study of 75 volunteer subjects using solid-state high-resolution manometry. Am J Physiol Gastrointest Liver Physiol 2006;291(3):G525–G531.
7. Pandolfino JE, Ghosh SK, Rice J, et al. Classifying esophageal motility by pressure topography characteristics: a study of 400 patients and 75 controls. Am J Gastroenterol 2008;103(1):27–37.
8. Kahrilas PJ, Ghosh SK, Pandolfino JE. Esophageal motility disorders in terms of pressure topography: the Chicago Classification. J Clin Gastroenterol 2008;42(5):627–635.
9. Pandolfino JE, Ghosh SK, Lodhia N, Kahrilas PJ. Utilizing intraluminal pressure gradients to predict esophageal clearance: a validation study. Am J Gastroenterol 2008;103(8):1898–1905.
10. Ayazi S, Lipham JC, Portale G, et al. Bravo catheter-free pH monitoring: normal values, concordance, optimal diagnostic thresholds, and accuracy. Clin Gastroenterol Hepatol 2009;7(1):60–67.
11. Ayazi S, Leers JM, Oezcelik A, et al. Measurement of gastric pH in ambulatory esophageal pH monitoring. Surg Endosc 2009;23(9):1968–1973.
12. Mekapati J, Knight LC, Maurer AH, et al. Transsphincteric pH profile at the gastroesophageal junction. Clin Gastroenterol Hepatol 2008;6(6):630–634.

13. Pandolfino JE, Lee TJ, Schreiner MA, et al. Comparison of esophageal acid exposure at 1 cm and 6 cm above the squamocolumnar junction using the Bravo pH monitoring system. Dis Esophagus 2006;19(3):177–182.
14. Kahrilas PJ, Ghosh SK, Pandolfino JE. Challenging the limits of esophageal manometry. Gastroenterology 2008;134(1):16–18.
15. Stein HJ, DeMeester TR, Naspetti R, et al. Three-dimensional imaging of the lower esophageal sphincter in gastroesophageal reflux disease. Ann Surg. 1991;214(4):374–383.
16. Code CF, Fyke FE, Schlegel JF. The gastroesophageal sphincter in healthy human beings. Gastroenterologia 1956;86(3):135–150.

J Gastrointest Surg (2009) 13:2121–2127
DOI 10.1007/s11605-009-1038-9

ORIGINAL ARTICLE

Does the Value of PET-CT Extend Beyond Pretreatment Staging? An Analysis of Survival in Surgical Patients with Esophageal Cancer

Boris Sepesi · Daniel P. Raymond · Marek Polomsky · Thomas J. Watson · Virginia R. Litle · Carolyn E. Jones · Rui Hu · Xing Qiu · Jeffrey H. Peters

Received: 30 June 2009 / Accepted: 2 September 2009 / Published online: 1 October 2009

Abstract
Background Studies of positron emission tomography (PET) have focused mainly on tumor staging. The role of PET in predicting survival has received less attention. We sought to assess the relationship of pretreatment maximum standard uptake value (SUV_{max}) to survival in surgical patients with esophageal cancer.
Methods The study consisted of 72 esophagectomy patients (60 with adenocarcinoma) undergoing resection between July 2005 and April 2009. PET combined with computed tomography (PET-CT) was performed at a single center, and SUV_{max} was recorded prior to any therapy. Survival was assessed at a median follow-up of 19 months.
Results The median SUV_{max} was 6.25. A receiver operating characteristic curve identified SUV_{max} 4.5 to optimally discriminate survival. Patients with low SUV_{max} (<4.5) had significantly ($p=0.0003$) better survival than those with high SUV_{max} (≥4.5). Stage 3 patients with low SUV_{max} had significantly better survival ($p=0.0069$) than those with high SUV_{max}. Likewise, N1 disease patients with low SUV_{max} had significantly better survival ($p=0.008$) than those with high SUV_{max}. Multivariate analysis identified SUV_{max} to be an independent predictor of survival ($p=0.0021$).
Conclusion Pretreatment PET-CT SUV_{max} independently predicts survival in patients with esophageal carcinoma undergoing resection. SUV_{max} may be a valuable marker of tumor biology that could potentially be exploited for prognostic and therapeutic purposes.

Presented at a poster session, Digestive Disease Week, Chicago 2009

B. Sepesi · D. P. Raymond · M. Polomsky · T. J. Watson · V. R. Litle · C. E. Jones · J. H. Peters
Division of Thoracic and Foregut Surgery,
University of Rochester Medical Center,
Rochester, NY, USA

R. Hu · X. Qiu
Department of Biostatistics and Computational Biology,
University of Rochester,
Rochester, NY, USA

J. H. Peters (✉)
Department of Surgery,
University of Rochester School of Medicine & Dentistry,
601 Elmwood Ave, BOX SURG,
Rochester, NY 14642, USA
e-mail: Jeffrey_Peters@urmc.rochester.edu

Keywords Esophageal cancer · Positron emission tomography (PET) · Maximum standard uptake value (SUV_{max}) · Overall survival

Introduction

Esophageal carcinoma is an aggressive and complex malignancy with a markedly increasing incidence and an historically poor prognosis. Over the past decade, increased awareness, advancements in diagnostic modalities, and improved treatment strategies have resulted in a significant improvement in survival of patients undergoing resection for esophageal cancer.[1,2] The initial assessment and treatment planning of nearly all cancers, including esoph-

Table 1 Postoperative Complications

Complications	Number	Percent (%)
Atrial fibrillation	2	3
Pneumonia	2	3
Chyle leak	2	3
Wound infection	7	10
Pulmonary embolism	2	3
Colon ischemia requiring partial colectomy	2	3
Anastomotic leak	14	19

ageal carcinoma, is based on accurate staging of the extent of disease. Since its approval as a diagnostic modality for esophageal cancer by the Centers for Medicare and Medicaid Services in 2005, combined positron-emission tomography and computed tomography (PET-CT) has become an essential diagnostic test which has significantly improved the accuracy of preoperative staging.[3–5] The main advantage of combined PET-CT over other diagnostic modalities lies in an improved ability to assess metabolic characteristics of the tumor and suspected metastases. PET-CT utilizes radioactively labeled ^{18}F-fluorodeoxyglucose (^{18}FDG), which is concentrated in metabolically active tissues such as neoplasms and regions of inflammation. The maximum extent of ^{18}FDG uptake is expressed as a maximum standard uptake value (SUV_{max}), a calculated value defined as the activity concentration in the tissue divided by the activity injected per unit body weight. An elevated SUV_{max} is an indicator of heightened metabolic activity and, thus, a potential malignancy. Studies of this semiquantitative parameter established its role in tumor diagnosis, staging, and monitoring of treatment efficacy.[3,6,7]

The utility of SUV_{max} in predicting survival has received considerably less attention. Currently published data assessing the prognostic value of SUV_{max} are inconsistent.[8–11] Our aim was to study the association between SUV_{max} on the initial diagnostic pretreatment PET-CT and overall survival of esophageal cancer patients treated with esophagectomy. Furthermore, our goal was to assess whether SUV_{max} value on pretreatment PET-CT independently predicts survival.

Methods

The study population consisted of 141 patients undergoing esophagectomy for esophageal cancer between July 2005 and April 2009. Seventy-six (54%) patients had initial diagnostic pretreatment PET-CT. Three of the 76 patients who had high-grade dysplasia on their final pathology and one patient who died during the 30-day postoperative period were excluded from the study. The perioperative death occurred in a 79-year-old woman with neurofibromatosis and dysphagia secondary to obstructing distal esophageal adenocarcinoma. Her pretreatment tumor SUV_{max} was 16 without ^{18}FDG uptake within lymph nodes. Although a high-risk patient, she elected to pursue an attempt at curative resection and underwent transhiatal esophagectomy with cervical esophago-gastrostomy. A swallow study showed no leak on postoperative day (POD) 8; however, on POD 9 the patient developed fever and leukocytosis. A computed tomography study was nondiagnostic. While a pyloroplasty leak was suspected, the patient declined further treatment and subsequently died.

The final study population consisted of 72 patients. There were 60 patients with esophageal adenocarcinoma and 12 with squamous cell carcinoma (SCC). Ten patients underwent neoadjuvant chemotherapy, and seven combined

Table 2 Demographic and Clinicopathological Characteristics

Study population	*N*=72
Age (median)	63
Sex (male)	57 (79%)
Adenocarcinoma	60 (83%)
Squamous cell carcinoma	12 (17%)
Median SUV_{max}	6.25
Median follow-up	19 months
Neoadjuvant therapy	17 (24%)
Pathologic stage	
Stage 0	1 (1%)
Stage 1	17 (24%)
Stage 2A	13 (18%)
Stage 2B	15 (21%)
Stage 3	26 (36%)
Tumor location	
Distal	20 (28%)
Gastroesophageal junction (GEJ)	46 (64%)
Middle	6 (8%)
Nodal involvement	
N0	31 (43%)
N1	41 (57%)
Grade	
Well differentiated	6 (8%)
Moderately differentiated	26 (37%)
Poorly differentiated	34 (47%)
Undifferentiated	5 (7%)
Complete pathologic response	1 (1%)
Surgery type	
En bloc esophagectomy	19 (26.5%)
Ivor Lewis esophagectomy	4 (5.5%)
Transhiatal esophagectomy	41 (57%)
McKeown esophagectomy	4 (5.5%)
Minimally invasive esophagectomy	4 (5.5%)

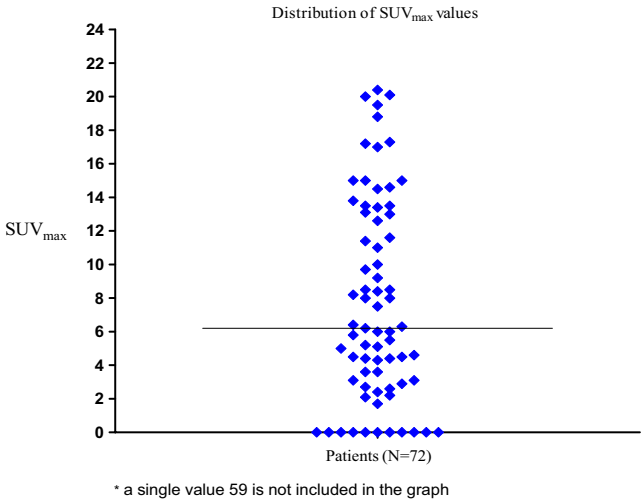


Figure 1 Distribution of SUV_{max} values and median of the study population. Single value 59 is not displayed on graph.

chemo-radiation prior to surgery. Seventeen patients had adjuvant chemotherapy or radiation; four patients abandoned adjuvant treatment after one cycle due to complications, and six patients received adjuvant therapy after discovery of metastatic disease. Only four patients (5%) received both neoadjuvant and adjuvant treatment.

Surgical resection was performed by five surgeons. The type of esophagectomy was individualized and based on surgeon's judgment, tumor location, and patient's fitness. Gastrointestinal continuity was reestablished with cervical esophago-gastrostomy in all types of esophageal resection except in Ivor Lewis esophagectomy. The majority (57%) of patients underwent transhiatal esophagectomy as described by Orringer et al.[12] with D2 abdominal and limited posterior mediastinal lymphadenectomy; 26.5% had en bloc esophageal resection as described by Rizzetto et al.[2] with extensive infra-carinal and D2 abdominal lymphadenectomy including intrathoracic ligation of the thoracic duct. Four patients underwent Ivor Lewis, four McKeown, and four minimally invasive esophagectomy (MIE) as previously described by Luketich et al.[13] with thoracosopic esophageal mobilization, laparoscopic gastric mobilization, and cervical esophago-gastrostomy. The mean number of harvested lymph nodes was 32 in en bloc, 19 in MIE, 15 in transhiatal, 13 in McKeown, and 12 in Ivor Lewis esophagectomy.

PET-CT scanning was performed at a single center prior to any therapy. Patients were imaged in the fasting state, and the blood glucose was measured prior to the injection of ^{18}FDG. Sixty minutes following the intravenous injection of ^{18}FDG, PET images were acquired from the skull base through the proximal thighs. A low-dose CT scan was performed for attenuation correction and localization of PET findings. PET-CT findings were reported by a certified radiologist with a calculated SUV_{max} value representing the highest uptake of ^{18}FDG within the tumor.

Patients' medical records were reviewed for the following variables: age, gender, clinical (cL) and pathologic tumor length, tumor location, maximum standard uptake value (SUV_{max}) on the initial pretreatment PET-CT, pathologic tumor (pT), node (pN), and metastasis (pM) stage, number of lymph nodes in the surgical specimen, number of lymph nodes positive for cancer, type, and grade of tumor. Postoperative complications included atrial fibrillation, pneumonia, chyle leak, wound infection, pulmonary embolism, colon ischemia requiring partial colectomy, and anastomotic leak. Complications had no influence on patients' survival and are documented in

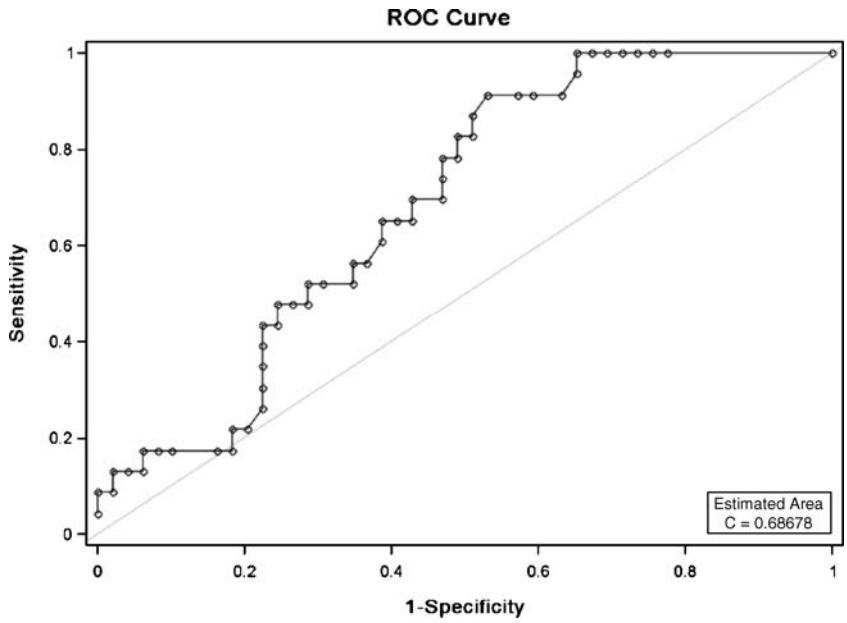


Figure 2 The ROC curve for survival prediction based on SUV_{max} yields an optimal cut-point of 4.5.

Table 1. Medical records and the Social Security Death Index were queried for information regarding survival. Survival was calculated from the time of operation to death. Living patients were censored as of October 7, 2008.

Statistical Analysis

The primary outcome measure was the association of maximum standard uptake value (SUV_{max}) on pretreatment PET-CT and overall survival following surgical resection. Cox proportional hazards regression was used to test the effects of several covariates, including clinical (cL) tumor length, SUV_{max}, pN, pT, tumor grade and stage, and their association with survival. Univariate and multivariate analysis (with and without model selection) were both conducted. Logistic regression was employed to study the association between SUV_{max} and mortality. A receiver operating characteristic (ROC) curve was drawn to assess the SUV_{max} value most optimally discriminating survival. Survival was assessed at a median follow-up of 19 months for surviving patients using the method of Kaplan and Meier. Individual survival curves were compared with log-rank test; p value less than 0.05 was considered significant. Statistical analyses were conducted using SAS 9.1 (SAS Institute Inc., Cary, NC, USA).

The study was approved by the University of Rochester Medical Center Research Subjects Review Board.

Results

There were 57 (79%) men and 15 (21%) women with a median age of 63 years.

Table 2 summarizes patients' demographics and clinical characteristics. Adenocarcinoma was a more prevalent tumor type by a ratio of almost 6:1. Ninety percent of tumors were located in the distal esophagus or cardia and the median clinical (cL) tumor length was 4 cm. Forty-three percent of patients presented with node negative disease, 36% with stage 3 disease, and 57% had histopathologicaly confirmed nodal metastasis following surgical resection. Surgical resection consisted of en bloc esophagectomy with abdominal and mediastinal lymphadenectomies in a quarter and transhiatal or transthoracic esophagectomy in the remaining.

Pretreatment SUV_{max} on PET-CT ranged from 0 to 59 with a median of 6.25 (Fig. 1). The SUV_{max} value that optimally discriminated survival (4.5) was determined via construction of a receiver operating characteristic curve (Fig. 2). Table 3 compares the characteristics of patients with SUV_{max} above and below 4.5. Patients with $SUV_{max} \geq 4.5$ had significantly longer clinical (cL) tumor length, more advanced stage, and a higher prevalence of cancer-positive lymph nodes and poor differentiation than those with $SUV_{max} < 4.5$.

Patients with low SUV_{max} (<4.5; $N=25$) had significantly ($p=0.0003$) better survival (median survival not reached) than those with high SUV_{max} (≥4.5; $N=47$; 19.23 months, Fig. 3). This was also true when comparing only stage 3 patients; those with low SUV_{max} ($N=7$) had significantly better survival ($p=0.0069$) than stage 3 patients with high SUV_{max} ($N=19$; Fig. 4). Patients with N1 disease and a low SUV_{max} ($N=10$) had significantly better survival ($p=0.0081$) than high SUV_{max} N1 patients ($N=31$; Fig. 5). Univariate proportional hazards regression analysis (Table 4) identified SUV_{max} ($p=0.00149$), positive nodal status pN ($p=0.0201$),

Table 3 Clinicopathological Characteristics of Low and High SUV_{max} Groups

	Low $SUV_{max}<4.5$ $N=25$	High $SUV_{max}\geq4.5$ $N=47$	
Age (median)	61	63	$p=0.934$
Sex (male vs female)	20/5	37/10	
Adeno vs SCC	22/3	38/9	
Median clinical tumor length (cL)	2 cm	5 cm	$p<0.0001$
Pathologic stage			
Stage 0	0	1 (2%) CR	
Stage 1	13 (52%)	4 (8.5%)	
Stage 2A	2 (8%)	12 (25.5%)	
Stage 2B	3 (12%)	11 (23%)	
Stage 3	7 (28%)	19 (40%)	$p=0.0069$
Median follow-up	24.7 months	12. 6 months	$p=0.0944$
Tumor location			
Distal	8 (32%)	12(25.5%)	
GEJ	17 (78%)	29 (61.5%)	
Middle	0	6 (13%)	
Nodal involvement			
N0	15 (60%)	16 (44%)	
N1	10 (40%)	31 (66%)	$p=0.0272$
Grade			
Well differentiated	4 (14%)	2 (4%)	
Moderately differentiated	8 (32%)	18 (38%)	
Poorly differentiated	10 (40%)	24 (51%)	
Undifferentiated	3 (12%)	3 (6%)	
Surgery type			
En bloc esophagectomy	4 (16%)	15 (32%)	
Ivor Lewis esophagectomy	3 (12%)	1 (2%)	
Transhiatal esophagectomy	17 (68%)	24 (51%)	
McKeown esophagectomy	0	4 (8.5%)	
Minimally invasive esophagectomy	1 (4%)	3 (6.5%)	

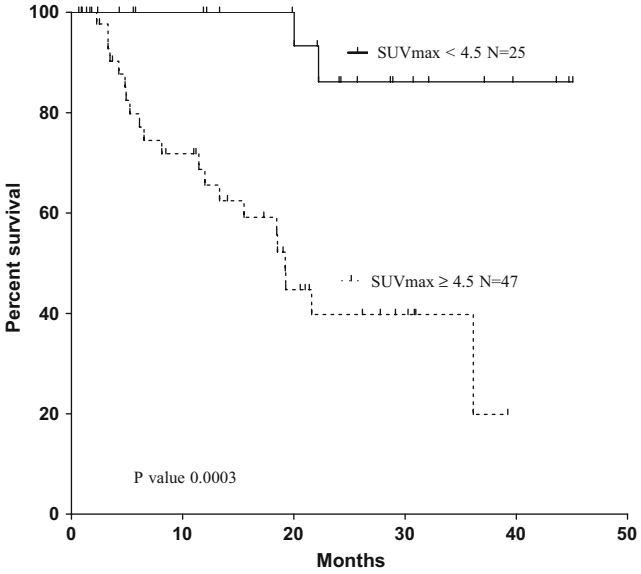


Figure 3 Survival proportion stratified by low and high SUV_{max}.

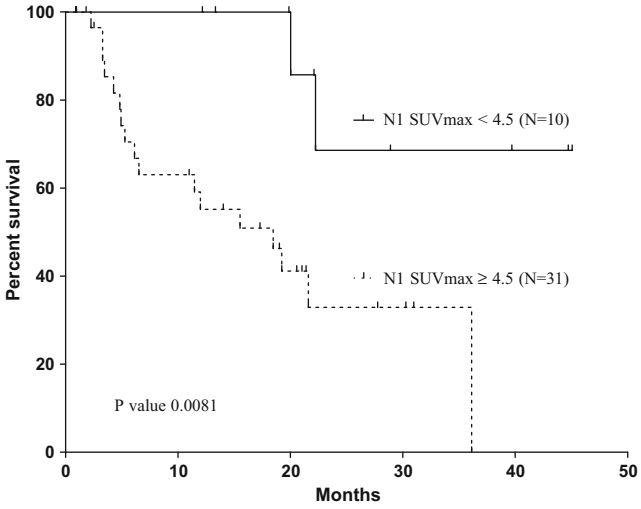


Figure 5 Survival proportion of pathologic N1 patients stratified by low and high SUV_{max}.

tumor invasion through the muscularis propria pT3 (p= 0.0128) and pathologic stages 2B+3 (p=0.0266) to be significantly associated with mortality. On multivariate analysis, with and without model selection, SUV_{max} remained an independent predictor of survival (Tables 5 and 6). On univariate logistic regression analysis, a one-unit rise in SUV_{max} increased the odds of mortality by 9.8% (p=0.0276; Table 7).

Discussion

Our primary aim was to assess the association between pretreatment PET SUV_{max} and patient survival in resectable esophageal carcinoma. We further evaluated whether SUV_{max} predicts survival independently of other well-known variables such as tumor stage or nodal status. The data showed that pretreatment SUV_{max} was strongly associated with overall survival in patients undergoing resection for esophageal cancer. This association remained significant on multivariate analysis when controlling for variables such as stage, grade, and nodal status. Logistic regression revealed that each incremental point increase in SUV_{max} on a pretreatment PET-CT translated into increased odds of death by 9.8%. Furthermore, pretreatment PET SUV_{max} retained its prognostic significance when comparing subgroups of patients limited to stage 3 disease or those with positive node metastases. In both groups of high-risk patients, a low SUV_{max} resulted in significantly prolonged survival compared to those with higher values. These observations support the hypothesis that low ^{18}FDG uptake within a tumor may represent more indolent tumor biology, and that high glucose metabolism within a cancer cell may signify aggressive behavior of the tumor.

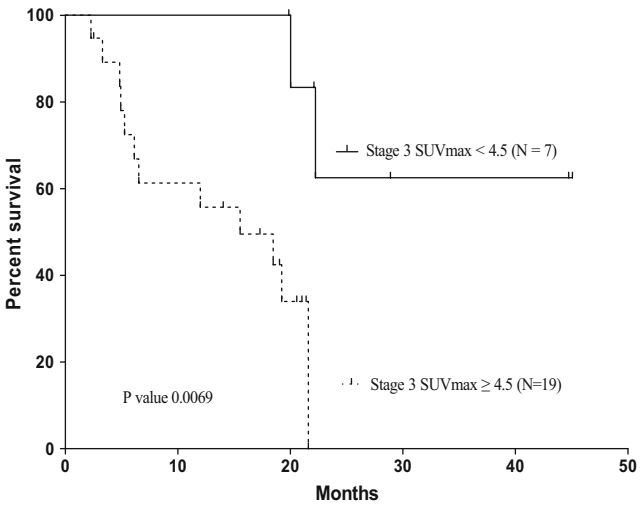


Figure 4 Survival proportion of stage 3 patients stratified by low and high SUV_{max}.

Table 4 Univariate Proportional Hazards Regression Analysis

Variable	p value	Hazard ratio	95% HR CI
Clinical tumor length (cL)	0.416	1.098	0.87–1.38
SUV_{max}	0.0149*	1.033	1.00–1.06
pN (pN1 vs pN0)	0.02*	3.601	1.22–10.61
pT (pT2 vs pT1)	0.334	2.415	0.40–14.45
pT (pT3 vs pT1)	0.026*	3.396	1.15–10.00
Grade (well + moderate vs poor)	0.567	0.782	0.33–1.81

The asterisks mark the values that are statistically significant p<0.05.

Table 5 Multivariate Proportional Hazards Regression Analysis with Model Selection

Variable	*p* value	Hazard ratio	95% HR CI
SUV_{max}	0.0021*	1.056	1.02–1.093
pN (1 vs 0)	0.0082*	5.73	1.57–20.90

The asterisks mark the values that are statistically significant $p<0.05$.

Since the concept of positron emission tomography was first introduced (1950s), PET has become an increasingly useful staging modality for malignant diseases including carcinomas of the lung, breast, head and neck, thyroid, colon, and esophagus, as well as for melanoma and lymphoma.[4] The clinical utility of PET was underscored in a review of 22,975 PET studies from 1,178 centers in the USA.[14] Comparing the management of patients with and without PET, PET studies were associated with a change in treatment decision in over one third of the patients (36.5%) and resulted in a significant decrease in the use of other diagnostic tests and biopsies. Studies focusing on resectability of esophageal cancer including the American College of Surgeons Oncology Group Z0060 trial have revealed that PET upstages 4.8–12% of patients previously deemed as surgical candidates for treatment of esophageal cancer.[3,5]

The basic mechanism underlying positron emission tomography, i.e., glucose metabolism, may not only permit clinicians to differentiate neoplastic from normal tissue or increase accuracy of staging but may also reflect specific metabolic characteristics of a neoplasm that could potentially be utilized in a manner similar to conventional histology for therapeutic decisions and prognostication.[15]

Pathologic tumor–node–metastases (TNM) staging has been considered the standard method for prognosticating survival of gastrointestinal malignancies. The magnitude of SUV_{max} uptake on the pretreatment PET-CT is presently not considered as an important variable in prognosticating survival. However, current TNM staging of esophageal cancer is widely recognized to be poor and in need of revision. Moreover, an increased use of neoadjuvant chemoradiotherapy significantly compromises prognostication of survival based on pathologic TNM staging.[16]

Table 6 Multivariate Proportional Hazards Regression Analysis Without Model Selection

Variable	*p* value	Hazard ratio	95% HR CI
Clinical tumor length (cL)	0.596	0.918	0.67–1.26
SUV_{max}	0.048*	1.057	1.0–1.12
pN (pN1 vs pN0)	0.0112*	6.55	0.64–66.9
pT (pT2 vs pT1)	0.533	0.452	0.03–5.47
pT (pT3 vs pT1)	0.837	0.795	0.08–7.15
Grade (well + moderate vs poor)	0.684	0.786	0.24–2.50

The asterisks mark the values that are statistically significant $p<0.05$.

Table 7 Univariate Logistic Regression Analysis

Variable	*p* value	Odds ratio	95% OR CI
SUV_{max}	0.0276*	1.098	1.01–119

The asterisk marks the value that is statistically significant $p<0.05$.

Initial studies of the prognostic value of SUV_{max}, including both surgical and nonsurgical patients, were conflicting. Investigators from the Netherlands studied whether SUV can be used as a predictor of survival in 40 esophageal cancer patients including 19 who underwent esophagectomy.[8] Using multivariate Cox regression analysis, they determined resection to be the only independent predictor of survival. Other studies limited to surgical candidates have suggested that SUV_{max} may be a predictor of outcome. Rizk et al. from Memorial Sloan-Kettering stratified 50 patients with esophageal cancer into low and high SUV_{max} groups compared to the median SUV_{max} (4.5).[9] Patients with low SUV_{max} had significantly ($p=0.02$) better survival. The survival advantage in patients with low SUV_{max} remained significant in early clinical ($p=0.008$) and early pathologic stage ($p=0.023$) tumors. They concluded that SUV_{max} predicts survival; however, multivariate analysis was not performed, making definitive conclusions difficult. Cerfolio and Bryant reported that stage and pre-operative SUV_{max} were independent predictors of survival in a cohort of 89 patients undergoing esophagectomy.[10] Linear regression showed better correlation between SUV_{max} and survival when compared to disease stage and survival. More recently, Kato and colleagues demonstrated SUV_{max} and the number of PET (+) lymph nodes to be independent predictors of survival in 184 patients treated with surgical resection for esophageal cancer.[11] This population, however, included mainly patients with squamous cell carcinoma (91%), whereas our study contained primarily adenocarcinoma (83%).

These results suggest that SUV_{max} may be a marker of tumor biology. Westerterp et al. have demonstrated a significant correlation between ^{18}FDG uptake and glucose transporter-1 (Glut-1) protein expression in esophageal cancer specimens.[15] This may suggest a molecular mechanism linking ^{18}FDG uptake/glucose metabolism with proliferative activity of a tumor and, ultimately, patient survival. In fact, the expression of Glut-1 transporter has been shown to be a stage-independent predictor of clinical outcome in adrenocortical carcinoma.[17] Whether or not ^{18}FDG avidity can be exploited for more accurate molecular staging or, potentially, targeted therapy remains an intriguing question.[18]

The limitations of our study include its retrospective design and relatively short patient follow-up. Despite these limitations, the differences in survival are discernible. Surgical resection was individualized, and not all patients underwent extensive lymphadenectomy, which has been demonstrated to impact patient survival.[19] The prevalence of positive lymph nodes was 40% in the group with low SUV_{max} and 66% in the high-SUV_{max} group ($p=0.0272$). Patients in the high-SUV_{max} group had a median 18 pathologically examined lymph nodes versus 12 lymph nodes in the low SUV_{max} group ($p=0.0076$). Despite the lesser lymphadenectomy in the low SUV_{max} group, survival was better.

In conclusion, the utility of pretreatment PET-CT scanning likely extends beyond staging in patients with esophageal carcinoma. Low SUV_{max} predicts improved survival in patients undergoing surgical resection of the esophagus for malignant disease independent of tumor size, tumor differentiation, and node status. A larger multi-institutional study could potentially determine whether pretreatment SUV_{max} on PET-CT could be used as an additional variable combined with TNM staging to prognosticate outcome of esophageal cancer patients.

References

1. Portale G, Hagen JA, Peters JH, Chan LS, DeMeester SR, Gandamihardja TA et al. Modern 5-year survival of resectable esophageal adenocarcinoma: Single institution experience with 263 patients. J Am Coll Surg 2006;202:588,96. discussion 596–598.
2. Rizzetto C, DeMeester SR, Hagen JA, Peyre CG, Lipham JC, DeMeester TR. En bloc esophagectomy reduces local recurrence and improves survival compared with transhiatal resection after neoadjuvant therapy for esophageal adenocarcinoma. J Thorac Cardiovasc Surg 2008;135:1228–1236.
3. Meyers BF, Downey RJ, Decker PA, Keenan RJ, Siegel BA, Cerfolio RJ et al. The utility of positron emission tomography in staging of potentially operable carcinoma of the thoracic esophagus: Results of the American College of Surgeons oncology group Z0060 trial. J Thorac Cardiovasc Surg 2007;133:738–745.
4. Larson SM. Practice-based evidence of the beneficial impact of positron emission tomography in clinical oncology. J Clin Oncol 2008;26:2083–2084.
5. Williams RN, Ubhi SS, Sutton CD, Thomas AL, Entwisle JJ, Bowrey DJ. The early use of PET-CT alters the management of patients with esophageal cancer. J Gastrointest Surg 2009;13:868–873.
6. Roedl JB, Colen RR, Holalkere NS, Fischman AJ, Choi NC, Blake MA. Adenocarcinomas of the esophagus: Response to chemoradiotherapy is associated with decrease of metabolic tumor volume as measured on PET-CT. comparison to histopathologic and clinical response evaluation. Radiother Oncol 2008;89:278–286.
7. Schmidt M, Bollschweiler E, Dietlein M, Monig SP, Kobe C, Vallboehmer D et al. Mean and maximum standardized uptake values in [18F]FDG-PET for assessment of histopathological response in oesophageal squamous cell carcinoma or adenocarcinoma after radiochemotherapy. Eur J Nucl Med Mol Imaging 2009;36:735–744.
8. van Westreenen HL, Plukker JT, Cobben DC, Verhoogt CJ, Groen H, Jager PL. Prognostic value of the standardized uptake value in esophageal cancer. AJR Am J Roentgenol 2005;185:436–440.
9. Rizk N, Downey RJ, Akhurst T, Gonen M, Bains MS, Larson S et al. Preoperative 18[F]-fluorodeoxyglucose positron emission tomography standardized uptake values predict survival after esophageal adenocarcinoma resection. Ann Thorac Surg 2006;81:1076–1081.
10. Cerfolio RJ, Bryant AS. Maximum standardized uptake values on positron emission tomography of esophageal cancer predicts stage, tumor biology, and survival. Ann Thorac Surg 2006;82:391,4. discussion 394–395.
11. Kato H, Nakajima M, Sohda M, Tanaka N, Inose T, Miyazaki T, et al. The clinical application of (18)F-fluorodeoxyglucose positron emission tomography to predict survival in patients with operable esophageal cancer. Cancer 2009;115(14):3196–3203.
12. Orringer MB, Marshall B, Chang AC, Lee J, Pickens A, Lau CL. Two thousand transhiatal esophagectomies: Changing trends, lessons learned. Ann Surg 2007;246:363,72. discussion 372–374.
13. Luketich JD, Alvelo-Rivera M, Buenaventura PO, Christie NA, McCaughan JS, Litle VR et al. Minimally invasive esophagectomy: Outcomes in 222 patients. Ann Surg 2003;238:486,94. discussion 494–495.
14. Hillner BE, Liu D, Coleman RE, Shields AF, Gareen IF, Hanna L et al. The national oncologic PET registry (NOPR): Design and analysis plan. J Nucl Med 2007;48:1901–1908.
15. Westerterp M, Sloof GW, Hoekstra OS, Ten Kate FJ, Meijer GA, Reitsma JB et al. 18FDG uptake in oesophageal adenocarcinoma: Linking biology and outcome. J Cancer Res Clin Oncol 2008;134:227–236.
16. Leers JM, Ayazi S, Hagen JA, Terterov S, Klipfel N, Oezcelik A et al. Survival in lymph node negative adenocarcinoma of the esophagus after R0 resection with and without neoadjuvant therapy: Evidence for downstaging of N status. J Am Coll Surg 2009;208:553–556.
17. Fenske W, Voelker HU, Adam P, Hahner S, Johanssen S, Wortmann S, et al. Glucose transporter GLUT1 expression is a stage-independent predictor of clinical outcome in adrenocortical carcinoma. Edocr Relat Cancer 2009;16(3):919–928.
18. Shaw RJ. Glucose metabolism and cancer. Curr Opin Cell Biol 2006;18:598–608.
19. Peyre CG, Hagen JA, DeMeester SR, Altorki NK, Ancona E, Griffin SM et al. The number of lymph nodes removed predicts survival in esophageal cancer: An international study on the impact of extent of surgical resection. Ann Surg 2008;248:549–556.

J Gastrointest Surg (2009) 13:2128–2135
DOI 10.1007/s11605-009-1044-y

2009 SSAT POSTER PRESENTATION

Intestinal Surgery for Crohn's Disease: Predictors of Recovery, Quality of Life, and Costs

Marco Scarpa · Cesare Ruffolo · Domenico Bassi · Riccardo Boetto · Renata D'Incà · Andrea Buda · Giacomo C. Sturniolo · Imerio Angriman

Received: 27 May 2009 / Accepted: 4 September 2009 / Published online: 25 September 2009

Abstract
Introduction The aim of this prospective study was to analyze the impact of different surgical techniques on patients undergoing intestinal surgery for Crohn's disease (CD) in terms of recovery, quality of life, and direct and indirect costs.
Patients and methods Forty-seven consecutive patients admitted for intestinal surgery for CD were enrolled in this prospective study. Surgical procedures were evaluated as possible predictors of outcome in terms of disability status (Barthel's Index), quality of life (Cleveland Global Quality of Life score), body image, disease activity (Harvey–Bradshaw Activity Index), and costs (calculated in 2008 Euros). Univariate and multivariate analyses were performed.
Results Significant predictors of a long postoperative hospital stay were the creation of a stoma, postoperative complications, disability status on the third post-operative day, and surgical access (R^2=0.59, p<0.01). Barthel's index at discharge was independently predicted by laparoscopic-assisted approach, ileal CD, and colonic CD (R^2=0.53, p<0.01). The disability status at admission showed to be an independent predictor of quality of life score at follow-up. The overall cost for intestinal surgery for CD was 12,037 (10,117–15,795) euro per patient and stoma creation revealed to be its only predictor (p=0.006).
Conclusions Laparoscopy was associated with a shorter postoperative length of stay; stoma creation was associated with a long and expensive postoperative hospital stay, and stricturoplasty was associated with a slower recovery of bowel function.

Keywords Crohn's disease · Laparoscopic assisted bowel resection · Strictureplasty · Ileostomy

Funding: This paper was funded, in part, by the Italian Ministry of the University and Research (MIUR) grant ex 60%.

Preliminary results of this study were presented as a poster at the 50th annual meeting of the Society for Surgery of the Alimentary Tract (Digestive Disease Week), May 30–June 3, 2009 Chicago, Illinois, USA.

M. Scarpa (✉)
Department of Oncological Surgery,
Veneto Oncological Institute,
via Gattamelata 74,
35128 Padova, Italy
e-mail: marcoscarpa73@yahoo.it

C. Ruffolo
IV Unit of Surgery, Regional Hospital Cà Foncello,
Treviso, Italy

D. Bassi · R. Boetto · R. D'Incà · A. Buda · G. C. Sturniolo · I. Angriman
Department of Surgical and Gastroenterological Sciences,
University of Padova,
Padova, Italy

Introduction

Eighty percent of patients affected by Crohn's disease (CD) will require at least one surgical procedure over their lifetime.[1] Surgery is among the most important concerns of patients affected by CD. In fact, concerns about having surgery and having an ostomy bag have a significant impact on health-related quality of life (HRQL) of CD patients, and having surgery increases concerns about body stigma.[2–4]

Minimally invasive surgery and stricturoplasty may reduce the negative impact of surgery in these patients. However, extensive colonic resection and/or stoma creation are still necessary in some cases. The early impact of surgery on HRQL is an important component of the patient's decisions regarding immediate and future surgery and understanding his or her recovery. Obviously, HRQL is

expected to improve after operative procedures. In most studies, a significant improvement in HRQL early in the post-operative period was observed.[5–7] Improvement, occurred irrespective of the disease activity measured with CDAI, the indication for surgery, type of procedure (abdominal or perineal), and history of previous surgery.[8] The impact on HRQL of recovery and namely the disability status of patients after surgery for CD have never been analyzed.

Hospitalization has been estimated to account for half of all direct medical costs for CD[9] and half of hospitalized CD patients undergo intestinal surgery.[9–11] In fact, of the total charges incurred by patients with CD admitted to the University of Chicago hospitals over a 12-month period, nearly 40% of costs were for surgical management.[9] In the Markov analysis by Silverstein et al. estimated charges were higher for patients requiring surgery but the duration of post-surgical remission was longer than for medically treated patients.[12] There are few data available to allow a prediction of the costs of surgical treatment and prospective, longitudinal studies addressing this question would be of interest.[13]

This prospective study aimed to analyze the impact of different surgical techniques on patients who underwent to intestinal surgery for CD in terms of recovery, quality of life, and direct and indirect costs.

Patients and Methods

Patients

The study was performed according to the Helsinki declaration principles and all patients gave their informed consent to be enrolled in the study. Forty-seven consecutive patients admitted for intestinal surgery for CD in our department from May 2006 to July 2008 were enrolled in this prospective study. Diagnosis of CD was made with clinical, endoscopic, and blood tests according to Lennard–Jones criteria.[14] Clinical disease activity was quantified using a modified version of the Harvey–Bradshaw Activity Index (HBAI).[15] Patients who were admitted for surgery for perineal CD were excluded because of the different surgical procedures and the important impact on quality of life of this disease location.

Study Design

Surgical predictors, such as laparoscopic-assisted bowel resection, stricturoplasty, stoma creation, ileal resection, and colonic resection as well as clinical predictors, such as age, gender, CD duration, activity and localization, and recurrent CD were evaluated. Postoperative course was evaluated with recovery parameters such as day of first bowel movement, postoperative hospital stay, and Barthel's physical disability score and complication analysis (medical and surgical complication and need of reoperation). After at least 3 months, patients were interviewed about their time to return to work, their disease activity, and they were submitted the Italian version of Cleveland Global Quality of Life (CGQL) score and the Body Image Score.

Surgical Technique

Bowel resection was performed removing all grossly involved bowel through a standard midline laparotomy or with laparoscopic assistance. In the laparoscopic-assisted ileo-colonic resection a three-trocar approach was used (subumbilical, 10 mm; left iliac fossa, 10 mm; suprapubic, 5 mm). The distal ileum and the right colon were fully mobilized and exteriorized by a 4–6 cm vertical incision through the umbilicus. In case of entero-sigmoid fistula or large inflammatory mass, a small Pfannestiel incision (8 cm) was used instead of the transumbilical incision (22). Vascular ligation, bowel division and anastomosis were performed extracorporeally. Stapled anastomoses were constructed in a side-to-side fashion using an 80-mm linear stapler (GIA75, US Surgical Corp., Norwalk, CT, USA). Hand-sewn anastomoses were created in a side-to-side orientation using a running suture of 3–0 Vicryl for the inner layer (mucosal) (Ethicon, Inc., Somerville, NJ, USA) and a running 3–0 TiCron (US Surgical Corporation, Norwalk, CT, USA) for the outer layer (sero-muscolar).

End ileostomy was typically used in cases of extensive colonic CD with macroscopic rectal disease, not responding to medical therapy. The ileal loop was delivered through a trephine in the abdominal wall. After closure of the laparotomy, the ileostomy was opened and the proximal component of loop was everted and then fixed to the skin with muco-cutaneous absorbable 3–0 Vicryl, (Ethicon, Inc., Somerville, NJ, USA) sutures. No stitches were placed to fix the ileostomy to the inner layer of the abdominal wall.

Stricturoplasty was constructed in case of ileal or jejunal skip lesions in order to minimize the extent of small bowel resected. The main site of disease (i.e. the ileo-colonic junction) was usually resected and in case of multiple disease sites, standard stricturoplasty was performed. The bowel was incised along its main axis on the anti-mesenteric side on a Crohn's stenosis and sutured transversally with absorbable 3–0 Vicryl, (Ethicon, Inc., Somerville, NJ, USA) stitches.

Barthel's Index

Barthel's Index provides an objective assessment of overall disability[16] and has been shown to be reliable with different observers in a wide variety of situations. It is a validated measure of physical disability[17] initially used in neurological setting but now commonly used to

assess the disability of patients in order to optimize nursing assistance. The assessment was independently made by ward staff during their regular rounds a minimum of three times, including on admission, on the third postoperative day, and at discharge.

Italian CGQL

The Cleveland Global Quality of Life instrument or Fazio score, developed to assess health-related quality of life (HRQL) in patients after ileal pouch-anal anastomosis and with CD,[18,19] consists of three items (current quality of life, current quality of health, and current energy level), each on a scale of 0 to 10 (with 0 the worst and 10 the best). Given its short framework, the Italian translation, recently validated in one of our previous studies[20] was considered a suitable instrument for telephone interviews.

Body Image Questionnaire

The Body Image Questionnaire (BIQ) is an instrument that explores body image and cosmesis after surgery and consists of eight items. The BIQ has already been tested in patients undergoing open and laparoscopic-assisted intestinal surgery.[21] The questionnaire consists of two sections concerning body image and cosmesis. The body image scale analyzes patients' perception of and satisfaction with their own body and investigates patients' attitudes toward their appearance. The reliability coefficients (values of Cronbach's alpha) for body image was 0.80.

Cost Analysis

The following assumptions were used as the basis for determining the cost analysis of the different surgical procedures. The median cost of the hospital stay and that of the operation were based on estimates of standard charges in an Italian setting (North-Eastern Italy) and were expressed in 2008 Euros. The daily cost of the hospital stay was estimated to be 960 euro per patient; the cost of the instruments for an open intestinal resection was 603.26 euro while that for a laparoscopic-assisted intestinal resection was 1,477.26 euro per patient. The social cost of lost working days was calculated based on standard Italian daily wages according to the different jobs. Patients were asked about their job and their mean monthly income were retrieved from Italian Ministry of Work database; housewives, retired patients, and students were considered to have no income. The overall cost was calculated by adding the cost of the hospital stay, the cost of the instruments necessary for the operation and the cost of the lost working days during sick leave.

Statistical Analysis

Data were expressed as median value (range) unless otherwise specified. Non-parametric Mann–Whitney *U* two-tailed test and Kruskal–Wallis ANOVA were used to compare dichotomous variables. Wilcoxon test and Friedman ANOVA were used in the case of paired data. Frequency analysis was performed using Fisher's exact test. Kendall rank correlation test was used to analyze the correlation between predictors and continuous outcome parameters. Given a level

Table 1 Patients Characteristics

Patients characteristics	
Patients operated on between 2007–2008	47
Gender: male/female	24 (51%)/23 (49%)
Age at operation (years)	38 (31–54)
Age at disease onset (years)	28 (19–44)
Disease duration (months)	79 (13–192)
Disease phenotype	
Fistulizing (patients)	11 (23%)
Obstructing (patients)	36 (77%)
Disease site	
Small bowel (patients)	38 (81%)
Large bowel (patients)	16 (34%)
Perianal (patients)	4 (9%)
Recurrent disease (patients)	9 (19%)
Operation (patients who had the procedure)	
Ileal/ileocolonic resection	32 (68%)
Colonic resection	16 (34%)
Ileostomy	6 (/13%)
Stricturoplasty	10 (21%)
Laparoscopy	25 (53%)
Duration of operation (minutes)	172 (120–225)
Outcome parameters	
First bowel movement	Third (first to sixth) post-operative day
Median post-operative stay	7 (5–20) days
Barthel's Index	
At admission	100 (0–100)
On the third postoperative day	45 (0–100)
At discharge	100 (30–100)
Complications	
Obstruction	3 (6%)
Anastomotic leak	2 (4%)
Re-operation	1 (2%)
Follow-up	
Median sick leave	30 (2–360) days
Harvey-Bradshaw Activity Index	3.5 (1–6.5)
Body image score	5 (5–8)
Cleveland Global Quality of Life score	7.7 (6.5–8.7)

of statistical significance (α) of 0.05, a power (1-β) of 0.80 and an expected correlation coefficient of 0.45, the consequent sample size required was 36 patients. Multiple linear regression models were constructed with predictors that were found to be significant on univariate analysis to assess the different role of each one. When the number of predictors exceeded 5, stepwise forward regression analysis was used. R^2 of each model, which is the proportion of variation in the duration of post-operative hospital explained by this model, was shown. Statistical significance was indicated by $p<0.05$.

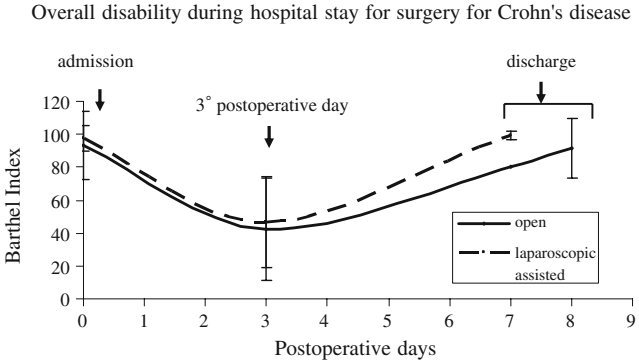


Figure 1 Disability status after intestinal surgery for CD.

Results

Patients

Median age of the patients was 38 (16–69) years and 23 (49%) of the patients were female. The median duration of CD was 79 (3–264) months, and 11 patients presented a fistulizing phenotype. CD was localized to the small bowel in 38 patients and in the large bowel in nine patients; seven patients had disease in both locations. In addition, four patients had also perineal CD but this was not the main indication for their surgery. Six patients had a stoma (five end ileostomy and a loop ileostomy) created at the time of surgery: five of them for severe colonic CD not responding to medical therapy, and one loop ileostomy proximal to a colo-rectal anastomosis. Patients' characteristics are shown in Table 1.

Predictors of Post-operative Recovery and Complications

In this series, the median time of first bowel movement was on the third (first to sixth) postoperative day. Patients who had stricturoplasty had their first bowel movement later than those who had bowel resection ($p=0.042$). The timing of the first bowel movement correlated significantly with the obstructing phenotype of CD and with stricturoplasty but none of them was found to be an independent predictor at multiple regression analysis.

The median postoperative stay was 7 (5–20) days and, as shown in Table 2, was significantly shorter in the group of patients who had ileal resection, and in those who underwent laparoscopic-assisted bowel resection. On multiple regression analysis creation of a stoma, postoperative complications, and disability status on the third post-operative day and open (non-laparoscopic) surgery were found to be significant predictors of duration of post-operative hospital stay (R^2 was 0.59, $p<0.01$).

Median Barthel's score at admission was 100 (0–100), on the third postoperative day was 45 (0–100), and at discharge was 100 (30–100; $p<0.001$) (Fig. 1). Barthel's score on the third post-operative day and at discharge was significantly lower in patients who had a stoma created. Barthel's score on the third postoperative day significantly correlated with number of intestinal sites involved by CD, stoma creation, perianal CD, and with postoperative day of first bowel movement. However, none of these parameters

Table 2 Surgical Techniques and Recovery Parameters

Surgical technique	Outcome measure	Yes: median (IQR)	No: median (IQR)	*p* level
Ileal resection	Discharge (days after operation)	7 (6–8)	9 (7–10)	0.038
	Sick leave duration (days)	30 (18–53)	45 (30–83)	0.063
Colonic resection	Discharge (days after operation)	9 (7–12)	7 (6–8)	0.025
	Barthel Index at discharge	100 (90–100)	100 (100–100)	0.016
Stricturoplasty	First bowel movement (days)	4 (3–5)	3 (2–4)	0.042
Laparoscopy	Discharge (days after operation)	7 (6–8)	8 (7–10)	0.001
	Body Image score	6 (5–8)	5 (0–7)	0.072
Ileostomy	Discharge (days after operation)	11 (8–16)	7 (6–9)	0.015
	Barthel Index at third post-operative day	3 (0–25)	45 (25–70)	0.020
	Barthel Index at discharge	93 (58–100)	100 (100–100)	0.048
	Sick leave duration (days)	71 (48–98)	30 (20–60)	0.071

were found to be an independent predictor at multivariate analysis. However, Barthel's score at discharge was independently predicted by laparoscopic-assisted approach, ileal CD, and colonic CD (R^2=0.53, p<0.01).

In this series, two anastomotic leaks, three intestinal obstructions, two intestinal bleeding, and a wound infection were recorded and two re-laparotomies were necessary in the post-operative period. Surgical complications correlated inversely with stricturoplasty and Barthel's Index score at admission but none of these parameters were found to be an independent predictor at multivariate analysis (Table 3).

Predictors of Quality of Life

Median sick leave was 30 (2–360) days and showed a trend to be significantly longer in patients who had surgery other than ileal resection and in those who had a stoma created. However at multiple regression analysis only physical burden of the job appeared to predict independently the sick leave duration.

After follow-up, CGQL score correlated with the Harvey–Bradshaw Activity Index, with surgical complications, and with the Barthel's Index at admission. At multiple regression analysis only the disability status at admission to the hospital was shown to be an independent predictor of the health-related quality of life score. No significant difference in terms of health-related quality of life was observed between patients who underwent laparoscopic-assisted colonic resection and those who had the same procedure performed open. The analysis of the late parameters of recovery is shown in Table 4.

At 3 months follow-up, BIQ score showed a trend to be higher in patients who had a laparoscopic-assisted intestinal surgery for CD and it was independently predicted by the disease activity, namely by HBAI (p=0.006), and by the use of laparoscopic-assisted surgery (p=0.036). BIQ scores predictors are shown in Table 4.

Predictors of Cost of Surgery for CD

The median cost of the hospital stay was 9,120 (7,680–11,520) euro per patient and that of the operation was estimated at 1,477 euro per patient. The social cost of the lost income due to hospital stay and sick leave was estimated to

Table 3 Predictors of Early Recovery Parameters

	Kendall's τ	p value	Multiple regression β	p value
Postoperative day of first bowel movement				
Fistulizing CD	−0.269	0.009	−0.183	0.237
Stricturoplasty	0.278	0.007	0.231	0.138
R^2=0.11				
Postoperative hospital stay (days)				
Laparoscopic-assisted approach	−0.420	0.000	−0.241	0.046
Barthel 's Index at third post-operative day	−0.250	0.022	−0.261	0.030
Stoma creation	0.323	0.002	0.390	0.003
surgical complications	0.255	0.014	0.410	0.001
R^2=0.59				
Barthel 's Index at third post-operative day				
Number of site affected by CD	−0.264	0.015	−0.224	0.502
Stoma creation	−0.311	0.004	−0.218	0.177
Perianal CD	−0.241	0.027	−0.517	0.098
Postopertive day of first bowel movement	−0.227	0.039	−0.223	0.222
R^2=0.25				
Barthel 's Index at discharge				
Laparoscopic-assisted approach	0.240	0.029	0.383	0.031
Fistulizing CD	−0.252	0.022	−0.254	0.091
Ileal CD	0.287	0.009	0.481	0.023
Colonic CD	−0.341	0.002	−0.523	0.023
Stoma creation	−0.305	0.006	−0.257	0.178
R^2=0.53				
Surgical complications				
Stricturoplasty	−0.229	0.026	−0.191	0.221
Barthel 's Index at admission	−0.316	0.004	−0.276	0.080
R^2=0.13				

Table 4 Predictors of Late Recovery Parameters

	Kendall's τ	*p* value	Multiple regression β	*p* value
Sick leave duration				
Ileal resection	0.261	0.025	0.045	0.803
Stoma creation	−0.300	0.010	0.026	0.883
Physical burden of job	0.468	0.000	0.403	0.028
R^2=0.16				
Body Image questionnaire				
Laparoscopic-assisted approach	0.234	0.020	0.331	0.036
Ileal resection	−0.254	0.012	−0.149	0.331
Harvey–Bradshaw Activity Index	0.296	0.011	0.426	0.006
R^2=0.33				
Cleveland Global Quality of Life score				
Harvey–Bradshaw Activity Index	−0.420	0.000	−0.258	0.123
Obstruction	−0.238	0.041	−0.089	0.580
Barthel 's Index at admission	0.290	0.018	0.381	0.026
R^2=0.26				

be 750 (0–2,130) euro per patient, therefore the overall cost for intestinal surgery for CD was 12,037 (10,117–15,795) euro per patient. The overall cost correlated directly with colonic resection, surgical complications onset, and with stoma creation. However, at multiple regression analysis only stoma creation was revealed to be an independent predictor (p=0.006) for overall costs. Patients who had an ileostomy reported significantly higher overall costs and higher costs for the hospital stay (p=0.050 and p=0.017, respectively). Patients who had laparoscopic-assisted bowel resection reported significantly lower costs for the hospital stay (p=0.021), but the overall costs were not different compared to those reported by patients who had open surgery. The analysis of cost of surgery for CD is shown in Table 5.

Discussion

More than the 75% of patients affected by CD undergo some sort of surgery over their lifetime.[1] Although minimally invasive surgery and stricturoplasty have reduced the impact of surgery, extensive bowel resection and/or stoma creation may be still necessary, and is relevant to the HRQL of patients affected by CD.[2–4] Moreover, the burden of surgery on patients with CD is not only limited to quality of life of patients affected and their relatives, but it is also a significant economic burden. In fact, in 1994, the direct costs associated with hospitalization for CD in Sweden amounted to approximately 7.8 million US dollars/year[10] and nearly 40% of all direct medical costs for CD were for surgical management.[9] Therefore, this prospective study aimed to analyze the impact of different surgical techniques on patients undergoing intestinal surgery for CD in terms of recovery, quality of life, and direct and indirect costs.

The laparoscopic-assisted approach for intestinal surgery for CD was associated with a significantly shorter postoperative hospital stay and a slightly better Barthel's score at discharge than open intestinal surgery. Although this was not a randomized study, the Barthel's score at

Table 5 Surgical Procedures Significantly Affecting Costs of Surgery for CD

	YES: median (IQR)	NO: median (IQR)	*p* level
Laparoscopic-assisted bowel resection			
Total lost working days	33 (15–53)	41 (29–71)	0.055
Lost gain for sick leave	0 (0–1,908)	1,170 (0–2,346)	0.325
Hospital stay cost	8,640 (7,680–10,560)	10,560 (8,640–13,440)	0.021
Overall cost	11,166 (10,117–14,707)	13,293 (10,203–17,056)	0.178
Stoma			
Total lost working days	61 (31–83)	37 (17–53)	0.147
Lost gain for sick leave	0 (0–3,200)	870 (0–2,100)	0.774
Hospital stay cost	15,360 (11,520–20,160)	8,640 (7,680–10,560)	0.017
Overall cost	19,003 (12,123–26,991)	11,495 (10,117–15,003)	0.050

All the costs are expressed in Euro

admission was similar in patients who had open and those who had laparoscopic surgery. Therefore, since this study was conducted out of any fast track setting, the earlier timing of discharge of these patients could be actually attributed to the faster recovery after laparoscopic approach. Moreover, the BIQ score after 3 months follow-up after intestinal surgery for CD was independently predicted by the use of laparoscopic-assisted approach. These data confirm observations by Dunkers et al. in 1998.[21] Despite the positive impact on body image, no improvement was detected in overall quality of life. In fact, in our series, no significant difference in terms of health-related quality of life was observed between patients who underwent laparoscopic-assisted colonic resection and those who had the same procedure performed open. This confirms the data of the Amsterdam group that in a randomized controlled trial concluded that generic quality of life was not different for laparoscopic-assisted compared with the open ileocolic resection.[22] Moreover, as McLeod et al. had already showed in patients with severe ulcerative colitis, in an our pervious study we showed that quality of life after surgery for CD appeared to be a function of therapeutic efficacy rather than of the surgical procedure used.[19,23] Laparoscopic surgery aims to reduce the need for large abdominal incisions with potential benefits both in terms of reduced hospital stay, recovery time, and 'cosmetic' result; however, data on cost effectiveness are limited.[24] In our series, the overall costs for open and laparoscopic-assisted surgery were medially higher that those reported by Maartense et al. probably because sick leave costs were included in the final count.[22] Moreover, differently from what observed by Maartense et al., in our series, patients who had laparoscopic-assisted surgery reported significantly lower costs for the hospital stay, but the overall costs were not different compared to those reported by patients who had open surgery, probably due to the higher costs of the surgical procedure itself outside a controlled clinical trial.[22]

The creation of a stoma during intestinal surgery for CD was found to be among the significant predictors of duration of post-operative hospital stay, and the Barthel's Index score on the third postoperative day and at discharge was significantly lower in patients who had a stoma created. Moreover, median sick leave seemed to be longer in patients who had a stoma created even if at multiple regression analysis only the physical burden of the job independently predicted sick leave duration. Curiously, although stoma creation was clearly associated with a slower recovery and it took time for patients to adapt to the new body situation,[25] it did not predict poor quality of life. In fact, although this concern has been rated among the most important factors in other studies of patients with CD,[26,27] in our series an ostomy bag did not seem to influence the early postoperative quality of life. On the other hand, failure to find significance in the quality of life associated with ostomy creation may be due to the small number of patients who had stoma. In addition, the slower recovery of patients who had stoma creation may be due also to their worse condition that leaded to a more aggressive surgery. In fact, the need for more aggressive surgery and the longer time to recovery were directly reflected by the overall cost of the procedure which correlated directly and independently with stoma creation. Therefore, patients who had an ostomy created reported significantly higher overall costs and higher costs for the hospital stay.

In our series, the first bowel movement occurred later in patients who had stricturoplasty than in those who had bowel resection. Although stricturoplasty is an effective means of alleviating obstructive Crohn's disease while conserving bowel length, it is associated with a 4.4% rate of obstruction and late recovery of the intestinal function in the immediate postoperative period.[28] In spite of a recent meta-analysis showing that after jejuno-ileal stricturoplasty septic complications occurred in 4% of patients,[29] in our series stricturoplasty seemed to correlate inversely with postoperative surgical complications. However, at multivariate analysis this unexpected association was not confirmed. In fact, stricturoplasty did not seem to have any influence on recovery, nor on the economic burden of surgery. In particular, despite the prolonged postoperative ileus stricturoplasty did not seem to affect the early postoperative quality of life, as already described in a retrospective German study.[30]

The main limit of this study is the relatively small group of patients and multiple different operations that makes the risk of error in statistical evaluation concrete. All consecutive patients presenting to our department for surgery for CD were enrolled to improve the sample size but the heterogeneity of manifestation of CD leaded to different surgical procedures. Therefore, a confirmatory multicentric study might be warranted after the results obtained with this small series.

In conclusion, the laparoscopic-assisted approach to intestinal surgery for CD was associated with a significantly shorter postoperative hospital stay, stoma creation was associated with a long and expensive postoperative hospital stay, and stricturoplasty was associated with a slower recovery of bowel function. Finally, health-related quality of life appeared to be unrelated to the type of surgical procedure adopted and it seemed related only to the disability status of the patients.

Acknowledgement We are extremely grateful to Umut Sarpel MD, Bellevue Hospital Center, New York University, NY, USA, for her kind help in the English language editing.

References

1. Singleton JW, Law DH, Kelley ML Jr, Mekhjian HS, Sturdevant RA. National Cooperative Crohn's Disease Study: adverse reactions to study drugs. Gastroenterology 1979;77:870–882.
2. Mussell M, Bocker U, Nagel N, Singer MV. Predictors of disease-related concerns and other aspects of health-related quality of life in outpatients with inflammatory bowel disease. Eur J Gastroenterol Hepatol 2004;16:1273–1280.
3. Etienney I, Bouhnik Y, Gendre JP, Lemann M, Cosnes J, Matuchansky C, Beaugerie L, Modigliani R, Rambaud JC. Crohn's disease over 20 years after diagnosis in a referral population. Gastroenterol Clin Biol 2004;28:1233–1239.
4. Canavan C, Abrams KR, Hawthorne B, Drossman D, Mayberry JF. Long-term prognosis in Crohn's disease: factors that affect quality of life. Aliment Pharmacol Ther 2006;23:377–385.
5. Tillinger W, Mittermaier C, Lochs H, Moser G. Health-related quality of life in patients with Crohn's disease. Influence of surgical operation—a prospective trial. Dig Dis Sci 1999;44:932–938.
6. Thirlby RC, Land JC, Fenster LF, Lonborg L. Effect of surgery on health related quality of life in patients with inflammatory bowel disease. Arch Surg 1998;133:826–832.
7. Yazdanpanah Y, Klein O, Gambiez L, Baron P, Desreumaux P, Marquis P, Cortot A, Quandalle P, Colombel JF. Impact of surgery on quality of life in Crohn's disease. Am J Gastroenterol 1997;92:1897–1900.
8. Delaney CP, Kiran RP, Senagore AJ, O'Brien-Ermlich B, Church J, Hull TL, Remzi FH, Fazio VW. Quality of life improves within 30 days of surgery for Crohn's disease. J Am Coll Surg 2003;196:714–721.
9. Cohen RD, Larson LR, Roth JM, Becker RV, Mummert LL. The cost of hospitalisation in Crohn's disease. Am J Gastroenterology 2000;95:524–530.
10. Blomqvist P, Ekbom A. Inflammatory bowel disease: health care and costs in Sweden in 1994. Scand J Gastrenterol 1997;32:1134–1139.
11. Bernstein CN, Papineau N, Zajaczkowski J, Rawsthorne P, Okrusko G, Blanchard JF. Direct hospital costs for patients with inflammatory bowel disease in a Canadian tertiary care university hospital. Am J Gastroenterol 2000;95:677–683.
12. Silverstein MD, Loftus EV, Sandborn WJ, Tremaine WJ, Feagan BG, Nietert PJ, Harmsen WS, Zinsmeister AR. Clinical course and costs of care for Crohn's disease: Markov Model analysis of a population-based cohort. Gastroenterology 1999;117:49–57.
13. Bodger K. Cost of illness of Crohn's disease. Pharmacoeconomics 2002;20:639–652.
14. Lennard-Jones JE. Classification of inflammatory bowel disease. Scand J Gastroenterol Suppl 1989;170:2–6.
15. Harvey RF, Bradshaw JM. A simple index of Crohn's disease activity. Lancet 1980;1(8167):514.
16. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. MD State Med J 1965;14:61–65.
17. Wade DT, Hewer RL. Functional abilities after stroke: measurement, natural history and prognosis. J Neurol Neurosurg Psychiatry 1987;50:177–182.
18. Kiran RP, Delaney CP, Senagore AJ, O'Brien-Ermlich B, Mascha E, Thornton J, Fazio VW. Prospective assessment of Cleveland Global Quality of Life and disease activity in Crohn's disease. Am J Gastroenterol 2003;98:1783–1789.
19. Scarpa M, Ruffolo C, D'Incà R, Filosa T, Bertin E, Ferraro S, Polese L, Martin A, Sturniolo GC, Frego M, D'Amico DF, Angriman I. Health related quality of life after ileo-colonic resection for Crohn's disease: long-term results. Inflamm Bowel Dis 2007;13:462–469.
20. Scarpa M, Ruffolo C, Polese L, Martin A, D'Incà R, Sturniolo GC, D'Amico DF, Angriman I. Quality of life after restorative proctocolectomy for ulcerative colitis: different questionnaires lead to different interpretations. Arch Surg 2007;142:158–165.
21. Dunker MS, Stiggelbout AM, van Hogezand RA, Ringers J, Griffioen G, Bemelman WA. Cosmesis and body image after laparoscopic-assisted and open ileocolic resection for Crohn's disease. Surg Endosc 1998;12:1334–1340.
22. Maartense S, Dunker MS, Slors JF, Cuesta MA, Pierik EG, Gouma DJ, Hommes DW, Sprangers MA, Bemelman WA. Laparoscopic-assisted versus open ileocolic resection for Crohn's disease: a randomized trial. Ann Surg 2006;243:143–149.
23. McLeod RS, Churchill DN, Lock AM. Quality of life of patients with ulcerative colitis preoperatively and postoperatively. Gastroenterology 1991;101:1307–1313.
24. Guillou PJ, Windsor AJ, Nejim A. The health care economic implications of minimal access gastrointestinal surgery. In Bodger K, Daly MJ, Heatley RV, eds. Clinical economics in gastroenterology, 1st ed. Oxford: Blackwell Science Ltd, 2000, pp 133–145.
25. Scarpa M, Sadocchi L, Ruffolo C, Iacobone M, Filosa T, Prando D, Polese L, Frego M, D'Amico DF, Angriman I. Rod in loop ileostomy: just an insignificant detail for ileostomy-related complications? Langenbecks Arch Surg 2007;392:149–154.
26. Drossman DA, Patrick DL, Mitchell CM, Zagami E, Applebaum MI. Health-related quality of life in inflammatory bowel disease. Dig Dis Sci 1989;34:1379–1386.
27. Blondel-Kucharski F, Chircop C, Marquis P, Cortot A, Baron F, Gendre JP, Colombel JF, Groupe d'Etudes Thérapeutique des Affections Inflammatoires Digestives (GETAID). Health-related quality of life in Crohn's disease: a prospective study in 231 patients. Am J Gastroenterol 2001;96:2915–2920.
28. Fearnhead NS, Chowdhury R, Box B, George BD, Jewell DP, Mortensen NJ. Long-term follow-up of stricturoplasty for Crohn's disease. Br J Surg. 2006;93:475–482.
29. Yamamoto T, Fazio VW, Tekkis PP. Safety and efficacy of stricturoplasty for Crohn's disease: a systematic review and meta-analysis. Dis Colon Rectum 2007;50:1968–1986.
30. Broering DC, Eisenberger CF, Koch A, Bloechle C, Knoefel WT, Izbicki JR. Quality of life after surgical therapy of small bowel stenosis in Crohn's disease. Dig Surg 2001;18:124–130.

J Gastrointest Surg (2009) 13:2136–2140
DOI 10.1007/s11605-009-1064-7

2009 SSAT POSTER PRESENTATION

Colonoscopic Splenic Injuries: Incidence and Management

Ashwin S. Kamath · Corey W. Iqbal · Michael G. Sarr · Daniel C. Cullinane · Scott P. Zietlow · David R. Farley · Mark D. Sawyer

Received: 3 June 2009 / Accepted: 29 September 2009 / Published online: 15 October 2009

Abstract
Purpose Splenic injuries that occur during colonoscopies are rare. There is no available incidence of this serious complication, and the literature is limited to case reports. Our study looks at single institution experience of splenic injuries during colonoscopy to define the incidence and management of this serious complication.
Methods All patients from 1980 through June 2008 sustaining a splenic injury during colonoscopy were reviewed.
Results Four patients (of 296,248 colonoscopies) sustained a splenic injury directly from colonoscopy performed at our institution (incidence 0.001%). Three additional patients were treated at our tertiary referral center after splenic injury from colonoscopy performed elsewhere. The mean age at the time of colonoscopy was 54 years (range 40–70 years). The most common presenting symptom was abdominal pain (n=4) with a mean decrease in hemoglobin of 6.5 g/dl (range 4.5–8.5 g/dl). Splenic injury was diagnosed by computed tomography in five patients. Six patients received a mean of 5.5 U of packed red blood cells (range 2–14 U). All patients were managed with splenectomy, six patients within 24 h of the index colonoscopy, and one patient presented more than 24 h after initial colonoscopy. There was no evidence of preexisting splenic disease in any of the patients by surgical pathology, and there were no postoperative complications or deaths. The mean duration of stay was 10 days (range 7–15 days). All patients are alive at a median follow up of 22 months (range 1–164 months).
Conclusion Splenic injury occurring during colonoscopy is a rare but serious complication. Patients presented with abdominal pain and a precipitous decrease in hemoglobin and have all required emergent splenectomy.

Keywords Splenic injury · Colonoscopy · Iatrogenic · Splenectomy

Introduction

Approximately 1.7 million colonoscopies are performed in the USA annually.[1] The most frequently seen complications of colonoscopy include bleeding (as high as 4.8% with biopsy) and perforation (0.07%).[2] Splenic injury is also a recognized complication of colonoscopy, and because this complication occurs with such low frequency, the existing literature is limited to case reports.[1,3–28]

We reviewed our experience with splenic injuries occurring during colonoscopy to define the incidence, management, and outcomes of this very rare but potentially fatal complication.

Methods

With approval from our institutional review board, we searched the Mayo Clinic Rochester medical and surgical databases to identify all patients sustaining a splenic injury during colonoscopy. The medical record was reviewed to obtain patient demographic data, indications for colono-

A. S. Kamath · C. W. Iqbal · M. G. Sarr · D. R. Farley
Department of GI and General Surgery, Mayo Clinic Rochester,
200 First Street S.W,
Rochester, MN 55905, USA

D. C. Cullinane · S. P. Zietlow · M. D. Sawyer (✉)
Division of Trauma, Critical Care, and General Surgery,
Mayo Clinic Rochester,
200 First Street S.W.,
Rochester, MN 55905, USA
e-mail: Sawyer.mark@mayo.edu

scopy, procedural characteristics, presenting signs and symptoms of splenic injury, diagnosis, management, and outcomes. Follow-up was complete for all but one patient (she was lost to follow-up after 1 month from dismissal from the hospital). The median duration of follow-up was 22 months (range 1–164 months).

Case Summaries

Patient 1 Patient 1 was a 70-year-old male who underwent colonoscopy for history of colonic polyps in the operating room immediately prior to an elective sigmoidectomy for diverticulitis. After incision, frank blood was discovered in the peritoneal cavity from a tear in the spleen requiring splenectomy. The patient did not require any blood products. There were no postoperative complications. He died of unrelated causes 72 months later.

Patient 2 Patient 2 was a 56-year-old male who underwent colonoscopy for intermittent bloody diarrhea. He presented about 24 h after colonoscopy with abdominal pain and was found to have a decrease in blood hemoglobin (Hgb) from 14.1 to 8.9 g/dl. Abdominal radiography demonstrated free air which prompted an emergency laparotomy; a splenic laceration was discovered, and splenectomy was performed. No other injuries or source of intraperitoneal free air was identified at the time of surgery, and the incision was closed. He received 4 U of packed red blood cells (pRBC) postoperatively. At follow-up of 32 months, he was doing well.

Patient 3 Patient 3 was a 46-year-old female who underwent colonoscopy for unexplained diarrhea. She presented to the emergency department within 24 h after colonoscopy with left lower quadrant abdominal pain, hypotension, and a decrease in Hgb from 18.6 to 10.8 g/dl. Abdominal computed tomography demonstrated splenic injury with hemoperitoneum. She received 5 U of pRBC's during emergent splenectomy. At 18 months of follow-up, she was doing well.

Patient 4 Patient 4 was a 40-year-old female who underwent colonoscopy for persistent diarrhea. She presented to the emergency department about 24 h after colonoscopy with lower abdominal pain, hypotension, and decrease in Hgb from 13.0 to 8.5 g/dl. Abdominal CT scan demonstrated splenic injury with hemoperitoneum, and she underwent an emergent splenectomy. She received 4 U of pRBCs. At 164 months of follow-up, she was doing well.

Patient 5 Patient 5 was a 45-year-old female who underwent colonoscopy elsewhere for chronic lower abdominal pain. She presented to the local emergency department the next day after an episode of syncope and was found to be hypotensive on exam. Her Hgb was 8.5 g/dl, and a CT scan demonstrated a splenic injury. During transfer to our institution, she received 6 U of pRBCs and underwent an emergent splenectomy. After 8 months of follow-up, she was doing well.

Patient 6 Patient 6 was a 64-year-old female who underwent colonoscopy elsewhere for chronic abdominal pain. She presented to the emergency department the next day with severe lower abdominal pain. Her Hgb had decreased from 17.0 to 8.5 g/dl; CT scan revealed injury to the spleen. She received 2 U of pRBCs prior to transfer to our facility where she underwent an emergent splenectomy. At 1 month of follow-up, she was doing well but has since been lost to follow-up.

Patient 7 Patient 7 was a 59-year-old female who underwent a screening colonoscopy at another institution. She presented to the emergency department 24 h later with an episode of syncope and was found to be hypotensive. Data regarding her hemoglobin level were not available. Abdominal CT demonstrated a splenic injury; she was transfused with 14 U of pRBCs during transfer to our institution where she underwent an emergent splenectomy. At 22 months of follow-up, she was doing well.

Results

A total of seven patients were identified. Of 296,248 colonoscopies performed at our institution during the study period, four patients sustained an iatrogenic splenic injury from colonoscopy (incidence 0.001%). In addition, three patients were treated at our tertiary care center with splenic injuries after colonoscopy performed elsewhere. The mean age of patients at the time of colonoscopy was 54 years (range 40–70 years). Indications for colonoscopy and additional patient demographic data are listed in Table 1. Two patients did have a history of prior abdominal surgery, and two additional patients had diverticular disease. Of those patients who underwent colonoscopy at our institution, all were noted to have adequate bowel prep. Two procedures were described as difficult by the endoscopist.

Most patients (n=6) presented with signs and symptoms of splenic rupture within 24 h of the index procedure. A single patient presented within 36 h of colonoscopy. The most common presenting symptoms were abdominal pain (n=4) and syncope (n=2) (see Table 2). The diagnosis of splenic injury was made via CT scan in five patients. Of the

Table 1 Patient Characteristics and Indications for Colonoscopy in Patients Sustaining an Iatrogenic Splenic Injury

Patient characteristics and indications for colonoscopy						
Pt	Age (year)	Sex	Prior abdominal operation	Diverticular disease	Indication for colonoscopy	Difficult colonoscopy
1	69	M	No	Yes	History of colon polyps	Yes
2	56	M	No	No	Gastrointestinal bleeding	No
3	46	F	No	No	Diarrhea	Yes
4	40	F	No	Yes	Diarrhea	No
5[a]	45	F	Yes	No	Abdominal pain	–
6[a]	64	F	No	No	Abdominal pain	–
7[a]	59	F	Yes	No	Colon and rectal cancer screening	–

[a] Patients transferred to our facility after sustaining an iatrogenic splenic injury from colonoscopy

– Data not available

seven patients, three suffered a Grade II splenic laceration and one patient suffered a Grade III splenic laceration. One patient did not have a CT scan performed due to free air on abdominal radiograph taken in the emergency department, and the other patient was a transfer from outside facility whose records (including a CT scan) were not available for review. Four patients had a significant drop in Hgb (mean 6.5 g/dl; range 4.5–8.5 g/dl), and although initial Hgb values were not available for two patients transferred to our facility, both of these patients required blood transfusion. A mean of 5.5 U (range 2–14 U) of packed red blood cells were transfused in all but one patient (see Table 2).

All patients were managed with emergent splenectomy. No abnormal pathologic findings were observed on gross or histologic examination of the spleen. There were no postoperative complications or deaths. The mean duration of stay was 10 days (range 7–15 days). Median follow-up was 22 months (range 1–164 months), and no patient suffered any squeal from splenectomy.

Discussion

Complications after colonoscopy are unusual and are predominately limited to intraluminal bleeding (typically associated with colonoscopic biopsy) and, less often, perforation.[29] Colonoscopic perforation, which occurs in less than 1 in 1,000 colonoscopies, often times necessitates emergent operative intervention and carries morbidity and mortality rates as high as 36% and 7%, respectively.[2] Splenic injury during colonoscopy is extremely rare. The literature is limited to case reports, making it difficult to establish the true incidence and management of this potentially life-threatening complication. With this case series, we have established a clearer incidence of splenic injury associated with colonoscopy and confirmed that it is, in fact, an unusual complication of colonoscopy occurring in less than 1 out of 100,000 colonoscopies. Fortunately, it also does not seem to carry the high morbidity and mortality rates associated with colonoscopic perforation.[30,31]

Table 2 Presentation and Diagnosis of Splenic Rupture after Colonoscopy

Presentation and diagnosis							
Pt	Symptoms	Time to presentation (hours)	Pre-Hb (g/dl)[a]	Post-Hb (g/dl)[b]	Method of diagnosis	Grade of splenic injury	PRBCs transfused (in units)
1	–	<24	–	–	Intraoperative finding	NA	–
2	Abdominal Pain	<24	14.1	8.9	Intraoperative finding	NA	2
3	Abdominal Pain	<24	18.6	10.8	CT	II Injury	5
4	Abdominal Pain	<24	13	8.5	CT	III Injury	4
5	Syncope	>24	–	–	CT	II Injury	6
6	Abdominal Pain	<24	17	8.5	CT	II Injury	2
7	Syncope	<24	–	–	CT	–	14

[a] Pre-Hgb is most recent hemoglobin prior to index colonoscopy

[b] Post-Hgb is the initial hemoglobin at presentation with a splenic injury

Hgb hemoglobin, *CT* computed tomography, *pRBCs* packed red blood cells, *NA* not applicable, – data not available

Most of the patients in this series presented in an acute manner with abdominal pain or syncope and were found to be hypotensive with a substantial decrease in serum hemoglobin requiring blood transfusion. Hypovolemia in a patient who has undergone colonoscopy recently should raise a concern for bleeding. In the absence of a gastrointestinal source (i.e., hematochezia), splenic injury should be considered in the differential diagnosis. Most patients with a splenic injury were diagnosed through the use of CT which is also useful in evaluating patients with suspected colonoscopic-related perforations.[2]

Emergency splenectomy was undertaken in all patients in this series reflecting the precipitous nature of their presentation. Although current literature reports a mortality rate as high as 8% in patients undergoing splenectomy secondary to trauma, there were no postoperative complications or deaths in the current series.[32] We speculate that this may be because the colonoscopic splenic injuries are isolated and occur in a healthcare setting, whereas the typical trauma patient is likely to have many other associated injuries contributing to greater morbidity and mortality rates. Nonoperative management of splenic injuries, however, has changed the role of emergency splenectomy in the setting of trauma,[30] and there are several reports of splenic injuries from colonoscopy being managed successfully without splenectomy.[33–35] However, none of our patients were managed nonoperatively. It is possible that there are patients who sustain splenic injuries during colonoscopy which are never diagnosed because they are asymptomatic or their symptoms are so mild they do not need to seek medical attention and/or further workup with a CT scan is never obtained. Due to this possibility, it is likely that the rate of splenic injury due to colonoscopy is greater than what we report and that the incidence we noted represents symptomatic or clinically important splenic injuries. Without prospective imaging for every patient after colonoscopy, it is difficult to estimate the incidence of this complication of colonoscopy.

Due to the small numbers in this case series, it is difficult to identify any potential risk factors regarding indications for colonoscopy or intra-procedural factors that may predispose patients to splenic injury at the time of colonoscopy. Many risk factors have been postulated as a cause for splenic injury during colonoscopy which mirror those proposed as risk factors for colonoscopic perforation.[2] Operator-dependent factors could include excessive traction on the splenic ligament particularly when traversing the splenic flexure, including the alpha maneuver (a maneuver used during colonoscopy by which the scope is rotated counterclockwise by 180° in the sigmoid colon to create a loop, thus, making it easier to pass the scope beyond. The loop can be straightened by rotating the scope clockwise once the scope is beyond the descending colon or has reached the splenic flexure). Patient factors could include pathology that leads to intra-abdominal adhesions such as prior abdominal surgery, cancer, inflammatory bowel disease, or diverticulitis.[34] Review of the case reports identified 59% of patients sustaining an iatrogenic splenic injury from colonoscopy had a history of prior abdominal surgery, but from our study, just two of the seven patients had prior history of abdominal surgeries.[3–13,15–22,26–28,34,35] Others have proposed underlying splenic pathology (specifically splenomegaly, anticoagulant medications, and pharmacologic treatment such as hematopoietic growth factors) as possible risk factors; again, this was not borne out by our series: no patients in our series had underlying splenic pathology or were receiving hematopoietic agents.[33,34]

Conclusion

Splenic injury after colonoscopy is a very rare but potentially life-threatening complication of colonoscopy; patients usually present in an acute fashion with signs and symptoms of hemorrhagic shock. A complete blood count and CT scan of the abdomen are usually diagnostic, and the acute nature and presentation of these splenic injuries have necessitated splenectomy in our experience.

References

1. Vijan S, Inadomi J et al. Projections of demand and capacity for colonoscopy related to increasing rates of colorectal cancer screening in the United States. Aliment Pharmacol Ther 2004;20 (5):507–515.
2. Iqbal CW, Cullinane DC et al. Surgical management and outcomes of 165 colonoscopic perforations from a single institution. Arch Surg 2008;143(7):701–706. discussion 706–707.
3. Adamek M, Wegener RJ et al. Splenic rupture following colonoscopy: an unusual complication. Z Gastroenterol 1992;30 (2):139–141.
4. Ahmed A, Eller PM, Schiffman FJ. Splenic rupture: an unusual complication of colonoscopy. Am J Gastroenterol 1997;92 (7):1201–1204.
5. Al Alawi I, Gourlay R. Rare complication of colonoscopy. ANZ J Surg 2004;74(7):605–606.
6. Bier JY, Ferzli G et al. Splenic rupture caused by colonoscopy. Gastroenterol Clin Biol 1989;13(2):224–225.
7. Castelli M. Splenic rupture: an unusual late complication of colonoscopy. CMAJ 1986;134(8):916–917.
8. Colarian J, Alousi M, Calzada R. Splenic trauma during colonoscopy. Endoscopy 1991;23(1):48–49.
9. Couderc LJ, Mosnier H et al. Splenic rupture after colonoscopy. Ann Med Interne (Paris) 1996;147(5):379.
10. Coughlin F, Aanning HL. Delayed presentation of splenic trauma following colonoscopy. S D J Med 1997;50(9):325–326.
11. Espinal EA, Hoak T et al. Splenic rupture from colonoscopy. A report of two cases and review of the literature. Surg Endosc 1997;11(1):71–73.
12. Goitein D, Goitein O, Pikarski A. Splenic rupture after colonoscopy. Isr Med Assoc J 2004;6(1):61–62.

13. Gores PF, Simso LA. Splenic injury during colonoscopy. Arch Surg 1989;124(11):1342.
14. Hamzi L, Soyer P et al. Splenic rupture following colonoscopy: report of an unusual case in the absence of underlying splenic disease. J Radiol 2003;84(3):320–322.
15. Heath B, Rogers A et al. Splenic rupture: an unusual complication of colonoscopy. Am J Gastroenterol 1994;89(3):449–450.
16. Holzer K, Thalhammer A, Bechstein WO. Splenic trauma–a rare complication during colonoscopy. Z Gastroenterol 2004;42(6):509–512.
17. Jaboury I. Splenic rupture after colonoscopy. Intern Med J 2004;34(11):652–653.
18. Janes SE, Cowan IA, Dijkstra B. A life threatening complication after colonoscopy. BMJ 2005;330(7496):889–890.
19. Kloer H, Schmidt-Wilcke HA, Schulz U. Splenic rupture as a consequence of coloscopy. Dtsch Med Wochenschr 1984;109 (46):1782–1783.
20. Merchant AA, Cheng EH. Delayed splenic rupture after colonoscopy. Am J Gastroenterol 1990;85(7):906–907.
21. Moses RE, Leskowitz SC. Splenic rupture after colonoscopy. J Clin Gastroenterol 1997;24(4):257–258.
22. Olshaker JS, Deckleman C. Delayed presentation of splenic rupture after colonoscopy. J Emerg Med 1999;17(3):455–457.
23. Reynolds FS, Moss LK et al. Splenic rupture following colonoscopy. Gastrointest Endosc 1986;32(4):307–308.
24. Schmilovitz-Weiss H, Weiss A et al. Predictors of failed colonoscopy in nonagenarians: a single-center experience. J Clin Gastroenterol 2007;41(4):388–393.
25. Stein DF, Myaing M, Guillaume C. Splenic rupture after colonoscopy treated by splenic artery embolization. Gastrointest Endosc 2002;55(7):946–948.
26. Strigard K. Splenic rupture in coloscopy. Lakartidningen 1995;92 (46):4337.
27. Sugar I et al. Splenic rupture: a rare complication of colonoscopy. Magy Seb 2000;53(2):73–75.
28. Tuso P, McElligott J, Marignani P. Splenic rupture at colonoscopy. J Clin Gastroenterol 1987;9(5):559–562.
29. Levin TR, Zhao W et al. Complications of colonoscopy in an integrated health care delivery system. Ann Intern Med 2006;145 (12):880–886.
30. Farley DR, Bannon MP et al. Management of colonoscopic perforations. Mayo Clin Proc 1997;72(8):729–733.
31. Iqbal CW, Chun YS, Farley DR. Colonoscopic perforations: a retrospective review. J Gastrointest Surg 2005;9(9):1229–1235. discussion 1236.
32. Harbrecht BG, Franklin GA et al. Is splenectomy after trauma an endangered species? Am Surg 2008;74(5):410–412.
33. Cappellani A, Di Vita M et al. Splenic rupture after colonoscopy: report of a case and review of literature. World J Emerg Surg 2008;3:8.
34. Lalor PF, Mann BD. Splenic rupture after colonoscopy. JSLS 2007;11(1):151–156.
35. Taylor FC, Frankl HD, Riemer KD. Late presentation of splenic trauma after routine colonoscopy. Am J Gastroenterol 1989;84 (4):442–443.

J Gastrointest Surg (2009) 13:2141–2151
DOI 10.1007/s11605-009-1050-0

2009 SSAT PLENARY PRESENTATION

Repeat Curative Intent Liver Surgery is Safe and Effective for Recurrent Colorectal Liver Metastasis: Results from an International Multi-institutional Analysis

Mechteld C. de Jong · Skye C. Mayo · Carlo Pulitano · Serena Lanella · Dario Ribero · Jennifer Strub · Catherine Hubert · Jean-François Gigot · Richard D. Schulick · Michael A. Choti · Luca Aldrighetti · Gilles Mentha · Lorenzo Capussotti · Timothy M. Pawlik

Received: 2 June 2009 / Accepted: 11 September 2009 / Published online: 1 October 2009

Abstract

Introduction Although 5-year survival approaches 55% following resection of colorectal liver metastasis, most patients develop recurrent disease that is often isolated to the liver. Although repeat curative intent surgery (CIS) is increasingly performed for recurrent colorectal liver metastasis, only small series have been reported. We sought to determine safety and efficacy of repeat CIS for recurrent colorectal liver metastasis as well as determine factors predictive of survival in a large multicenter cohort of patients.

Methods Between 1982 and 2008, 1,706 patients who underwent CIS—defined as curative intent hepatic resection/radiofrequency ablation (RFA)—for colorectal liver metastasis were identified from an international multi-institutional database. Two hundred forty-six (14.4%) patients underwent 301 repeat CIS. Data on clinico-pathologic factors, morbidity, and mortality were collected and analyzed.

Results Following initial CIS, 645 (37.8%) patients had recurrence within the liver. Of these, 246 patients underwent repeat CIS for recurrent disease. The majority had hepatic resection alone as initial therapy (n=219; 89.0%). A subset of patients underwent third (n=46) or fourth (n=9) repeat CIS. Mean interval between surgeries was similar (first → second, 19.1 months; second → third, 21.5 months; third → fourth, 11.3 months; P=0.20). Extent of hepatic resection decreased with subsequent CIS (≥hemihepatectomy: first CIS, 30.9% versus second CIS, 21.1% versus third/fourth CIS, 16.4%; P=0.004). RFA was utilized in one quarter of patients undergoing repeat CIS (second CIS, 21.1% versus third/fourth CIS, 25.5%). Mortality and morbidity were similar following second, third, and fourth CIS, respectively (all P>0.05). Five-year

Support: Dr. Pawlik is supported by grant number 1KL2RR025006-01 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH.

Presented at Plenary Session, June 2nd, 2009 at the Annual Meeting of the Society of Surgery of the Alimentary Tract, Chicago, IL

M. C. de Jong · S. C. Mayo · R. D. Schulick · M. A. Choti · T. M. Pawlik (✉)
Department of Surgery,
Johns Hopkins University School of Medicine,
Harvey 611 600 N Wolfe Street,
Baltimore, MD 21287, USA
e-mail: tpawlik1@jhmi.edu

C. Pulitano · L. Aldrighetti
Ospedale San Raffaele,
Milan, Italy

S. Lanella · D. Ribero · L. Capussotti
Ospedale Mauriziano Umberto I,
Turin, Italy

J. Strub · G. Mentha
Hôpitaux Universitaires de Genève,
Geneva, Switzerland

C. Hubert · J.-F. Gigot
Saint-Luc University Hospital, Université Catholique de Louvain,
Brussels, Belgium

survival was 47.1%, 32.6%, and 23.8% following the first, second, and third CIS, respectively. Presence of extra-hepatic disease was predictive of worse survival (HR=2.26, P=0.01).
Conclusion Repeat CIS for recurrent colorectal liver metastasis can be performed with low morbidity and near-zero mortality. Patients with no extra-hepatic disease are best candidates for repeat CIS. In these patients, repeat CIS can offer the chance of long-term survival.

Keywords Colorectal cancer · Metastasis · Liver · Repeat · Resection

Introduction

The cumulative lifetime risk of colorectal cancer is approximately 5%, making colorectal cancer the third most common cancer worldwide.[1,2] In the USA, over 55,000 deaths are attributed to colorectal cancer each year, making it the second most common cause of cancer-related deaths in the USA.[3] Roughly one half of patients with colorectal cancer develop liver metastasis during the course of their disease.[4] Of these, 15% to 25% present with synchronous liver metastasis,[5–7] while an additional 20% to 25% develop metachronous hepatic tumors.[8–10] In 30% of patients with synchronous or metachronous liver metastasis, the liver is the only site of metastatic disease.[11] Surgical therapy of liver metastasis remains the only therapy with potential for cure.[12,13] In most series, the overall 5-year survival rates reported following hepatic resection with curative intent range from 35% to 58%.[14–23]

Although advances in surgical and medical oncology have resulted in prolongation of survival for patients with colorectal liver metastasis, many patients still develop recurrent disease. Following hepatic resection of colorectal liver metastasis, 50% to 60% of patients will have recurrence.[24–28] In a subset of patients, the disease will recur solely as isolated intra-hepatic disease.[25,26,28,29] In fact, our group recently reported that the first site of recurrence following curative intent surgery for colorectal liver metastasis was intra-hepatic only in over 40% of patients.[28] Repeat liver-directed surgery may therefore be indicated in this subset of patients. While several single-institution series have been published on the topic of repeat curative intent surgery for recurrent colorectal liver metastasis, the data are limited. Most studies reporting on outcome following surgical management of recurrent colorectal metastasis have focused solely on resection rather than combined modality approaches that include resection plus ablation.[27,30–36] In addition, most series on the topic of repeat liver resection of recurrent colorectal metastasis have been single-institution series that are limited by small sample sizes.[30,36–41] Because patients with colorectal liver metastasis often recur in the liver only and may benefit from repeat surgery, information on the safety and efficacy of repeat curative intent live surgery for recurrent colorectal liver metastasis is critical. In the current study, we sought to determine the safety and efficacy of repeat curative intent surgery for recurrent colorectal liver metastasis. Specifically, we examine the short- and long-term outcomes of patients who were managed with curative intent repeat resection and/or ablation for recurrent colorectal liver metastasis. In addition, we identify those factors predictive of long-term survival following repeat curative intent liver surgery in a large international multicenter cohort of patients.

Methods

Between October 1982 and October 2008, 1,706 patients treated with curative intent surgery for colorectal liver metastasis were identified from five major hepatobiliary centers in the USA (Johns Hopkins School of Medicine, Baltimore, MD) and Europe (Hôpitaux Universitaires de Genève, Geneva, Switzerland; Ospedale San Raffaele, Milan, Italy; Ospedale Mauriziano Umberto I, Turin, Italy; Saint-Luc University Hospital, Université Catholique de Louvain, Brussels). The study was approved by the Institutional Review Boards of the respective institutions. Of the 1,706 patients who underwent an initial liver surgery for colorectal liver metastasis, 246 (14.4%) patients underwent 301 repeat liver-directed curative intent surgeries for recurrent intra-hepatic disease and are the subject of the current study.

Patients were selected for repeat curative intent liver surgery based on the same criteria as for the initial surgery.[28] Specifically, only patients with colorectal liver metastasis who were operated on with curative intent were included in the study population. Curative intent surgery (CIS) included resection, radiofrequency ablation (RFA), or combined resection plus ablation. Patients were deemed to have resectable hepatic disease only if it was anticipated that the metastasis could be completely resected, at least two adjacent liver segments could be spared, vascular inflow and outflow could be preserved, and the volume of the liver remaining after resection would be adequate.[12,42] RFA was considered curative in intent when, under intra-operative ultrasound guidance, the probe could be optimally positioned to achieve complete destruction of the tumor and at least a 1-cm zone of normal liver parenchyma. Only RFA treatments that were performed at the time of surgery were included; patients who underwent percutaneous RFA

were excluded. If the patient had extra-hepatic disease at the time of the intra-hepatic recurrence, CIS was only considered if all disease (both intra- and extra-hepatic) could be resected with a microscopically negative (R0) margin.

As previously reported,[28] all patients were evaluated with a baseline history and physical examination, serum laboratory tests, and appropriate imaging studies (e.g., computed tomography or magnetic resonance imaging scan of the abdomen and pelvis and chest radiography or a chest computed tomography) at the discretion of the treating physician. Following surgery, all patients were regularly followed and prospectively monitored for recurrence by serum carcinoembryonic antigen (CEA) levels and a computed tomography or magnetic resonance imaging scan of the abdomen every 3 to 4 months up to 2 years and then every 6 months thereafter. When an intra-hepatic recurrence was noted, repeat CIS surgery was undertaken at the discretion of the attending surgeon based on established criteria.[12,13]

Data Collection

Standard demographic and clinico-pathologic data were collected on each patient including sex, age, carcinoembryonic antigen level, as well as data on tumor characteristics. Specifically, data were collected on primary tumor location, American Joint Commission on Cancer (AJCC) stage (T, N, M), and presentation (synchronous versus metachronous). Clinico-pathologic and operative data from each CIS were recorded. Specifically, the number, size, and distribution of the hepatic metastasis at each repeat operation were noted. Resection at the time of each surgery was classified as less than a hemihepatectomy (e.g., segmentectomy or subsegmentectomy), hemihepatectomy, or extended hepatectomy (>5 liver segments).[43] The utilization of ablation was also noted. Dates of last follow-up, as well as vital status, were collected on all patients.

Statistical Analyses

Summary statistics were obtained using established methods and presented as percentages or median values. Time to recurrence and survival were estimated using the non-parametric product limit method (Kaplan and Meier).[44] Differences in survival were examined using the log-rank test. Factors associated with survival were examined using univariate and multivariate Cox regression analyses. The hazard ratio and the 95% confidence intervals (CI) were estimated, and a P value less than 0.05 was considered significant. All statistical analyses were performed using SPSS version 13.0 (Chicago, IL).

Results

Patient and Tumor Characteristics

Table 1 shows the clinico-pathologic features of the 246 patients in the study. The majority of patients were male (n=165; 67.1%). The median patient age was 59 years (range, 18 to 83 years) at the time of the initial CIS versus 60 years (range, 17 to 84 years) at the second CIS versus 63 years (range, 37 to 80 years) at the time of the third/fourth CIS. Most patients who underwent liver-directed surgery for colorectal liver metastasis had a primary colon tumor (n=178; 72.4%), while 68 (27.6%) had a primary rectal lesion. Most primary colorectal tumors were staged as T3/T4 (n=181; 73.6%), while a minority of patients (n=32; 13.0%) had T1/T2 disease. Primary tumor T stage was unknown in 33 (13.4%) patients. Among the 218 patients who had primary tumor data on nodal status available, the majority of patients had colorectal primaries that were associated with lymph node metastasis (n=139; 63.8%). Most patients (n=163; 66.3%) received systemic chemotherapy sometime during their therapeutic course. Of the 137 cases in which the chemotherapy regimen was known, some patients were treated with 5-flurouracil-based monotherapy (n=69; 50.4%); other patients received either oxaliplatin-based (FOLFOX; n=61; 44.5%) or irinotecan-based (FOLFIRI; n=7; 5.1%) therapy.

Of the 246 patients who underwent repeat CIS, all had a second CIS, whereas a subset of patients underwent a third (n=46) or fourth (n=9) CIS. The mean interval between surgeries was similar (initial to second CIS, 19.1 months versus second to third CIS, 21.5 months versus third to fourth CIS, 11.3 months; P=0.21; Table 2). Tumor characteristics changed with each subsequent CIS (Table 3). Most patients had multiple tumors at the initial CIS (56.7%); however, subsequent repeat CIS were performed on patients who were less likely to have multiple hepatic lesions (second CIS, 41.7%; third CIS, 35.5%; fourth CIS, 11.1%; P<0.001). The median size of the largest hepatic lesion was smaller with each subsequent repeat CIS (initial CIS, 3.8 cm; second CIS, 3.2 cm; third CIS, 3.3 cm; fourth CIS, 2.5 cm; P=0.03). Bilateral involvement of the liver with hepatic metastases was also less common with subsequent repeat CIS (initial CIS, 33.9%; second CIS, 21.2%; third CIS, 16.7%; fourth CIS, 22.2%; P=0.01). In contrast, patients who underwent repeat CIS had similar rates of extra-hepatic disease (initial CIS, 22.8%; second CIS, 15.0%; third CIS, 19.6%; fourth CIS, 33.3%; P=0.19; Table 3).

Operative Details

The surgical procedures undertaken in the first and repeat CIS are summarized in Table 4. At the time of the initial liver-

Table 1 Characteristics of Patients and Primary Colorectal Tumors

	Hepatic surgery			
	First (n=246)	Second (n=246)	Third (n=46)	Fourth (n=9)
Age (years)	58.6±10.0	60.0±12.2	63.4±10.4	63.1±6.3
Gender, *n* (%)				
Male	165 (67.1)	165 (67.1)	19 (41.3)	6 (66.7)
Female	81 (32.9)	81 (32.9)	27 (58.7)	3 (33.3)
Primary tumor, *n* (%)				
Colon	178 (72.4)	178 (72.4)	35 (76.1)	7 (77.8)
Rectum	68 (27.6)	68 (27.6)	11 (23.9)	2 (22.2)
AJCC T category (%)				
T1	2.8	2.8	0	0
T2	12.2	12.2	14.3	25.0
T3	70.9	70.9	73.8	62.5
T4	14.1	14.1	11.9	12.5
AJCC N category (%)				
N0	36.2	36.2	36.6	50.0
N1	44.1	44.1	43.9	37.5
N2	18.8	18.8	19.5	12.5
N3	0.9	0.9	0	0
Differentiation grade (%)				
Well	5.9	5.9	0	0
Well–moderate	3.0	3.0	6.7	0
Moderate	52.7	52.7	46.7	40.0
Moderate–poor	25.4	25.4	33.3	40.0
Poor	13.0	13.0	13.3	20.0
Adjuvant chemotherapy (%)	66.3	66.3	69.6	77.8

directed surgery, surgical treatment was resection only (n=219; 89.0%), resection plus RFA (n=21; 8.6%), or RFA alone (n=6; 2.4%). Of the 219 procedures in which resection alone was undertaken at the time of the initial CIS, the extent of hepatic resection was less than a hemihepatectomy in 150 (68.5%), a hemihepatectomy in 53 (24.2%), and an extended hepatectomy in 16 (7.3%). A subset of patients underwent resection plus RFA (n=21; 8.6%) or RFA alone (n=6; 2.4%) at the time of the initial CIS. With repeat CIS, the rate of resection either alone or in combination with RFA decreased (Table 4). In addition, among those patients who did undergo resection, the extent of hepatic resection decreased with repeat CIS (≥hemihepatectomy: first CIS, 30.9% versus second CIS, 21.1% versus third/fourth CIS, 16.4%; P=0.004). No patient underwent an R2 resection. On final pathological analysis, the rate of microscopically negative (R0) resections was higher following repeat versus initial CIS (initial CIS, 79.8% versus second CIS, 90.2% versus third/fourth CIS, 87.5%; P=0.01).

At the time of initial CIS, patients who underwent RFA plus resection were less likely to undergo either a hemihepatectomy (n=5; 23.8%) or an extended hepatic resection (n=2; 9.5%; both P<0.05). Those patients who underwent resection plus RFA at the time of initial CIS (n=2; range, 2 to 8) had a higher median number of treated hepatic metastases compared with patients who underwent either resection (n=1; range, 1 to 11) or RFA alone (n=1; range, 1 to 3). Nonresection isolated ablation therapy was increas-

Table 2 Intervals Between Operations in Patients Undergoing Liver-Directed Therapy for Liver Metastases of Colorectal Carcinoma

	Duration			
	Total (*n*)	Number of months mean (range)	<1year (%)	≥1year (%)
Colectomy to 1st CIS	246	12 (0–57)	61.1	38.9
1st → 2nd CIS	246	20 (6–76)	31.6	68.4
2nd → 3rd CIS	46	22 (5–60)	23.5	76.5
3rd → 4th CIS	9	9 (5–17)	50.0	50.0

Table 3 Characteristics of Hepatic Metastases

	Hepatic surgery			
	First (n=246)	Second (n=246)	Third (n=46)	Fourth (n=9)
Maximum tumor size (%)				
<3 cm	41.5	47.0	55.6	55.6
3–5 cm	39.6	42.6	35.6	44.4
>5 cm	18.9	10.4	8.8	0
Number of nodules (%)				
1	43.3	58.3	64.5	88.9
2	24.5	23.9	22.2	0
3	13.0	9.1	4.4	11.1
≥4	19.2	8.7	8.9	0
Serum CEA (ng/mL)	113.0±536.1	44.5±141.2	26.8±24.2	25.6±14.2
Extra-hepatic disease, n	56 (22.8)	37 (15.0)	9 (19.6)	3 (33.3)

ingly utilized with subsequent CIS (initial CIS, 2.4% versus second CIS, 15.4% versus third/fourth CIS, 20.0%; P=0.006). In fact, ablation was utilized either alone or in combination with resection in up to one quarter of patients who underwent repeat CIS (Table 4).

Perioperative Morbidity and Mortality

The median length of stay following each iterative CIS was the same (median, 6 days; Table 5). There was only one death reported within 30 days of any CIS, regardless of the number of CIS attempted. As such, the perioperative mortality rate following CIS was the same for repeat CIS compared with initial CIS.

Overall operative morbidity was also similar following initial CIS (22.5%) compared with second CIS (21.0%) or third/fourth CIS (21.6%; P=0.94). Most complications following initial (72.3%) or repeat (74.3%) CIS were minor (Clavien Grade I–II; Table 5). The most common complications included infection (n=25) or pleural effusion (n=15). No patient developed liver insufficiency or died of liver failure.

Long-Term Outcome and Predictors of Survival

The median overall survival following the initial CIS was 51.1 months (95% CI, 36.2–65.7), and the 1-, 3-, and 5-year actuarial overall survival rates were 97.9%, 69.9%, and 47.1%, respectively. For patients undergoing a second CIS, the median survival was 42.0 months (95% CI, 34.5–49.5), and overall 5-year survival was 32.6% (Fig. 1). For patients undergoing a third CIS, the median survival was 41.0 months (95% CI, 24.9–57.2), and overall 5-year survival was 23.8% (Fig. 2). For the nine patients who had a fourth CIS, the

Table 4 Details of Surgical Procedures

	Hepatic surgery			
	First (n=246)	Second (n=246)	Third (n=46)	Fourth (n=9)
Type of liver-directed therapy, n=246				
Resection only	219 (89.0)	194 (78.9)	34 (73.9)	7 (77.8)
Nonresection only	6 (2.4)	38 (15.4)	9 (19.6)	2 (22.2)
Both	21 (8.6)	14 (5.7)	3 (6.5)	0
Type of liver resection, n=240				
Wedge resection	112 (46.7)	92 (44.2)	16 (43.2)	1 (14.3)
Segmentectomy (1)	51 (21.3)	64 (30.8)	15 (40.5)	5 (71.4)
Segmentectomy (>1)	33 (13.8)	22 (10.6)	0	0
(Extended) right hepatectomy	50 (20.8)	41 (19.7)	4 (10.8)	0
(Extended) left hepatectomy	26 (10.8)	11 (5.3)	4 (10.8)	1 (14.3)
Type of nonresectional liver-directed therapy, n=27				
Radiofrequency ablation	22 (81.5)	41 (78.8)	9 (75.0)	2 (100.0)
Cryoablation	5 (18.5)	11 (21.2)	3 (25.0)	0

Table 5 Perioperative Morbidity and Mortality

	Hepatic surgery			
	First (n=246)	Second (n=246)	Third (n=46)	Fourth (n=9)
Operative blood loss (%)				
<100 mL	50.0	53.8	61.9	100
100–500 mL	30.0	30.8	28.6	0
>500–1000 mL	14.2	11.5	4.8	0
>1000 mL	5.8	3.8	4.7	0
Perioperative mortality (%)	0	0.4	0	0
Perioperative morbidity (%)	22.5	21.0	23.7	16.7
Grade <3 (%)	72.3	69.2	100	100
Grade ≥3 (%)	27.7	30.8	0	0
Length of in-hospital stay, days	7±6	9±10	8±8	7±4

median survival was 18.8 months (95% CI, 18.8–57.2). When estimated from the time of the initial CIS, 5-year survival was 56.6%, 78.1%, and 89.3% for patients who underwent two, three, or four attempts at CIS.

On univariate analyses, standard clinico-pathologic factors were analyzed to determine their association with survival from the time of the second CIS (Table 6). Only the presence of extra-hepatic disease was significantly associated with a worse long-term prognosis (P<0.001). Location of the primary colorectal cancer, lymph node status of the primary colorectal cancer, synchronous presentation, CEA level prior to the second CIS, receipt of chemotherapy, R1 margin status, tumor size and number, and receipt of ablation were not associated with prognosis (all P>0.05). In contrast, the presence of extra-hepatic disease at the time of repeat CIS was strongly associated with prognosis. Specifically, patients with extra-hepatic disease at the time of repeat CIS had a median survival of 27.0 months compared with 50.0 months for patients who had intra-hepatic disease only (P<0.001; Fig. 3). After controlling for competing risk factors with multivariate analysis, the presence of extra-hepatic disease at the time of repeat CIS remained independently associated with a worse survival (HR=2.26, P=0.01), whereas receipt of chemotherapy tended to be associated with an improved survival (HR=0.62; P=0.07).

Discussion

Liver recurrence following initial hepatectomy is relatively common and is associated with a poor prognosis if not managed surgically, as long-term survival with chemotherapy alone remains limited. In fact, roughly 50% to 70% of

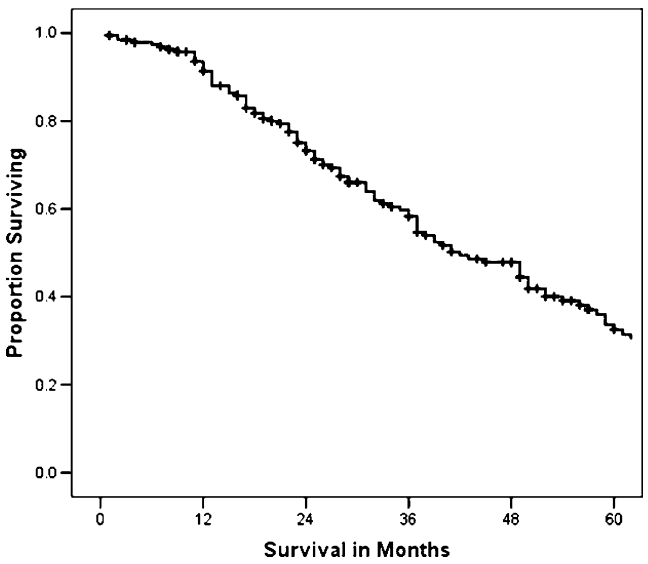


Figure 1 Overall Kaplan Meier survival of patients who underwent second CIS for colorectal liver metastasis.

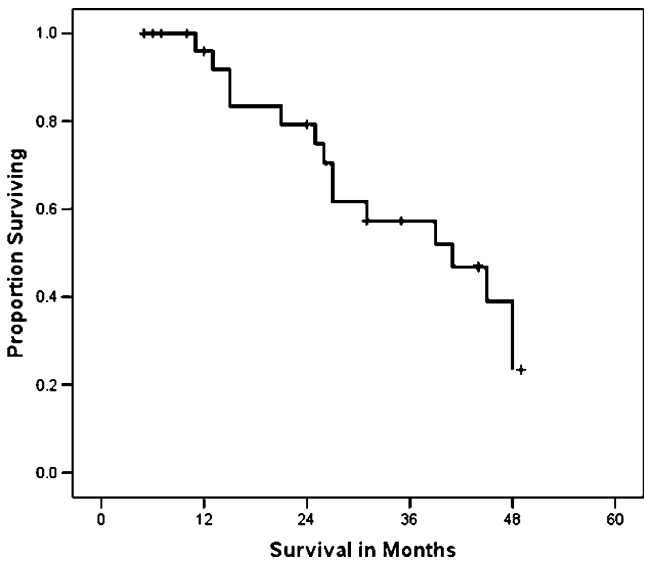


Figure 2 Overall Kaplan Meier survival of patients who underwent third CIS for colorectal liver metastasis.

Table 6 Prognostic Factors Associated with Risk of Worse Overall Survival

Prognostic factor	Univariate			Multivariate		
	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Rectal primary tumor	0.79	0.47–1.34	0.39	–	–	–
Primary LN metastasis	1.36	0.88–2.12	0.17	1.27	0.78–2.05	0.34
Synchronous metastasis	0.88	0.60–1.28 0.49	–	–	–	
CEA <200 ng/ml	0.53	0.19–1.46	0.22	–	–	–
Hepatic lesion >5 cm	1.54	0.86–2.76	0.15	1.41	0.65	0.39
Hepatic lesions >4	1.40	0.71–2.77	0.34	–	–	–
Receipt of chemotherapy	0.69	0.43–1.11	0.12	0.62	0.37–1.05	0.07
Receipt of RFA	0.88	0.49–1.58	0.67	–	–	–
Extra-hepatic disease	2.59	1.63–4.12	<0.001	2.26	1.20–4.25	0.01
≥Hemihepatectomy	1.39	0.89–2.18	0.15	0.77	0.44–1.36	0.37

CI confidence interval, *LN* lymph node, *CEA* carcinoembryonic antigen

patients will experience recurrence after initial hepatectomy.[25,27,28,45] Our group recently reported that about 40% of patients developed intra-hepatic disease as a component of the first site of recurrence following initial CIS.[28] Repeat hepatectomy has been advocated as a treatment for recurrent colorectal metastasis to the liver. Management of these patients can be challenging to the surgeon, and there has been a perception that the increased technical difficulties associated with repeat hepatectomy lead to increased morbidity and mortality.[46,47] While the survival benefit associated with repeat hepatectomy has been reported,[27,30–36] these data have been limited. Most series have been single-institutional studies,[27,30–36] with only two previous multi-institutional studies published to date.[48,49] Most of these series included fewer than 100 patients and were limited by their small sample size. The current study is important because it reports the largest multi-institutional experience with repeat CIS for recurrent colorectal liver metastasis. In addition, unlike most previously reported studies, we included ablative techniques in our analyses. The inclusion of both resection and ablative approaches makes the current analysis more relevant to the practicing liver surgeon who frequently may employ both of these techniques—especially in the repeat CIS setting. The data in the current study demonstrate that repeat CIS is safe with a corresponding low perioperative morbidity and a near-zero operative mortality. We also report that repeat CIS can provide long-term survival for some patients with recurrent colorectal liver metastasis. In aggregate, these data strongly suggest that repeat CIS is safe and efficacious in the treatment of recurrent colorectal liver metastasis and should be performed when oncologically appropriate.

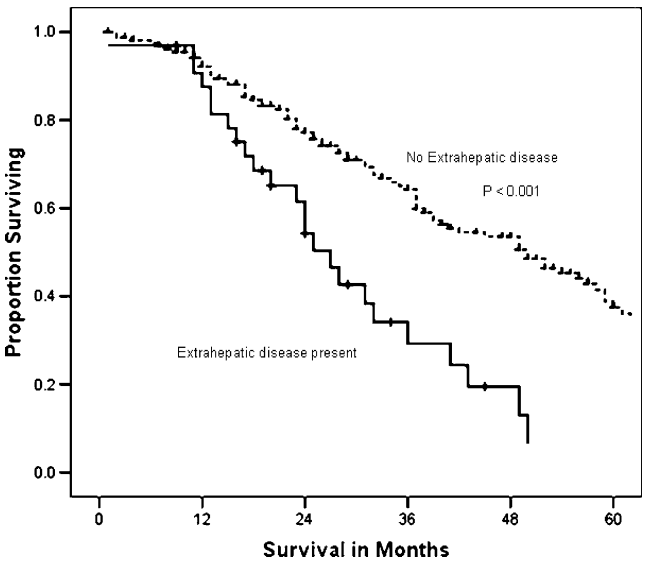


Figure 3 Overall Kaplan Meier survival of patients who underwent repeat CIS stratified by the presence or absence of extra-hepatic disease at the time of surgery.

Most hepatobiliary centers have reported that about 10% to 15% of patients who underwent liver resection for colorectal metastasis eventually underwent a second operation.[27,32–34,45] In the current study, we similarly reported that 246 out of 1,706 (14.4%) patients who underwent an initial CIS for colorectal liver metastasis went on to undergo a repeat CIS. The clinico-morphological characteristics of the disease for which CIS was undertaken, however, did change with subsequent surgeries. Patients who underwent repeat CIS were more likely to have solitary metastasis and a smaller median tumor diameter (Table 3). Sa Cunha et al.[34] had similarly reported less hepatic tumor burden in patients undergoing repeat liver resection due to recurrent colorectal metastasis. The exact reason for the difference in the clinico-morphologic features of the intra-hepatic tumor burden of patients undergoing repeat versus initial CIS is probably multifactorial. In part,

the decrease in hepatic tumor burden at the time of repeat hepatectomy may reflect more strict patient selection on the part of the surgeon. Patients who have had previous liver surgery may also have less residual hepatic parenchyma, and therefore only patients with more limited disease may be amenable to repeat surgery. Regardless of the extent of disease, repeat hepatectomy should only be employed according to the same criteria as the initial CIS.[12,27,33] In particular, surgery should only be undertaken when all disease can be resected with a microscopically negative (R0) margin. In the current study, the rate of microscopically negative (R0) resections actually increased following second, third and fourth CIS versus the initial CIS.

Advances in surgical technique have made ablative treatments of colorectal liver metastasis a safe therapeutic option that can be used either alone or in combination with hepatic resection.[50] In patients who have had previous major liver resections, ablative therapy may provide a chance at CIS that otherwise may not have been feasible. Some investigators have even advocated ablation as the preferred alternative approach over repeat hepatectomy for recurrent liver metastasis, stressing that repeat hepatectomy is only indicated when ablation is contraindicated.[51] Although each case has to be individualized, most investigators,[39,45,48] including the current authors, still advocate for hepatic resection of recurrent disease when it is feasible. However, ablation is a useful tool at the liver surgeon's disposal, especially in patients with recurrent disease. As noted in the current study, with each repeat CIS, the extent of the hepatic resection decreased, while the use of ablation increased. In fact, ablation was utilized in about one quarter of the repeat CIS performed. Ablation of recurrent intra-hepatic disease in patients who have no surgical resection option due to a previous surgery should be strongly considered. Whether such ablation of recurrent disease will result in equivalent short- and long-term outcomes remains controversial.[52] Previous data have suggested that ablation may be associated with the risk of intra-hepatic recurrence but not overall survival.[28,53] In the current study, receipt of ablation was not associated with long-term survival following repeat CIS (Table 6).

A major concern around the use of repeat CIS for recurrent colorectal metastasis has been the perceived risk of associated morbidity. As repeat hepatic surgery in some ways entails a larger, more technically challenging operation than the initial CIS, there has been a fear that perioperative morbidity would also be increased. In the current study, both operative estimated blood loss and length of stay were similar for initial versus repeat CIS. Our data also indicated that perioperative morbidity was similar following initial and repeat CIS (Table 5). In addition, data from the current study demonstrate that, while the morbidity rate was about 20% to 25%, the majority (70% to 100%) of perioperative complications following repeat CIS were minor (Clavien Grade I or II). Most complications did not require either any therapy or a simple routine intervention. Most series report a death rate of less than 5% for first hepatic resection.[17,20,24,54] Others studies have reported a similar low mortality rate following repeat liver surgery[33,35,55] with several studies reporting a perioperative mortality rate of zero.[27,32,36] In the current study, perioperative mortality was also very low (only one death out of 301 repeat CIS procedures). In aggregate, the data show that repeat CIS for recurrent colorectal liver metastasis is safe and has comparable perioperative outcomes as patients undergoing first resections.

The overall 5-year survival of 47.1% and 32.6%, respectively, for the initial and second CIS are comparable to previously published survival data.[33,34,41,48] Specifically, Brachet et al.[41] reported a 5-year survival following initial and second hepatectomy of 40% and 31%, respectively. In a separate study, Adam et al.[48] reported similar 5-year survivals for initial and second hepatic resections, as well as a 5-year survival of 32% following third hepatic resection—which was comparable, albeit slightly better than, the survival of 23.8% reported in the current study. These data compare very favorably to the poor survival of non-operated patients with recurrent disease (5% at 3 years), as well as the prognosis of patients with repeat intra-hepatic recurrence following second hepatectomy who were not offered a third CIS (15% at 2 years).[48] Repeat CIS when technically and oncologically appropriate is therefore warranted as there appears to be a demonstrable survival benefit. Repeat CIS for recurrent colorectal liver metastasis should be cautiously considered, however, in patients with extra-hepatic disease. Specifically, long-term survival was significantly worse in the presence of extra-hepatic disease (Fig. 3). Other investigators[32,34,56] have also noted an adverse impact of extra-hepatic disease on outcome in patients undergoing repeat surgery for colorectal liver metastasis. These results, in combination with the observation that receipt of chemotherapy tended to be associated with an improved outcome, suggest that patients with extra-hepatic disease may perhaps be best managed with pre-operative systemic chemotherapy to facilitate observation of the underlying tumor biology to best select those patients who may benefit most from repeat CIS.

In conclusion, about 15% of patients who underwent liver resection for colorectal metastasis eventually underwent a second operation. The clinico-morphological characteristics of the disease for which CIS was undertaken changed with subsequent surgeries, with more patients having solitary metastasis and smaller liver lesions on subsequent CIS. The use of ablative techniques increased with repeat hepatectomy, perhaps increasing the number of patients who would otherwise not have been potential candidates for repeat CIS. Repeat CIS was associated with

a near-zero operative mortality and a low perioperative morbidity. Although patients with recurrent colorectal liver metastasis can derive a long-term survival benefit from repeat CIS, the benefit of repeat CIS in patients with concurrent extra-hepatic disease is more limited. Treatment with systemic chemotherapy, as well as utilization of future relevant tumor biomarkers, will hopefully help better identify which patients can most benefit from repeat CIS.

References

1. Howe HL, Wu X, Ries LA, et al. Annual report to the nation on the status of cancer, 1975–2003, featuring cancer among U.S. Hispanic/Latino populations. Cancer 2006;107(8):1711–1742.
2. Rudy DR, Zdon MJ. Update on colorectal cancer. Am Fam Physician 2000;61(6):1759–1770. 1773–1774.
3. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. CA Cancer J Clin 2005;55(1):10–30.
4. Steele G Jr., Ravikumar TS. Resection of hepatic metastases from colorectal cancer. Biologic perspective. Ann Surg 1989;210(2): 127–138.
5. Cady B, Monson DO, Swinton NW. Survival of patients after colonic resection for carcinoma with simultaneous liver metastases. Surg Gynecol Obstet 1970;131(4):697–700.
6. Blumgart LH, Allison DJ. Resection and embolization in the management of secondary hepatic tumors. World J Surg 1982;6 (1):32–45.
7. Jatzko G, Wette V, Muller M, et al. Simultaneous resection of colorectal carcinoma and synchronous liver metastases in a district hospital. Int J Colorectal Dis 1991;6(2):111–114.
8. Finlay IG, McArdle CS. Occult hepatic metastases in colorectal carcinoma. Br J Surg 1986;73(9):732–735.
9. Scheele J, Stang R, Altendorf-Hofmann A, Paul M. Resection of colorectal liver metastases. World J Surg 1995;19(1):59–71.
10. Altendorf-Hofmann A, Scheele J. A critical review of the major indicators of prognosis after resection of hepatic metastases from colorectal carcinoma. Surg Oncol Clin N Am 2003;12(1):165–192. xi.
11. Scheele J, Stangl R, Altendorf-Hofmann A, Gall FP. Indicators of prognosis after hepatic resection for colorectal secondaries. Surgery 1991;110(1):13–29.
12. Pawlik TM, Schulick RD, Choti MA. Expanding criteria for resectability of colorectal liver metastases. Oncologist 2008;13(1): 51–64.
13. Pawlik TM, Choti MA. Surgical therapy for colorectal metastases to the liver. J Gastrointest Surg 2007;11(8):1057–1077.
14. Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg 2004;239(6):818–825. discussion 825–827.
15. Scheele J, Stangl R, Altendorf-Hofmann A. Hepatic metastases from colorectal carcinoma: impact of surgical resection on the natural history. Br J Surg 1990;77(11):1241–1246.
16. Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg 2002;235(6):759–766.
17. Hughes KS, Rosenstein RB, Songhorabodi S, et al. Resection of the liver for colorectal carcinoma metastases. A multi-institutional study of long-term survivors. Dis Colon Rectum 1988;31(1):1–4.
18. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 1999;230(3):309–318. discussion 318–321.
19. Adson MA, van Heerden JA, Adson MH, et al. Resection of hepatic metastases from colorectal cancer. Arch Surg 1984;119(6): 647–651.
20. Gayowski TJ, Iwatsuki S, Madariaga JR, et al. Experience in hepatic resection for metastatic colorectal cancer: analysis of clinical and pathologic risk factors. Surgery 1994;116(4):703–710. discussion 710–711.
21. Jenkins LT, Millikan KW, Bines SD, et al. Hepatic resection for metastatic colorectal cancer. Am Surg 1997;63(7):605–610.
22. Jamison RL, Donohue JH, Nagorney DM, et al. Hepatic resection for metastatic colorectal cancer results in cure for some patients. Arch Surg 1997;132(5):505–510. discussion 511.
23. Pawlik TM, Scoggins CR, Zorzi D, et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. Ann Surg 2005;241(5):715–722. discussion 722–724.
24. Nordlinger B, Quilichini MA, Parc R, et al. Hepatic resection for colorectal liver metastases. Influence on survival of preoperative factors and surgery for recurrences in 80 patients. Ann Surg 1987;205(3):256–263.
25. Bozzetti F, Doci R, Bignami P, et al. Patterns of failure following surgical resection of colorectal cancer liver metastases. Rationale for a multimodal approach. Ann Surg 1987;205(3):264–270.
26. Ekberg H, Tranberg KG, Andersson R, et al. Pattern of recurrence in liver resection for colorectal secondaries. World J Surg 1987;11 (4):541–547.
27. Adam R, Bismuth H, Castaing D, et al. Repeat hepatectomy for colorectal liver metastases. Ann Surg 1997;225(1):51–60. discussion 60–62.
28. de Jong MC, Pulitano C, Ribero D, Strub J, Mentha G, Schulick RD, Choti MA, Aldrighetti L, Capussotti L, Pawlik TM. Rates and patterns of recurrence following curative intent surgery for colorectal liver metastases: an international multi-institutional analysis of 1669 patients. Ann Surg 2009;250 (3):440–448.
29. Lange JF, Leese T, Castaing D, Bismuth H. Repeat hepatectomy for recurrent malignant tumors of the liver. Surg Gynecol Obstet 1989;169(2):119–126.
30. Pinson CW, Wright JK, Chapman WC, et al. Repeat hepatic surgery for colorectal cancer metastasis to the liver. Ann Surg 1996;223(6):765–773. discussion 773–776.
31. Nishio H, Hamady ZZ, Malik HZ, et al. Outcome following repeat liver resection for colorectal liver metastases. Eur J Surg Oncol 2007;33(6):729–734.
32. Yamamoto J, Kosuge T, Shimada K, et al. Repeat liver resection for recurrent colorectal liver metastases. Am J Surg 1999;178 (4):275–281.
33. Petrowsky H, Gonen M, Jarnagin W, et al. Second liver resections are safe and effective treatment for recurrent hepatic metastases from colorectal cancer: a bi–institutional analysis. Ann Surg 2002;235(6):863–871.
34. Sa Cunha A, Laurent C, Rault A, et al. A second liver resection due to recurrent colorectal liver metastases. Arch Surg 2007;142 (12):1144–1149. discussion 1150.
35. Nordlinger B, Vaillant JC, Guiguet M, et al. Survival benefit of repeat liver resections for recurrent colorectal metastases: 143 cases. Association Francaise de Chirurgie. J Clin Oncol 1994;12 (7):1491–1496.
36. Tuttle TM, Curley SA, Roh MS. Repeat hepatic resection as effective treatment of recurrent colorectal liver metastases. Ann Surg Oncol 1997;4(2):125–130.
37. Stone MD, Cady B, Jenkins RL, et al. Surgical therapy for recurrent liver metastases from colorectal cancer. Arch Surg 1990;125(6):718–721. discussion 722.

38. Vaillant JC, Balladur P, Nordlinger B, et al. Repeat liver resection for recurrent colorectal metastases. Br J Surg 1993;80(3):340–344.
39. Fong Y, Blumgart LH, Cohen A, et al. Repeat hepatic resections for metastatic colorectal cancer. Ann Surg 1994;220(5):657–662.
40. Nagakura S, Shirai Y, Suda T, Hatakeyama K. Multiple repeat resections of intra- and extrahepatic recurrences in patients undergoing initial hepatectomy for colorectal carcinoma metastases. World J Surg 2002;26(2):141–147.
41. Brachet D, Lermite E, Rouquette A, et al. Prognostic factors of survival in repeat liver resection for recurrent colorectal metastases: review of sixty-two cases treated at a single institution. Dis Colon Rectum 2009;52(3):475–483.
42. Clavien PA, Emond J, Vauthey JN, et al. Protection of the liver during hepatic surgery. J Gastrointest Surg 2004;8(3):313–327.
43. Strasberg SM. For the International Hepato-Pancreato-Biliary Association Terminology Committee Survey. The Brisbane 2000 Terminology of Liver Anatomy and Resections. HPB 2000;2 (3):333–339.
44. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. Am Stat Assoc J 1958;53:457–480.
45. Fernandez-Trigo V, Shamsa F, Sugarbaker PH. Repeat liver resections from colorectal metastasis. Repeat Hepatic Metastases Registry. Surgery 1995;117(3):296–304.
46. Aramaki M, Kawano K, Kai T, et al. Postoperative complications of repeat hepatectomy for liver metastasis from colorectal carcinoma. Hepatogastroenterology 2000;47(32):478–480.
47. Elias D, Lasser P, Hoang JM, et al. Repeat hepatectomy for cancer. Br J Surg 1993;80(12):1557–1562.
48. Adam R, Pascal G, Azoulay D, et al. Liver resection for colorectal metastases: the third hepatectomy. Ann Surg 2003;238(6):871–883. discussion 883–884.
49. Ishiguro S, Akasu T, Fujimoto Y, et al. Second hepatectomy for recurrent colorectal liver metastasis: analysis of preoperative prognostic factors. Ann Surg Oncol 2006;13(12):1579–1587.
50. Pawlik TM, Izzo F, Cohen DS, et al. Combined resection and radiofrequency ablation for advanced hepatic malignancies: results in 172 patients. Ann Surg Oncol 2003;10(9):1059–1069.
51. Elias D, De Baere T, Smayra T, et al. Percutaneous radiofrequency thermoablation as an alternative to surgery for treatment of liver tumour recurrence after hepatectomy. Br J Surg 2002;89(6):752–756.
52. Tsai S, Pawlik TM. Outcomes of ablation versus resection for colorectal metastases: are we comparing apples to oranges? Ann Surg Oncol 2009;16(9):2422–2428.
53. Gleisner AL, Choti MA, Assumpcao L, et al. Colorectal liver metastases: recurrence and survival following hepatic resection, radiofrequency ablation, and combined resection-radiofrequency ablation. Arch Surg 2008;143(12):1204–1212.
54. Asiyanbola B, Chang D, Gleisner AL, et al. Operative mortality after hepatic resection: are literature-based rates broadly applicable? J Gastrointest Surg 2008;12(5):842–851.
55. Muratore A, Polastri R, Bouzari H, et al. Repeat hepatectomy for colorectal liver metastases: A worthwhile operation? J Surg Oncol 2001;76(2):127–132.
56. Pessaux P, Lermite E, Brehant O, et al. Repeat hepatectomy for recurrent colorectal liver metastases. J Surg Oncol 2006;93(1):1–7.

Mechteld C. De Jong, presenter (medical student from the Netherlands)

Discussant

Dr. Sean Mulvihill (Salt Lake City, UT): For those of you who missed it, Miss DeJong is a medical student. Very nicely done. I hope this experience encourages you to seek a career in surgery.

This is the largest reported series of repeat, curative intent liver surgery for colorectal metastases to the liver. But these operations were uncommon. By my calculation, only about two operations were done per center, per year, given that there were five centers over 20-some years in this study.

In our own hospital it seems like this scenario is increasing in frequency, and I wonder if that's been your experience? I think we would agree that these could be technically difficult operations in terms of dissecting the liver off the diaphragm, stomach and colon, particularly at the site of the prior resection. And that makes me wonder whether we should be considering use of some anti-adhesion barrier, such as Seprafilm, at the time of the primary liver resection.

Staging is critically important to ensure identification of all disease, and I'm sure that over the 20-odd years in this study the methods of staging changed. And I wonder if could you tell us what your current standard for axial imaging of the chest and abdomen is, and your current use of PET.

I was surprised that chemotherapy was only used in about two-thirds of the patients in this series. And I think, from what we heard today, there is some difference of opinion about the use of chemotherapy. We would favor it on both a neoadjuvant and postoperative adjuvant basis for liver resection for colorectal metastasis. Please tell us what your current standard for the use of chemotherapy is.

Closing discussant

Mechteld C. De Jong: Thank you for your questions. Because of my English I will ask if Dr. Pawlik can assist in responding to your questions.

Closing discussant

Dr. Timothy M. Pawlik (Johns Hopkins, Baltimore, Maryland): Thank you very much for reviewing our paper.

With regard to your first question, there was a trend over time whereby repeat hepatectomies were more frequently performed over the last decade. I think repeat hepatectomy may be more frequently used because liver resection is now associated with a much lower operative morbidity and mortality and we are armed with more effective, systemic chemotherapy to complement surgery. However, you are correct in that the study did occur over a long time period and this should be considered when interpreting the conclusions.

We did not investigate the use of Seprafilm or other anti-adhesive agents. I personally do not routinely use

Seprafilm at the time of initial hepatic resection. The field is also quickly changing and perhaps as more and more initial hepatectomies are performed either laparoscopically or with the robot, we may find that repeat hepatectomies may become an easier operation.

Your third question related to the use of cross-sectional imaging. Most centers used CT scans. At Johns Hopkins, we generally obtain both a CT scan as well as a pre-operative PET scan. However, many of the centers—including those in Europe—did not routinely obtain a pre-operative PET scan.

In general, we use chemotherapy in the adjuvant setting for patients who have resectable liver disease and use it preoperatively for those patients with borderline or unresectable disease in the hopes of converting them to surgical resection. For those patients who present with synchronous disease with an asymptomatic primary colorectal cancer in place, we strongly favor treating this group of patients with preoperative chemotherapy. Also, for those patients who have both intra- and extra-extra-hepatic disease (who constituted about 20% of the current study) we also strongly favor preoperative chemotherapy. The use of chemotherapy in the setting of repeat hepatectomy is more complicated and may depend not only on the interval from their recurrence, but also on how long the patient has been chemo naive, what chemotherapy they may have received in the past, etc. The chemotherapy question in these patients needs to be addressed on an individual case-by-case basis.

Discussant

Dr. Kaye M. Reid Lombardo (Mayo Clinic , Rochester, MN): In the group of patients who had extra-hepatic disease, what was the extent of their disease? Did they have multiple sites involved? And/or whether or not they were surgically treated as well?

Closing discussant

Mechteld C. De Jong: Thank you for your question. The majority of patients who had extra-hepatic disease had a solitary, lung metastasis. Only patients who had limited, extra-hepatic disease were included in our study. In general, patients with intra- and extra-hepatic disease were first treated with systemic chemotherapy and had a demonstrable response or stable disease following chemotherapy. Only patients in whom both the intra- and extra-hepatic disease could be resected with an R0 margin were included in the study.

J Gastrointest Surg (2009) 13:2152–2162
DOI 10.1007/s11605-009-1051-z

2009 SSAT PLENARY PRESENTATION

Preoperative Nomogram to Predict Risk of Perioperative Mortality Following Pancreatic Resections for Malignancy

Chandrakanth Are · Chantal Afuh · Lavanya Ravipati · Aaron Sasson · Fred Ullrich · Lynette Smith

Received: 4 June 2009 / Accepted: 11 September 2009 / Published online: 6 October 2009

Abstract
Introduction The majority of pancreatic resections for malignancy are performed in older patients with major comorbidities. The aim of this study was to develop a preoperative nomogram based on the presence of comorbidities to predict risk of perioperative mortality.
Materials and Methods The National Inpatient Sample database was queried to identify patients that underwent pancreatectomy for malignancy. The preoperative comorbidities identified as predictors were used, and a nomogram was created. Sample A (2000–2004) was utilized to develop the model, and sample B (2005) was utilized to validate this model.
Results The overall actual observed perioperative mortality rate for samples A and B was 6.3% and 5.2%, respectively. The mean total points calculated for sample A by the nomogram was 131.7 that translates to a nomogram-predicted mortality rate of 4.9%, which is similar to the actual mortality. The mean total points for sample B was 128.1, which translates to a nomogram-predicted mortality rate of 4.6%. The similarity of mortality rates as predicted by the nomogram and a concordance index of 0.76 shows good agreement between the data and the nomogram.
Conclusion This preoperative nomogram has been shown to accurately predict the risk of perioperative mortality following pancreatectomy for malignancy.

SSAT, 2009, Chicago, IL, Plenary session—June 2nd 2009

C. Are · A. Sasson
Division of Surgical Oncology, Department of Surgery,
Eppley Cancer Center, University of Nebraska Medical Centre,
Omaha, NE, USA

C. Afuh
University of Nebraska College of Medicine,
Omaha, NE, USA

L. Ravipati
Department of Pathology, University of Nebraska Medical Center,
Omaha, NE, USA

F. Ullrich · L. Smith
Department of Biostatistics, College of Public Health,
University of Nebraska Medical Centre,
Omaha, NE, USA

C. Are (✉)
Division of Surgical Oncology,
Department of Surgery/Genetics Cell Biology and Anatomy,
University of Nebraska Medical Center,
Omaha, NE 68198, USA
e-mail: care@unmc.edu

Keywords Pancreatectomy · Malignancy · Mortality · Nomogram

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related death in the USA.[1] In the year 2008, 37,680 new cases of pancreatic cancer were diagnosed that accounted for 34,290 deaths.[2] Surgical resection is the only modality that may offer hope for prolonging survival with reported 5-year survival rates ranging from 18% to 41% in selected patients.[3,4] The advancement of surgical techniques has led to a significant decrease in perioperative mortality over the decades.[3–6]

Pancreatic cancer is a disease that predominantly afflicts the elderly who are more likely to be infirm and suffer from multiple pre-existing comorbidities. The pros and cons of subjecting these patients to such major operations need to be carefully weighed. The preoperative counseling of these potentially operable and high-risk patients is critical to

obtaining an adequately informed and shared consent. The majority of surgeons rely on the published literature to educate the individual patient on the likely rates of perioperative mortality associated with the proposed procedures. Although we have seen a decrease in the perioperative mortality overall, there is a difference in the reported perioperative morality rates published in the literature.[3–6] The single-institution studies have reported a low perioperative mortality rate of 1–2%, which may not be possible to replicate at other institutions.[3–5] In contrast, population-based studies have reported a higher perioperative mortality rate ranging from 7.8% to 4.6%.[6] Although the population-based data are a more accurate estimate of the national perioperative mortality rates, it may be too generalized to be applicable to that particular patient.

There is currently no specific method available to estimate the risk of perioperative mortality for the individual patient scheduled to undergo pancreatectomy for malignancy. Nomograms are graphical devices or models that use algorithms or mathematical formulae to estimate the probability of an outcome and are optimized for predictive accuracy for each individual patient. The aims of this study were to (1) develop a nomogram consisting of easily available variables that can be utilized in the preoperative setting to counsel individual patients about the perioperative mortality associated with pancreatectomy for malignancy and (2) to validate the proposed nomogram.

Materials and Methods

Data Source

The Nationwide Inpatient Sample (NIS) database was used to look at inpatient mortality following pancreatectomy for pancreatic neoplasms. The data were obtained from the Nationwide Inpatient Sample, a database developed as part of the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality. The NIS is designed to approximate a 20% sample of US hospitals. In 2005, the NIS data contained discharge data from 1,054 hospitals located in 37 states (HCUP, Nationwide Inpatient Sample, Rockville, MD: Agency for Health Care Research and Quality; 2005). Additional information about "NIS Overview" can be found at http://www.hcup-us.ahrq.gov/nisoverview.jsp.

The data for this study were compiled from the 2000–2005 versions of the NIS. All patients discharged with *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) procedure codes for pancreatectomy (5251—proximal pancreatectomy, 5252—distal pancreatectomy, 5253—radical subtotal pancreatectomy, 5259—other partial pancreatectomy, 526—total pancreatectomy, and 527—radical pancreatectomy) and diagnosis codes for malignant neoplasms of the pancreas (157.0—head of pancreas, 157.1—body of pancreas, 157.2—tail of pancreas, 157.3—pancreatic duct, 157.8—other specified pancreas sites, and 157.9—pancreas, part unspecified) were included. Data on patient age and sex, admission type, hospital size and type, and pancreatectomy type were extracted from the database. Perioperative mortality in the NIS database is defined as any mortality following pancreatectomy during that same hospital admission. Preoperative comorbid conditions were identified using the taxonomy published by Elixhauser et al.[7] A sample definition of some of the comorbidities is shown in Table 1. A detailed description of all the comorbidities used can be found in the taxonomy published by Elixhauser et al.[7] The years 2000–2004 (sample A) were used to create a predictive model, and year 2005 (sample B) was used for validation of the model. The analysis was limited to adults (age ≥18 years).

Statistical Methods

SAS software (SAS Institute Inc., Cary, NC, USA) and SUDAAN®[8] software were used for all statistical analysis to account for the complex sampling design of NIS. Weighted sample estimates, standard errors, and 95% confidence limits were calculated using the Taylor expansion method. All statistical tests were two-sided, and p values less than 0.05 were considered to be statistically significant.

Chi-square tests were used to compare perioperative mortality rates by patient and hospital characteristics. We developed a nomogram to estimate the probability of perioperative mortality following pancreatectomy for pancreatic neoplasm. We first identified potential predictors of perioperative mortality with a combination of clinical experience, significance from the univariate chi-square tests, and availability at the time of admission. Multivariate logistic regression was used to find a predictive model of perioperative mortality. A nomogram was built using the techniques described by Iasonos et al.[9] and Brittain et al.[10] using NIS data from 2000 to 2004 (sample A). This nomogram was validated using calibration plots and with a concordance index using data from NIS 2005 (sample B). Briefly, the concordance index is calculated by comparing the patients that had died to those that are alive in sample B. All possible pairs are constructed between those who died and those alive. For each pair, if the nomogram assigns a higher probability of death to the patient who died than the one alive, then the model matches the data, and the pair is said to be concordant. The concordance index is the probability of being concordant out of all possible dead/alive patient pairs. A 95% confidence interval is presented for the concordance index based on 10,000 bootstrapped samples. A calibration

Table 1 Definition of Some of the Preoperative Comorbidities Used to Construct the Nomogram as per the Taxonomy Published by Elixhauser et al.[7]

Renal failure	
403.11	Hypertensive renal disease, benign with renal failure
403.91	Hypertensive renal disease, unspecified with renal failure
404.12	Hypertensive heart and renal disease, benign with congestive heart failure
404.92	Hypertensive heart and renal disease, unspecified with congestive heart failure
585	Chronic renal failure
586	Renal failure, unspecified
V42.0	Kidney transplant
V45.1	Renal dialysis status
V56.0	Extracorporeal dialysis
V56.8	Other dialysis
Liver disease	
070.32	Viral hepatitis B without mention of hepatic coma, chronic without mention of hepatitis delta
070.33	Viral hepatitis B without mention of hepatic coma, chronic with hepatitis delta
070.54	Chronic hepatitis C without mention of hepatic coma
456.0	Esophageal varices with bleeding
456.1	Esophageal varices without mention of bleeding
456.20	Esophageal varices in diseases classified elsewhere, with bleeding
456.21	Esophageal varices in diseases classified elsewhere, without mention of bleeding
571.0	Alcoholic fatty liver
571.2	Alcoholic cirrhosis of liver
571.3	Alcoholic liver damage, unspecified
571.40–571.49	Chronic hepatitis
571.5	Cirrhosis of liver without mention of alcohol
571.6	Biliary cirrhosis
571.8	Other chronic nonalcoholic liver disease
571.9	Unspecified chronic liver disease without mention of alcohol
572.3	Portal hypertension
572.8	Other sequelae of chronic liver disease
V42.7	Liver transplant
Hypertension, uncomplicated	
401.1	Essential hypertension, benign
401.9	Essential hypertension, unspecified
Hypertension, complicated	
402.10	Hypertensive heart disease, benign, without congestive heart failure
402.90	Hypertensive heart disease, unspecified, without congestive heart failure
404.10	Hypertensive heart and renal disease, benign
404.90	Hypertensive heart and renal disease, unspecified
405.11	Secondary hypertension, benign renovascular
405.19	Secondary hypertension, benign other
405.91	Secondary hypertension, unspecified renovascular
405.99	Secondary hypertension, unspecified other
Diabetes, uncomplicated	
250.00–250.33 other	Diabetes mellitus without complication, with ketoacidosis, with hyperosmolarity, with other coma
Diabetes, complicated	
250.40–250.73	Diabetes with renal or ophthalmic or neurological manifestations or peripheral circulatory disorders
250.90–250.93	Diabetes with unspecified complications

plot is constructed by plotting predicted probabilities from the nomogram versus the actual probabilities. For sample A, deciles (quartiles for sample B due to smaller sample size) of the predicted probabilities for the patients who died were found, and the observed mortality proportions were determined for the decile groups, along with 95% confidence intervals, and plotted. A perfectly predictive nomogram should result in the observed and expected probabilities falling along the 45° line.

Results

The total number of patients included in the study was 5,481 (weighted frequency of n=26,958). The mean age of our sample was 64.9 (range, 18–98) with males accounting for 51% of the patients. The number of patients included in samples A and B were 4,482 (weighted n=21,981) and 999 (weighted n=4,977), respectively. The overall perioperative mortality rate for the entire cohort of patients was 6.1%. The perioperative mortality rate for samples A and B was 6.3% and 5.2%, respectively.

Tables 2 and 3 show the demographic, hospital, tumor characteristics, and preoperative comorbidity details for samples A and B as well as the estimated perioperative mortality rates. The distribution of patient characteristics is similar between samples A and B sets. There are some differences in the significance level of perioperative mortality comparisons between samples A and B, but the majority of these differences are probably due to smaller sample sizes in the 2005 dataset.

Table 4 shows the results of the multivariate models used to predict perioperative mortality using the 2000–2004 dataset (sample A). Variables selected for the multivariate model were chosen from a combination of clinical experience and statistical significance. If the variable was significant at the 0.05 level from the univariate chi-square tests presented in Tables 2 and 3, they were included in the model. If they were not significant at the 0.05 level but

Table 2 Demographics, Hospital Status, Location of Neoplasm, and Type of Resection

		2000–2004 (sample A)				2005 (sample B)			
		Weighted frequency	Percent	Mortality	*p*	Weighted frequency	Percent	Mortality	*p*
Age	≤70	13,920	63.3	4.7	<0.0001	3,103	62.3	4.2	0.077
	>70	8,060	36.7	9.0		1,874	37.7	7.0	
Sex	Male	11,293	51.4	7.3	0.0055	2,447	49.4	3.6	0.019
	Female	10,682	48.6	5.3		2,509	50.6	6.9	
Race	White	13,241	79.7	5.9	0.70	2,704	76.0	4.7	0.022
	Non-white	3,363	20.3	6.3		855	24.0	8.9	
Admission type	Non-elective	5,212	26.9	9.7	<0.0001	1,000	24.3	8.4	0.017
	Elective	14,136	73.1	5.0		3,117	75.7	4.5	
Length of stay	≤10 days	8,379	39.0	5.4	0.078	2,274	45.7	4.4	0.29
	>10 days	13,601	61.0	6.8		2,703	54.3	5.9	
Hospital size	Small	1,290	5.9	9.4	0.030	345	6.9	10.1	0.0012
	Medium	3,754	17.1	7.6		806	16.2	10.3	
	Large	16,937	77.1	5.8		3,826	76.9	3.7	
Hospital type	Non-teaching	6,065	27.6	9.3	<0.0001	1,175	23.6	8.9	0.0035
	Teaching	15,916	72.4	5.1		3,802	76.4	4.1	
Pancreas Neoplasm Location	Head	13,641	62.1	6.0	0.31	3,006	60.4	5.5	0.70
	Other site	8,339	37.9	6.7		1,971	39.6	4.9	
Pancreatectomy type	Proximal	346	1.6	5.7	0.027	51	1.0	0.0	NE
	Distal	3,770	17.2	5.1		982	19.7	3.0	

NE not estimable

deemed important based on clinical experience, they were also included in the model. Due to the overlap in the ICD-9 codes, statistical requirements, and to keep the nomogram simple, we used the pancreatectomy codes for "distal," "radical," and "other" only for inclusion. Presented are adjusted odds ratios with 95% confidence intervals, the β coefficient and standard error, the Wald *p* value, and the total points for that variable estimated from the multivariate logistic model. These variables were used to construct a nomogram as shown in Fig. 1. For each patient, all the variables will be plotted in the nomogram to calculate the total number of points. The total points are now added to obtain an estimate of the likely perioperative mortality following pancreatectomy. For example, a patient seen in our clinic with the preoperative comorbidities as shown in Fig. 2 will be assigned a total of 208.2 points that translates to a nomogram-predicted perioperative mortality of approximately 18%.

Validation of the Nomogram

The total number of points was calculated for each patient in sample A (2000–2004 dataset). The mean total points for the entire sample A is 131.7 (SE=1.54) and ranges from 7.7 to 339.8. The mean total points for sample A of 131.7 correspond to approximately a 5% nomogram-predicted perioperative mortality rate which is similar to the actual observed perioperative mortality rate of 6.3%. The nomogram was validated using the NIS 2005 dataset (sample B). The mean total points for sample B is 128.1 (SE=1.62) and ranges from 7.7 to 367.9. This approximates to a nomogram-predicted perioperative mortality rate of 4.6%, which is close to the actual observed perioperative mortality rate of 5.2%. The concordance index was found to be excellent at 0.76 with a 95% confidence interval of 0.69 to 0.83.

In addition to the concordance index, we performed validation of the nomogram by creating calibration plots. Calibration of the nomogram was examined by looking at the observed perioperative mortality versus the model-predicted perioperative mortality. First, we looked at the 2000–2004 data (sample A) that were used to build the nomogram (Fig. 3). The predicted probabilities extend from a minimum of 0.0054 to a maximum of 0.687. The observed perioperative mortality rates were calculated for the predicted probability deciles along with 95% confidence intervals and plotted against the predicted probabilities. There is excellent agreement between the observed and predicted probabilities. In the validation set, sample B (Fig. 4), the predicted probabilities extend from a minimum of 0.0054 to a maximum of 0.786. The observed perioperative mortality

Table 3 Preoperative Comorbidities

Comorbidities		2000–2004 (sample A)				2005 (sample B)			
		Weighted frequency	Percent	Mortality	*p*	Weighted frequency	Percent	Mortality	*p*
CHF	No	21,092	96.0	5.8	<0.0001	4,761	95.7	4.6	<0.0001
	Yes	889	4.0	18.5		216	4.3	18.5	
Cardiac arrhythmia	No	19,665	89.5	5.7	<0.0001	4,292	86.2	4.8	0.14
	Yes	2,315	10.5	11.1		685	13.8	7.9	
Valvular disease	No	21,396	97.3	6.2	0.12	4,803	96.5	5.1	0.37
	Yes	584	2.7	9.8		175	3.5	8.6	
Pulmonary circ disorder	No	21,906	99.7	6.2	0.026	4,956	99.6	5.3	NE
	Yes	75	0.3	20.3		21	0.4	0.0	
Peripheral vascular disease	No	21,565	98.1	6.2	0.45	4,855	97.5	5.3	0.82
	Yes	415	1.9	8.2		123	2.5	4.2	
Hypertension, uncomplicated	No	14,093	64.1	7.4	<0.0001	2,835	57.0	7.8	<0.0001
	Yes	7,887	35.9	4.3		2,142	43.0	1.9	
Hypertension complicated	No	21,903	99.6	6.3	0.97	4,972	99.9	5.2	NE
	Yes	78	0.4	6.1		5	0.1	0.0	
Paralysis	No	21,956	99.9	6.3	NE	4,967	99.8	5.2	NE
	Yes	25	0.1	0.0		10	0.2	0.0	
Other neurological disease	No	21,766	99.0	6.1	0.0002	4,936	99.2	4.9	<0.0001
	Yes	215	1.0	20.5		41	0.8	48.9	
COPD	No	19,394	88.2	6.1	0.11	4,434	89.1	5.3	0.71
	Yes	2,586	11.8	7.8		543	10.9	4.5	
Diabetes uncomplicated	No	16,796	76.4	6.8	0.0079	3,905	78.5	6.0	0.026
	Yes	5,185	23.6	4.6		1,072	21.5	2.3	
Diabetes complicated	No	21,638	98.4	6.3	0.92	4,886	98.2	5.3	NE
	Yes	343	1.6	6.0		91	1.8	0.0	
Hypothyroid	No	20,655	94.0	6.5	0.014	4,611	92.6	5.4	0.40
	Yes	1,326	6.0	2.9		366	7.4	3.1	
Renal failure	No	21,776	99.1	6.0	<0.0001	4,913	98.7	5.1	0.14
	Yes	205	0.9	35.6		64	1.3	14.1	
liver disease	No	21,283	96.8	6.0	0.0002	4,819	96.8	5.2	0.82
	Yes	697	3.2	13.6		159	3.2	6.1	
Peptic ulcer	No	21,597	98.3	6.3	0.29	4,903	98.5	5.2	0.79
	Yes	384	1.7	3.5		74	1.5	6.8	
AIDS	No	21,963	99.9	6.3	NE	4,972	99.9	5.2	NE
	Yes	18	0.1	0.0		5	0.1	0.0	
Obesity	No	21,532	98.0	6.4	0.12	4,867	97.8	5.4	NE
	Yes	449	2.0	2.3		110	2.2	0.0	
Comorbidities	<3	19,975	90.9	6.2	0.54	4,439	89.2	5.3	0.73
	≥3	2,006	9.1	7.0		538	10.8	4.5	

CHF chronic heart failure, *COPD* chronic obstructive pulmonary disease, *NE* not estimable

rates were calculated for the predicted probability quartiles along with 95% confidence intervals and plotted against the predicted probabilities. There is excellent agreement between the observed and predicted probabilities for the last three quartiles and a slight over estimate of the mortality rate in the first quartile.

Discussion

The majority of patients that present with pancreatic malignancies are elderly with likely multiple pre-existing comorbidities. The preoperative counseling to obtain consent is vital before subjecting this group of high-risk

Table 4 NIS Data 2000–2004 (Sample A) Looking at Inpatient Mortality Following Pancreatectomy for Pancreatic Neoplasm: Multivariate Models

		OR	Lower 95% CI	Upper 95% CI	β coefficient	SE β	Wald F *p* value	Total points
Intercept					−5.36	0.52		
Renal failure	Yes vs no	6.13	2.88	13.08	1.81	0.39	<0.0001	100
Other neurological disease	Yes vs no	3.81	1.6	9.07	1.34	0.44	0.0025	74.0
Hypothyroid	No vs yes	2.66	1.11	6.38	0.98	0.45	0.028	54.1
CHF	Yes vs no	2.29	1.42	3.69	0.83	0.24	0.0007	45.9
Liver disease	Yes vs no	1.99	1.08	3.66	0.69	0.31	0.026	38.1
Age	>70	1.84	1.38	2.46	0.61	0.15	<0.0001	33.7
Admission type	Non-elective	1.77	1.32	2.37	0.57	0.15	0.0002	31.5
Hypertension, uncomplicated	No vs yes	1.66	1.22	2.26	0.5	0.2	0.0013	28.2
Hospital type	Non-teaching	1.5	1.1	2.05	0.41	0.16	0.011	22.7
Cardiac arrhythmia	Yes vs no	1.48	0.99	2.22	0.39	0.21	0.055	21.5
Hospital size	Small/medium	1.41	1.01	1.96	0.34	0.17	0.045	18.8
Diabetes uncomplicated	No vs yes	1.34	0.95	1.89	0.29	0.18	0.10	16.0
COPD	Yes vs no	1.21	0.83	1.77	0.19	0.19	0.32	10.5
Sex	Male	1.17	0.89	1.54	0.16	0.14	0.26	8.8
Pancreatectomy type	Radical vs distal	1.15	0.78	1.69	0.14	0.2	0.52	7.7
	Other vs distal	1.36	0.8	2.33	0.31	0.27		17.1

CHF chronic heart failure, *COPD* chronic obstructive pulmonary disease

patients to complex pancreatic resections. It is during this counseling that the risks and benefits of the procedure are explained to provide the platform upon which an informed consent is obtained. The published perioperative mortality rates following pancreatectomy are conflicting and range from 1–2% (single-institution data) to 7–8% (population-based data).[3–6] Asiyanbola et al.[11] noted a similar discrepancy in perioperative mortality rate for hepatic resections between single-institution and population-based studies.

Similarly, the data on the effect of several variables on the perioperative outcome following pancreatectomy for malignancy are also conflicting. Sohn et al.[12] analyzed their single-institution database of 727 patients and noted that pancreaticoduodenectomy can be safely performed in octogenarians with outcomes similar to younger patients. In an update on the single-institution data, Makary et al.[13] concluded that pancreaticoduodenectomy can be safely performed in nonagenarians. In contrast, a population-based study from Texas[14] found that unadjusted in-hospital mortality increased with increasing age from 2.4% (<60 years) to 11.4% (>80 years of age).

The benefit of undergoing resection at high-volume centers has led to regionalization of care for patients with pancreatic malignancies.[15,16] The data are confusing in defining what is high volume and also whether volume should be defined based on the physician or the hospital. In a study of the National Inpatient Sample database, Meguid et al.[17] noted that volume alone accounted for less than 2% of data variance in perioperative mortality following pancreatic resection. This led them to suggest that volume alone is an imperfect surrogate of outcomes. Similarly, Riall et al.[18] noted significant variability even among high-volume centers reiterating that volume is not a reliable single measure of quality or outcomes following pancreatic surgery.

The current data make it difficult to estimate the individual risk for each particular patient. The ability to estimate the individual risk of perioperative mortality following pancreatectomy for malignancy is important for the patient as well as the surgeon. Nomograms are graphical devices or models that use algorithms or mathematical formulae to estimate the probability of an outcome and are optimized for predictive accuracy for each individual patient.[19,20] Nomograms allow physicians to tailor decisions to the individual patient rather than applying a "one-size fits all" approach to medical decision-making. Nomograms permit the use of all the important available parameters or risk factors so that an accurate prediction model can be constructed. Nomograms allow continuous variables to remain continuous to maximize the predictive power. More importantly, nomograms can be continuously updated based on available new clinical information thereby adding to the accuracy of the predictions.

The benefit of post-operative nomograms in predicting long-term survival has been proven in patients with cancer of various organ systems.[21–23] These nomograms obtained

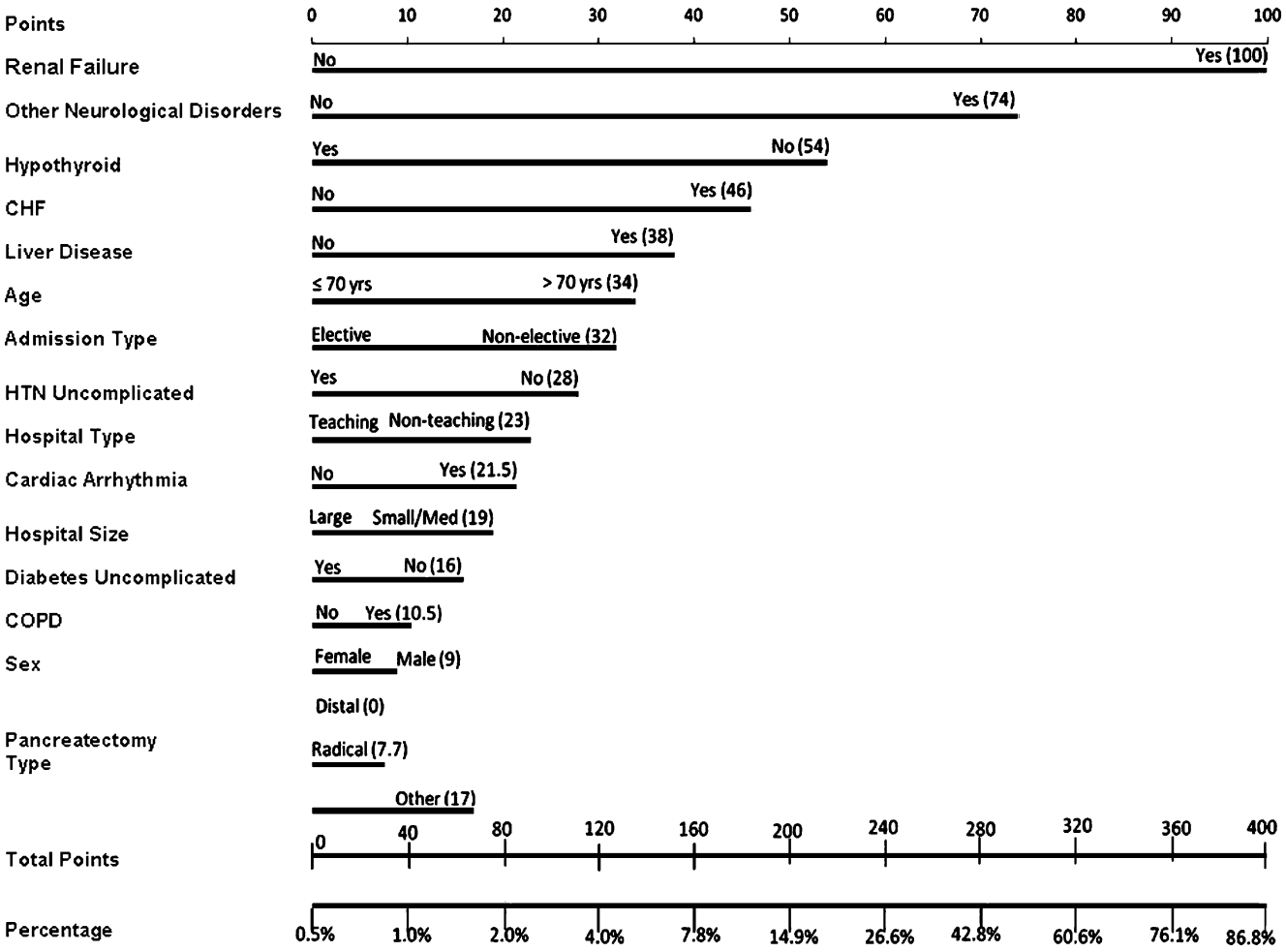


Figure 1 The constructed nomogram.

in the postoperative period consist of various known prognostic factors and are used to define and predict long-term outcome. Recently, we have seen the development of preoperative nomograms to predict the risk of complications associated with particular surgical procedures.[24,25] Lin et al.[24] developed a preoperative nomogram to predict complications associated with various types of breast reconstruction procedures following mastectomy. Lagarde et al.[25] constructed a nomogram that can help predict the severity of complications in the preoperative setting for patients scheduled for esophagectomy. The aim of this study therefore was to develop and validate a nomogram consisting of easily available variables that can be utilized in the preoperative setting to counsel individual patients about the perioperative mortality associated with pancreatectomy for malignancy.

The results of our study revealed good correlation between the nomogram-predicted perioperative mortality rate and the actual observed perioperative mortality rate for both samples A and B. The concordance index was found to be 0.76 with a 95% confidence interval of 0.69 to 0.83 and is evident with the good agreement between the predicted and observed perioperative mortality rates. In addition, we found excellent agreement between the observed and nomogram-predicted perioperative mortality rates on the calibration plots for both samples A and B.

The variables selected for use in constructing the nomogram were based on statistical significance on multivariate analysis as well as clinical significance. The clinical variables included were the ones known to have a likely impact on clinical outcome. It is known that omitting clinically relevant variables can compromise predictive accuracy of the nomogram.[9,26] Brennan et al.[23] developed a prognostic nomogram for patients with adenocarcinoma of the pancreas that included several nonsignificant variables such as sex, margin status, number of negative nodes, and T stage. Although these included variables were not significant on multivariable analysis, the developed nomogram predictions discriminated better than the American Joint Commission on Cancer staging (0.64 vs 0.56, $p<0.001$). Similarly, Wong et al.[27] developed a prognostic nomogram for melanoma patients that included clinician-

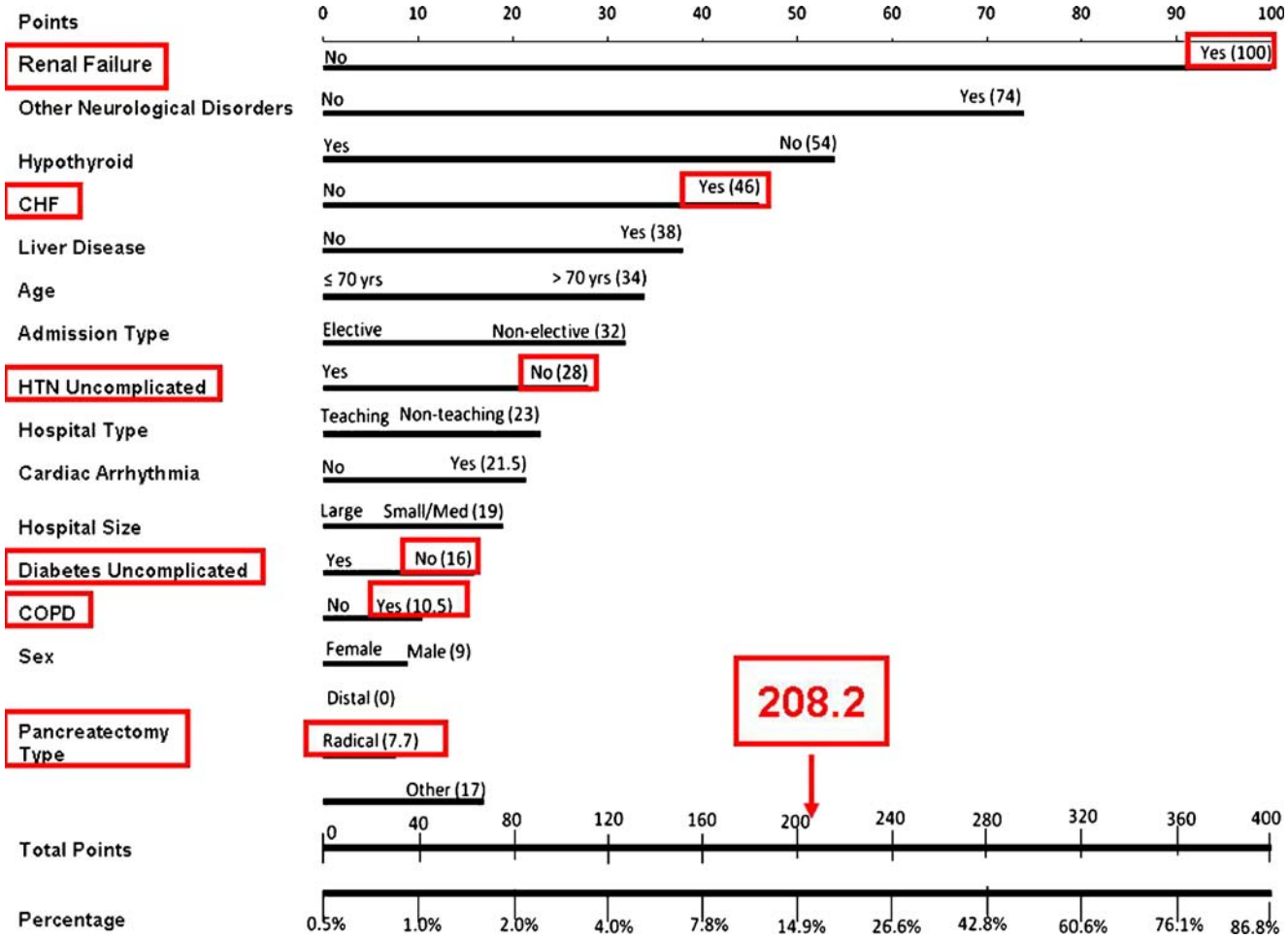


Figure 2 An example of using the nomogram. This 68-year-old female patient seen in our clinic with multiple shown preoperative comorbidities has a total of assigned points of 208.2 that translates to a nomogram-predicted perioperative mortality rate of approximately 18%.

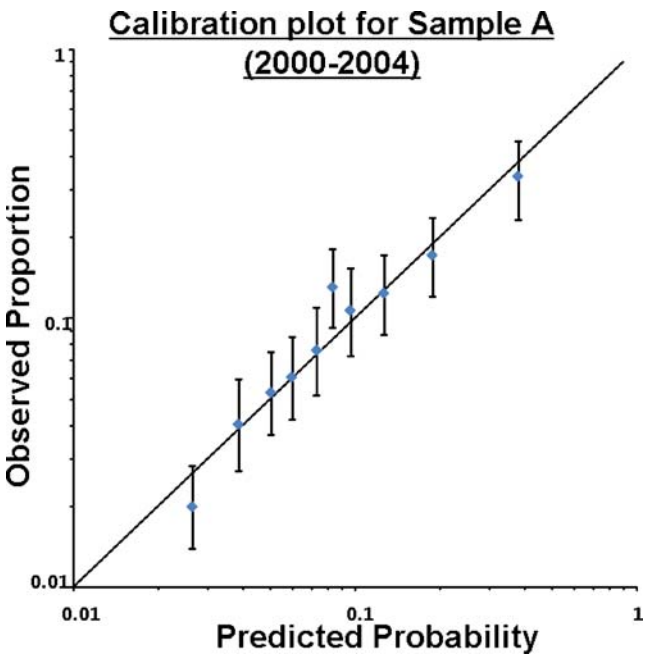


Figure 3 Validation of sample A (2000–2004).

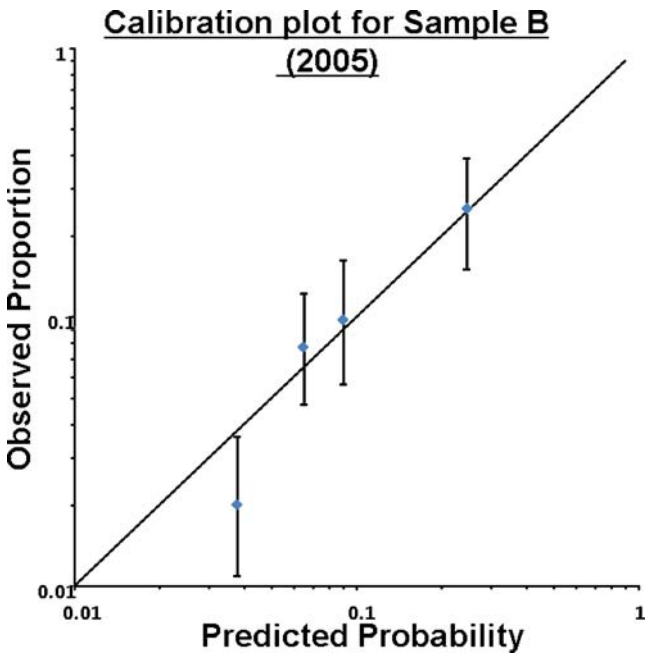


Figure 4 Validation of sample B (2005).

selected variables only based on their practical prognostic values.

There are several limitations to our study. The nomogram does not include some other known risk factors and perioperative variables such as ASA status, serum albumin, coronary artery disease, texture of gland, size of duct, and blood loss. Although these other variables are important determinants of outcome, some of this perioperative information is only available after the patient has already consented for the procedure. Similarly, the addition of more variables may increase the complexity and limit the universal applicability. The limitations of the utilized data source (NIS) allowed us to use the preoperative comorbidities as categorical variables rather than continuous variables. It is likely that a nomogram that incorporates them as continuous variables may be more beneficial. The purpose of this study was to develop a nomogram by using variables that are widely and easily available in the preoperative setting. This nomogram is not intended to substitute for experience of the surgeon or to replace the established process of obtaining an informed and shared consent. It is hoped that this nomogram will play an additional role in counseling these high-risk patients prior to surgery. The simplicity of using this nomogram in the preoperative clinic setting makes it easy for the individual patient to understand their individual estimated risk of the proposed procedure. In addition, this may also permit referring physicians without expertise in pancreatic surgery to counsel patients before referring to specialized institutions. The nomogram is currently available for use at the following website- http://www.unmc.edu/publichealth/pancreas_nomogram.html.

Conclusion

In summary, we have developed a preoperative nomogram to predict perioperative mortality following pancreatic resection for malignancy. The nomogram was developed by using variables that are easily and widely available in the preoperative setting. The ease of use of this nomogram will make it an additional tool in the preoperative counseling of these high-risk patients prior to obtaining an informed and shared consent. The value of this nomogram can be confirmed following external validation.

Acknowledgments The authors would like to extend their sincere thanks to Dr. Murray F Brennan for his kind review of the manuscript and valuable suggestions.

References

1. http://www.cancer.org/downloads/STT/Cancer_Statistics_2008.ppt—accessed March 2009.
2. http://www.cancer.org/downloads/STT/2008CAFFfinalsecured.pdf—accessed March 2009.
3. Winter JM, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J, Hodgin MB, Sauter PK, Hruban RH, Riall TS, Schulick RD, Choti MA, Lillemoe KD, Yeo CJ. 1423 pancreaticoduodenectomies for pancreatic cancer: a single-institution experience. J Gastrointest Surg 2006;10:1199–1210.
4. Cameron JL, Riall TS, Coleman J, Belcher KA. One thousand consecutive pancreaticoduodenectomies. Ann Surg 2006;244:10–15.
5. Vin Y, Sima CS, Getrajdman GI, Brown KT, Covey A, Brennan MF, Allen PJ. Management and outcomes of postpancreatectomy fistula, leak and abscess: results of 908 patients resected at a single institution between 2000 and 2005. J Am Coll Surg 2008;207:490–498.
6. McPhee JT, Hill JS, Whalen GF, Zayaruzny M, Litwin DE, Sullivan ME, Anderson FA, Tseng JF. Perioperative mortality for pancreatectomy. A national perspective. Ann Surg 2007;246:246–253.
7. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care 1998;36:8–27.
8. Research Triangle Institute. SUDAAN Language Manual, Release 10.0 Research Triangle Park. 2008.
9. Iasonos A, Schrag D, Raj GV, Panageas KS. How to build and interpret a nomogram for cancer prognosis. J Clin Oncol 2008;26:1364–1370.
10. Brittain E. Probability of coronary heart disease developing. West J Med 1982;136:86–89.
11. Asiyanbola B, Chang D, Gleisner AL, Nathan H, Choti MA, Schulick RD, Pawlik TM. Operative mortality after hepatic resection: are literature-based rates broadly applicable? J Gastrointest Surg 2008;12:842–851.
12. Sohn TA, Yeo CJ, Cameron JL, Lillemoe KD, Talamini MA, Hruban RH, Sauter PK, Coleman J, Ord SE, Grochow LB, Abrams RA, Pitt HA. Should pancreaticoduodenectomy be performed in octogenarians? J Gastrointest Surg 1998;2:207–216.
13. Makary MA, Winter JM, Cameron JL, Campbell KA, Chang D, Cunningham SC, Riall TS, Yeo CJ. Pancreaticoduodenectomy in the very elderly. J Gastrointest Surg 2006;10:347–356.
14. Riall TS, Reddy DM, Nealon WH, Goodwin JS. The effect of age on short-term outcomes after pancreatic resection: a population-based study. Ann Surg 2008;248:459–467.
15. Lieberman MD, Kilburn H, Lindsey M, Brennan MF. Relation of perioperative deaths to hospital volume among patients undergoing pancreatic resection for malignancy. Ann Surg 1995;222:638–645.
16. Fong Y, Gonen M, Rubin D, Radzyner M, Brennan MF. Long term survival is superior after resection for cancers in high-volume centers. Ann Surg 2005;242:540–544.
17. Meguid RA, Ahuja N, Chang DC. What constitutes a "high-volume" hospital for pancreatic resection? J Am Coll Surg 2008;206:622.
18. Riall TS, Nealon WH, Goodwin JS, Townsend CM Jr, Freeman JL. Outcomes following pancreatic resection: variability among high-volume providers. Surgery 2008;144:133–140.
19. Eastham JA, Kattan MW, Scardino PT. Nomograms as predictive models. Semin Urol Oncol 2002;20:108–115.
20. Kattan MW. Comparison of Cox regression with other methods for determining prediction models and nomograms. J Urol 2003;170:S6–S9.
21. Kattan MW, Leung DH, Brennan MF. Postoperative nomogram for 12-year sarcoma-specific death. J Clin Oncol 2002;20:791–796.
22. Kattan MW, Karpeh MS, Mazumdar M, Brennan MF. Postoperative nomogram for disease-specific survival after an R0 resection for gastric carcinoma. J Clin Oncol 2003;21:3647–3650.
23. Brennan MF, Kattan MW, Klimstra D, Conlon K. Prognostic nomogram for patients undergoing resection for adenocarcinoma of the pancreas. Ann Surg 2004;240:293–298.

24. Lin KY, Johns FR, Gibson J, Long M, Drake DB, Moore MM. An outcome study of breast reconstruction: presurgical identification of risk factors for complications. Ann Surg Oncol 2001;8:586–591.
25. Lagarde SM, Reitsma JB, Maris AD, van Berge Henegouwen MI, Busch OR, Obertop H, Zwinderman AH, van Lanschot JJ. Preoperative prediction of the occurrence and severity of complications after esophagectomy for cancer with use of a nomogram. Ann Thorac Surg 2008;85:1938–1946.
26. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361–387.
27. Wong SL, Kattan MW, McMaster KM, Coit DG. A nomogram that predicts the presence of sentinel node metastasis in melanoma with better discrimination than the American Joint Committee on Cancer staging system. Ann Surg Onc 2005;12:282–288.

Discussant

Dr. Keith D. Lillemoe (Indianapolis): I'd like to congratulate you for a great presentation. Your style of presentation and knowledge of the data were great. It was an outstanding job by a medical student.

The authors have constructed a nomogram based upon preoperative risk factors to predict perioperative mortality following pancreatic resection. The product of their efforts has been validated using a second patient sample from the same database. This work seems like a natural extension from prior publications from Memorial Sloan Kettering, the institution where the senior author, Dr. Are did his fellowship. Dr. Brennan and others at Memorial have constructed nomograms to predict the long term survival for many common tumors. The logic behind those nomograms is that they can be used to guide adjuvant therapy for patients at the greatest risk for recurrent disease.

I understand the reasons that you have provided us for this nomogram and how it might be useful, but, again, to bring up the point that was brought up on Saturday at the Pancreas Club, Karl Bilimoria from Northwestern has already demonstrated that we have a problem with people with resectable cancers of the pancreas being denied surgery, or even surgical consultation, because the opinions of either their primary care physicians or other physicians, that they are not surgical candidates.

This nomogram could provide ammunition for non-surgeons to calculate their own predictions of mortality and potentially deny resectable patients the potential for surgery.

Is this really what we want, to take these decisions out of the hands of the surgeons and leave them in the hands of a non-surgeon who can evaluate a nomogram based on a series of risk factors that they can measure but without surgical judgment.

I know databases have limitations, but you're missing a lot of important factors that might contribute to perioperative risk such as serum albumin, ASA class, weight loss, and coronary artery disease. You use size of hospital and teaching hospitals as a surrogate, but these factors do not necessarily reflect hospital volume or surgeon experience in pancreatic surgery. You also could have included Leap Frog criteria.

Finally, imitation is the highest form of flattery. At Saturday's Pancreas Club meeting, Jennifer Tseng and her group presented an almost identical nomogram addressing the same points that you did, only with a different database.

Despite the fact that these are both very nice papers, I predict that I will never use them. Rather, I am going to sit down with the patient, going to look at all their comorbidities, at my own experience, and I am going to look at the tumor, and I am going to put all these points together, make the decision whether to offer the patient an operation. I am not going to make this decision based on a calculated nomogram, but surgical judgment and experience.

I have one final question. After using the nomogram to determine that the lady you described with an 18% mortality, Dr. Are, did you offer her an operation? And if you did, then I can't believe you really are going to ever apply this nomogram.

Discussant

Dr. Sean Mulvihill (University of Utah, Salt Lake City, Utah): I think Dr. Lillemoe was a little hard on you. I think it actually would be useful to have a nomogram that you could use to sit down with a patient and predict mortality.

The problem with your study is that it's not applicable to any individual hospital. So, for instance, in my own hospital, of the last 173 Whipple resections we have done there was one perioperative death, for a mortality rate of 0.7%. But in your inpatient sample, the mortality rate is far higher. So we couldn't use your nomogram except to attribute an average mortality across the country. I think most of us would believe that the average results in the country are unacceptably poor right now.

The other weakness is that the inpatient sample is notoriously inaccurate at describing patient comorbidities. And if one looks, in contrast to your nomogram, at the model that we have previously published from the NSQIP program where the variables are more closely controlled, it's quite different. And so I think your study is useful, but probably not the answer to this problem of prediction of outcome.

Closing discussant

Chantal Afuh: That is a good point. As Dr. Are mentioned, this is not a tool to replace experience. It is something that may be used to help discuss these risks with patients.

One may say to the patient, based on your health status, the comorbidities you have, you may have an increased risk, whether it be slightly increased risk to another patient who does not have these additional health concerns.

There definitely are some institutions that have better outcomes than the national average. It is possible that this is something you may not wish to use at your institution to replace what you all have done, but it may be useful to supplement the conversation you have with the patient so that they can better understand and provide informed consent.

Dr. Carlos Fernandez Del Castillo (Boston, MA): A quick comment as I rise and share Dr. Lillemoe's concern that this study, as well as the one from the University of Massachusetts, could generate nihilism in terms of the applicability of pancreatic resection for patients with pancreatic cancer, and can be used as an argument against surgery.

Currently only 30% of pancreatic resections are done for pancreatic cancer. Many others are done for benign disease, like cystic tumors, where the risk profile could be very different, including a higher risk of fistula, which in turn can be a cause of death. So, I'm not really sure this is really generalizable.

Closing discussant

Chantal Afuh: That is a very good comment as well. The purpose of our nomogram, however, is to be used when patients do have a primary adenocarcinoma.

So this isn't necessarily something that can be applicable at large to different disease conditions of the pancreas or periampullary conditions. It's something to be used in this particular situation, which is perioperative mortality following pancreatectomy for pancreatic malignancy.

J Gastrointest Surg (2009) 13:2163–2169
DOI 10.1007/s11605-009-1046-9

2009 SSAT POSTER PRESENTATION

A Matched Case-Control Study of Preoperative Biliary Drainage in Patients with Pancreatic Adenocarcinoma: Routine Drainage Is Not Justified

James J. Mezhir · Murray F. Brennan · Raymond E. Baser · Michael I. D'Angelica · Yuman Fong · Ronald P. DeMatteo · William R. Jarnagin · Peter J. Allen

Received: 22 June 2009 / Accepted: 4 September 2009 / Published online: 23 September 2009

Abstract
Background Preoperative biliary drainage (PBD) prior to pancreaticoduodenectomy (PD) continues to be routine in many centers despite retrospective and randomized data showing that PBD increases perioperative infectious complications.
Methods Review of a prospectively maintained database identified 340 consecutive patients with pancreatic adenocarcinoma who underwent PD between 2000 and 2005. From this cohort, 94 PBD and 94 nonstented (no-PBD) patients were matched for age, gender, preoperative albumin, and bilirubin levels (PBD group: prestent bilirubin; no-PBD group: preoperative bilirubin).
Results The majority of PBD patients (89%) underwent internal endoscopic biliary drainage. Stent-related complications occurred in 46 patients (23%) and resulted in a significant delay in time to resection. In the matched-pair comparison, there was more operative blood loss in PBD patients, but similar operative times, transfusions, and hospital stay. Bile cultures were positive in 82% of PBD patients versus 7% no PBD. There was a statistically significant increase in infectious complications including wound infections and intra-abdominal abscess in PBD patients, but equal incidence of anastomotic leak.
Conclusions In this case-matched control study, PBD was associated with a stent-related complication rate of 23% and resulted in a twofold increase in postpancreatectomy infectious complications. The routine use of PBD remains unjustified.

Keywords Biliary drainage · Pancreatic cancer · Pancreaticoduodenectomy · Complications

Introduction

Biliary drainage prior to pancreaticoduodenectomy (PD) remains controversial.[1] Proponents advocate routine preoperative biliary drainage (PBD) in an effort to reduce the incidence of hepatic dysfunction and perioperative complications in patients with obstructive jaundice.[2–5] Preoperative biliary drainage was practiced by Allen O. Whipple who reported on the potential value of performing a cholecystogastrostomy 4 weeks prior to pancreatectomy in order to allow for resolution of jaundice.[6]

Despite effective correction of hyperbilirubinemia, the majority of prospective and retrospective studies of PBD have not demonstrated improvement in operative outcomes following this procedure. Several small prospective randomized trials have suggested no benefit to PBD.[7–9] These studies reported no difference in perioperative mortality or complications and revealed the considerable risk associated with drainage procedures.[8] More recently, a meta-analysis of 15 studies including one prospective randomized trial was published.[10] This study demonstrated that PBD patients have a significant increase in wound infections; however, no other significant differences in complications were noted. A recent Cochrane review reported an increase in morbidity and hospital stay in

Presented at the 50th Annual Meeting of the Society for Surgery of the Alimentary Tract, Digestive Diseases Week, June 2, 2009, Chicago, IL.

J. J. Mezhir · M. F. Brennan · M. I. D'Angelica · Y. Fong · R. P. DeMatteo · W. R. Jarnagin · P. J. Allen (✉)
Department of Surgery, Memorial Sloan-Kettering Cancer Center,
1275 York Avenue,
New York, NY 10065, USA
e-mail: allenp@mskcc.org

R. E. Baser
Department of Epidemiology and Biostatistics,
Memorial-Sloan Kettering Cancer Center,
New York, NY, USA

PBD patients and again found no identifiable benefit to preoperative stenting.[11]

Numerous retrospective studies have also demonstrated a significant increase in perioperative complications in patients who undergo PBD. Prior work from this institution demonstrates that PBD is associated with an increase in complications including infectious complications, intra-abdominal abscess, and postoperative death.[12,13] Other centers have also shown a correlation between PBD and operative time and blood loss, positive bile cultures, wound infections, and pancreatic fistulae.[14–19] In addition to perioperative complications, PBD procedures can result in significant complications that can potentially delay operative intervention.[16]

Despite these data, PBD continues to be routine. Proponents of this procedure argue that the majority of prior randomized trials are not currently applicable because they primarily describe external biliary drainage and often included patients undergoing palliative bypass.[7–9] The purpose of the current study was to evaluate the complications associated with PBD and operative outcomes in the presence and absence of PBD in a contemporary population of patients undergoing PD for adenocarcinoma. We utilized a prospective complication database and a matched group of patients. The primary method of PBD was internal drainage.

Patients and Methods

A prospectively maintained database was queried for patients who underwent pancreatic resection for pancreatic adenocarcinoma between January 1, 2000 and December 31, 2005. Data were available for 432 consecutive patients. Patients with lesions in the body or tail (n=79) were not included. Patients who had undergone prior operative biliary bypass or neoadjuvant therapy were also excluded (n=13). Permission to perform this study was obtained from Memorial Sloan-Kettering Cancer Center's Institutional Review Board.

Clinical variables were confirmed by retrospective chart review. Patient variables included age, gender, comorbidities (cardiac or pulmonary disease, diabetes mellitus), and tobacco and alcohol use. Selected laboratory values included prestent bilirubin and preoperative bilirubin and albumin. Details of all preoperative procedures performed including endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), endoscopic ultrasound (EUS), and fine needle aspiration (FNA) were ascertained. Details included the indication for drainage and type of stent placed at the initial and any subsequent procedures. Operative variables included operative time, blood loss, and hospital stay. Peak postoperative international normalized ratio (INR) was obtained as well as requirements for red blood cell or fresh frozen plasma transfusion. Bile was typically sampled when the bile duct was divided and sent for gram stain and culture. Positive cultures were categorized into polymicrobial, gram negative, anaerobic, and containing yeast.

Routine administration of one dose of a second generation cephalosporin prior to skin incision is routine and protocol for PD patients; redosing for prolonged cases occurs at 6 h after skin incision. Patients did not routinely undergo extended lymphadenectomy. Reconstruction was performed almost solely by creation of a pancreaticojejunostomy with duct to mucosa anastomosis. Intraperitoneal drainage was not a standard practice due to the results of a previous prospective randomized trial from our institution failing to demonstrate benefit to routine placement of operative drains.[20]

Postoperative complications were recorded prospectively into the Department of Surgery complication database. This method of complication reporting has been previously validated and is an accurate and reproducible method for reporting postoperative complications.[21,22] All complications were entered by surgical attendings and house staff who were directly involved in patient care. Entries were reviewed at weekly or monthly morbidity and mortality conferences. All events recorded within 90 days after operation were considered to be postoperative complications.

Complications were grouped into infectious, gastrointestinal, and cardiopulmonary. Infectious complications include postoperative fever, wound infection, bacteremia, or intra-abdominal abscess. Gastrointestinal complications include delayed gastric emptying, pancreatic leak or fistula, gastrointestinal bleeding, ileus, and diarrhea. For this study, pancreatic leak or fistula was evaluated as a separate category. Cardiopulmonary complications include any arrhythmia, myocardial infarction, pulmonary embolism, respiratory failure, atelectasis, pleural effusion, and pneumonia. The complication grading system utilized is as follows: grade 1—oral medication and bedside interventions; grade 2—intravenous medications, enteral nutrition, total parenteral nutrition, or blood; grade 3—procedure required including interventional radiology, therapeutic endoscopy, intubation, angiography, or operation; grade 4—residual and lasting disability requiring major rehabilitation or organ resection; grade 5—death.[23]

Statistical Analysis

To perform a matched case-control analysis, 94 patients who had not undergone PBD (no PBD) were matched to 94 patients who had PBD from the data set of 340 patients. Of the 137 no-PBD patients, 43 patients (31%) were excluded due to incomplete data or the failure to find a statistical match in the PBD group based on the predefined matching criteria. Patients

were matched 1:1 by categories of age (≤70, >70), preoperative albumin (≤4, >4), prestent/operative bilirubin (<5.8, 5.8 to 12.9, >12.9), and sex. To control for bilirubin levels, the prestent bilirubin in the PBD group was matched to the preoperative bilirubin in the no-PBD group.

Descriptive statistics were calculated separately for the matched patients by stent group. Differences between the matched groups were evaluated using the Wilcoxon signed-ranks test for continuous variables and the McNemar's chi-square test for paired proportions for categorical variables. All statistical analyses were conducted using SAS software (Version 9.1, SAS Institute). Descriptive statistics were also calculated for the nonmatched sample of 340 patients.

Results

Demographics of 340 Patients

There were 163 males (48%) and the median age was 71 years (range 44–92). The procedures performed prior to PD are presented in Table 1. Preoperative biliary instrumentation was performed in 225 patients (66%); 24 patients had a failed ERCP. Preoperative biliary drainage was performed in 201 of 340 patients (60%) and was accomplished by ERCP in 174 (87%) patients. Additional endoscopic studies included EUS in 85 patients (25%) and FNA for cytology in 94 patients (28%).

The procedural details of 201 PBD patients are listed in Table 2. The most common indication for PBD was obstructive jaundice (97%); seven patients (3%) had cholangitis at the time of stent placement. Of the seven patients with cholangitis, two developed cholangitis after a failed ERCP. Prestent bilirubin was significantly higher than preoperative bilirubin ($p<0.001$). Of note, 26 patients (17%) had serum bilirubin levels ≤5 mg/dL at the time of PBD placement. The majority of patients (89%) had internal stents. There were 344 procedures performed in 201 patients, and 99 patients (50%) had two or more invasive procedures performed prior to PD. A stent-related complication occurred in 46 patients (23%). Cholangitis occurred in 23 patients (11%) following stent placement, and two additional patients had cholangitis with pancreatitis (1%). Stent occlusion resulting in stent replacement was the second most common complication occurring in 17 patients (8%). Pancreatitis ($n=3$) and duodenal perforation ($n=1$), although less common, resulted in significant morbidity requiring prolonged hospitalization and antibiotics.

The median time from stent placement to resection is outlined in Table 3. Twenty-four (17%) of the no-PBD patients had an ERCP procedure without stent placement and went directly to resection typically within 14 days from presentation. The median time to operative intervention in PBD patients without a complication was 25 days. Factors associated with longer time to operation in uncomplicated PBD patients were higher preoperative albumin ($p=0.01$) and older age ($p=0.0004$). Serum bilirubin level and type of stent were not associated with operative delays. As outlined in Table 3, a complication from stent placement significantly delayed operative intervention compared to PBD patients without a complication. Time to surgery was not a significant predictor of infectious complication rates. Of

Table 1 Procedures Performed in 340 Patients Prior to Pancreaticoduodenectomy

Variable	Number of patients (%)
Preoperative biliary instrumentation	225 (66)
ERCP with stent placement	174 (77)
ERCP without stent placement	24 (11)
Primary PTC stent	3 (1)
PTC stent after failed ERCP	24 (11)
Preoperative endoscopic ultrasound	85 (25)
Preoperative fine needle aspiration	94 (28)
During EUS	64 (68)
During ERCP	14 (15)
Percutaneous	10 (11)
Other/unknown	6 (6)

Table 2 Clinical Variables of 201 PBD Patients

Variable	Number of patients (%)
Indication for biliary drainage	
Obstructive jaundice	194 (97%)
Cholangitis	7 (3%)
Median prestent bilirubin (mg/dL)	10.9 (range 0.6–31.2)
Median preoperative bilirubin (mg/dL)	1.6 (range 0.4–29.2)
Type of stent	
Internal	178 (89%)
Plastic stent	171 (96%)
Metal stent	7 (4%)
Internal/external	23 (11%)
Number of procedures per patient	
1 procedure	102 (51%)
2 procedures	66 (33%)
≥3 procedures	33 (16%)
Stent-related complications	46 (23%)
Cholangitis	23 (11%)
Blockage requiring replacement	17 (8%)
Pancreatitis	3 (1%)
Pancreatitis and cholangitis	2 (1%)
Duodenal perforation	1 (1%)

Table 3 Time from Procedure to Operative Intervention

Procedure	Number	Median (range) time to operation (days)	
ERCP without stent placement	20[a]	13.5 (3–56)	<0.001[b]
ERCP or PTC with stent placement	201	27 (4–157)	
Stent placement (no complication)	155	25 (4–157)	
Stent placement (complication)	46	33 (11–137)	

[a] Data available for 20 of 24 patients

[b] Based on a Kruskal–Wallis test comparing time to procedure among ERCP without stent placement (N=20), ERCP or PTC with stent placement and no complication (N=155), and ERCP or PTC with stent placement and complication (N=46)

patients with delays to operation at or below the overall median of 26 days, 22% experienced an infectious complication compared to 29% of patients with delays greater than 26 days (p=NS).

Matched Case-Control Analysis

Characteristics of 188 Matched Patients

There were 188 patients who met criteria for matching (PBD=94, no PBD=94). Characteristics of these patients are shown in Table 4. Groups were similar with regard to comorbid conditions although the PBD group had a trend toward more alcohol use (p=0.068). The median prestent bilirubin in PBD patients was 11.8 mg/dL (range 0.6–31.2). In the PBD group, there were 24 patients (26%) with prestent bilirubin levels ≤5 mg/dL, 22 patients (23%) with levels of 5.1–10 mg/dL, and 48 patients (51%) with levels ≥10.1 mg/dL.

The median preoperative bilirubin in the no-PBD group was significantly higher (11.2 mg/dL, range 0.2–36.6) than the PBD group (2.2 mg/dL, range 0.4–27.4, p<0.001). Preoperative biliary drainage was performed by ERCP with internal stent in the majority of patients (89%). Preoperative EUS and FNA procedures were performed equally between groups. There were 22 patients (23%) who had a stent related complication.

Perioperative Variables in Matched Patients

Median hospital stay was 10 days (range 6–72) for PBD patients and 10 days (range 2–59) for no PBD (p=NS). As shown in Table 5, there was no significant difference between groups in operative time. Mean operative blood loss was higher in PBD patients (964±767 mL) compared to no-PBD patients (733±514 mL, p=0.04). Peak postoperative INR and requirements for red blood cell and fresh frozen plasma transfusion were similar between groups. PBD patients had significantly more positive intraoperative bile cultures (82%) compared to no PBD patients (7%; p< 0.001). Both groups had gram-negative and anaerobic organisms in the majority of the positive cultures. However, among the patients with positive cultures, 80% of PBD patients had polymicrobial growth and 36% had yeast; 40% of the nonstented patients with positive cultures had polymicrobial growth and 0% had yeast grow in their culture.

Postoperative Complications in Matched Patients

Postoperative complications are outlined in Table 6. There was at least one complication in 39 (41%) of the no-PBD patients versus 48 (51%) of the PBD patients (p=NS). Infectious complications occurred in 12 no-PBD patients (13%) compared to 30 (32%) PBD patients (p=0.002). Infectious complications included wound infections and intra-abdominal abscesses. There were significantly more patients in the PBD group with wound infections (20% versus 7%, no PBD, p=0.01) and intra-abdominal abscesses (12% versus 3%, no PBD, p=0.03). Wound infections were either grade 1 or 2 complications and all intra-abdominal abscesses were grade 3 complications. Anastomotic breakdown or fistula did not differ between no-PBD (6%) and PBD (4%) patients (p=NS).

There were five deaths within 30 days of operation among the 188 matched patients (mortality rate=2.7%). The five postoperative deaths occurred in no-PBD patients (5.3% versus 0 in PBD patients, p=0.06). Fatal pulmonary embolism occurred in two patients, myocardial infarction occurred in two patients, and one experienced cardiopulmonary arrest several days after diagnosis of portal vein thrombosis. The preoperative bilirubin was elevated in one of the five patients.

Discussion

In patients undergoing pancreatic resection, multiple previous reports of PBD have not only failed to show a clinical benefit but have also suggested an adverse impact on perioperative outcome and specifically an increase in postoperative infectious complications.[12–15,17–19] Despite these data, PBD continues to be a frequently performed procedure in patients being considered for resection of periampullary malignancy. In the current study, the majority of patients (59%) who underwent PD for pancreatic adenocarcinoma at our institution between 2000 and 2005 underwent PBD during their diagnostic evaluation. The vast majority of patients underwent PBD at referring centers prior to consultation at our institution.

Table 4 Clinical Characteristics and Comorbidities of 188 Matched Patients

Variable	No PBD (*N*=94)	PBD (*N*=94)	*p* value
Age (mean±SD, years)[a]	69±9	68±10	0.33
Gender[a]			
Male	47 (50%)	48 (51%)	0.56
Female	47 (50%)	46 (49%)	
History of cardiac disease			
Yes	23 (26%)	16 (17%)	0.27
No	66 (74%)	76 (83%)	
History of pulmonary disease			
Yes	8 (9%)	5 (5%)	0.56
No	81 (91%)	86 (95%)	
History of diabetes mellitus			
Yes	17 (18%)	13 (14%)	0.43
No	77 (82%)	81 (86%)	
History of tobacco use			
Yes	25 (32%)	19 (23%)	0.20
No	53 (68%)	62 (77%)	
History of alcohol use			
Yes	16 (21%)	27 (33%)	0.07
No	62 (80%)	54 (67%)	
Median prestent bilirubin (mg/dL)	–	11.8 (0.6–31.2)[a]	–
Prestent bilirubin			
≤5 mg/dL	–	24 (26%)	–
5.1–10 mg/dL		22 (23%)	
≥10.1 mg/dL		48 (51%)	
Median preoperative bilirubin (mg/dL)	11.2 (0.2–36.6)[a]	2.2 (0.4–27.4)	<0.001
Median preoperative albumin (mg/dL)[a]	4.0 (2.5–4.8)	3.9 (1.3–4.9)	0.51
Indication for preoperative drainage			
Obstructive jaundice	–	89 (95%)	–
Cholangitis	–	5 (5%)	
Preoperative biliary stent			
ERCP with internal stent	–	83 (89%)	–
PTC with internal/external stent	–	11 (11%)	
Endoscopic ultrasound			
Yes	21 (23%)	24 (26%)	0.60
No	72 (77%)	70 (74%)	
Fine needle aspiration			
Yes	21 (22%)	25 (27%)	0.51
No	73 (78%)	69 (73%)	
Complication from stent placement	–	22 (23%)	–

[a] Groups were matched for these variables

Table 5 Perioperative Variables of Matched Patients

Variable	No PBD (*N*=94)	PBD (*N*=94)	*p* value
Mean operative time (min)	288±78	302±76	0.22
Mean operative blood loss (mL)	733±514	964±767	0.04
Mean peak postoperative INR (mg/dL)	1.24±0.2	1.26±0.2	0.90
Red blood cell transfusion (patients)	48 (51%)	49 (52%)	0.88
Fresh frozen plasma transfusion (patients)	14 (15%)	13 (14%)	0.84
Positive intraoperative bile cultures	5 (7%)	72 (82%)	<0.001

Table 6 Postoperative Complications in Matched Patients

Type of complication	No PBD (N=94)	PBD (N=94)	p value
Any complication	39 (41%)	48 (51%)	0.21
Cardiopulmonary complication	10 (11%)	6 (6%)	0.29
Gastrointestinal complication	7 (7%)	7 (7%)	1.00
Infectious complication	12 (13%)	30 (32%)	0.002
Wound infection	7 (7%)	19 (20%)	0.01
Intra-abdominal abscess	3 (3%)	11 (12%)	0.03
Anastomotic leak or fistula	6 (6%)	4 (4%)	0.53
Death	5 (5%)	0 (0%)	0.06[a]

Patients may have had more than one complication

[a] Due to the lack of events among PBD patients, p value was determined with an exact test calculated using conditional logistic regression analysis

Patients who present with symptomatic hyperbilirubinemia may require PBD prior to resection. Patients with symptoms of cholangitis should undergo expeditious biliary drainage in an effort to prevent sepsis. Patients who present with obstructive jaundice and resultant renal failure, dehydration, coagulopathy, or profound malnutrition should undergo biliary drainage and resuscitation as these life-threatening consequences of severe hyperbilirubinemia must be corrected prior to operative resection. Recalcitrant pruritus is an additional relative indication for PBD when staging and operative intervention cannot be performed in a timely manner. Arterial involvement with tumor such as with a replaced right hepatic artery is another indication for PBD in the jaundiced patient to prevent postoperative hepatic necrosis if the vessel must be sacrificed. Finally, patients with biliary obstruction being considered for neoadjuvant therapy should undergo PBD because the risk of developing the complications noted above during the preoperative therapy is significant.[24]

The majority of patients in the current study, however, underwent PBD in the absence of any of the above indications. In the current study, 97% of the 201 PBD patients were stented for obstructive jaundice during diagnostic workup and only seven patients (3%) had prestent cholangitis. Among the 201 patients who underwent PBD, 17% had a serum bilirubin <5 mg/dL at the time of drainage. None of the patients with bilirubin levels in this range had cholangitis as an indication for PBD.

There was a complication rate of 23% associated with PBD, similar to other reports.[16] When stent-related complications occur, patients frequently require prolonged hospitalization and antibiotics with or without supplemental nutrition. Patients who underwent ERCP without stent placement underwent resection 12 days earlier on average than those who had an uncomplicated procedure. A complication from PBD such as cholangitis, pancreatitis, or stent blockage requiring replacement delayed operation by nearly 3 weeks and often subjected patients to multiple additional invasive procedures.

In a study of 240 patients treated at our institution from 1994 to 1997, 126 patients (53%) had biliary drainage performed, with significant increase in intra-abdominal abscess in patients who had PBD (19%) compared to no PBD (8%).[13] PBD was the only predictive factor for intra-abdominal abscess found in this study. PBD was predictive of postoperative death on univariate analysis. The limitations of this prior study were its retrospective nature, the primary usage of external drainage, and the lack of a specific grading system for complications. Preoperative bilirubin levels were not controlled for or comparable between groups.

Wound infections were primarily managed noninvasively while all intra-abdominal abscesses in matched PBD patients required an invasive drainage procedure either operatively or by interventional radiology. We have previously shown the organisms contained in the infected bile are those found in intra-abdominal abscesses or wound infections.[25] Positive bile cultures secondary to PBD have been linked to infectious complications in other retrospective studies.[18,26,27]

There was a statistical trend toward an increased risk of death in the no PBD patients. Among the five patients who died postoperatively, two had known operative complications at the time of their death; one patient had an anastomotic leak and the other patient died secondary to a portal vein thrombosis. Among matched patients, there was no difference in the rate of these complications. It is difficult to draw firm conclusions regarding the impact of stenting on operative mortality with the small number of events in this study. Furthermore, four of the five patients were not jaundiced preoperatively.

There are several limitations to this study. Patient data were retrospectively collected, and therefore, there is at inherent risk for selection bias. We attempted to control for selection bias by including only patients with pancreatic adenocarcinoma and matching for preoperative factors that would affect the decision to place a preoperative stent (i.e., prestent bilirubin in PBD patients was matched to preoperative bilirubin in patients without PBD). Furthermore, many of the patients were referred from outside institutions, introducing the potential for referral bias into the patient population being studied.

The recent meta-analysis by Velanovich et al. demonstrated a marginal (5%) increase in wound infections in patients with PBD, but failed to show an increase in significant perioper-

ative complications.[10] The study also failed to demonstrate a benefit to PBD. The study is limited by a lack of standardized complication grading systems, heterogeneity of patient populations, and inclusion of patients with external drainage and prior biliary bypass. Herein, we report with a matched controlled study using a prospective complication database that PBD delays operative intervention is associated with a 23% complication rate and increased rates of infectious complications.

We await the results of a large multicenter randomized controlled trial of PBD versus immediate surgery for patients with periampullary tumors and obstructive jaundice.[28] The results of the present study suggest routine PBD will result in a procedure-related complication rate of approximately 20% and an increase in operative infectious complications.

References

1. van der Gaag NA, Kloek JJ, de Castro SM, Busch OR, van Gulik TM, Gouma DJ. Preoperative biliary drainage in patients with obstructive jaundice: history and current status. J Gastrointest Surg 2008;13:814–820.
2. Armstrong CP, Dixon JM, Taylor TV, Davies GC. Surgical experience of deeply jaundiced patients with bile duct obstruction. Br J Surg 1984;71:234–238.
3. Dixon JM, Armstrong CP, Duffy SW, Davies GC. Factors affecting morbidity and mortality after surgery for obstructive jaundice: a review of 373 patients. Gut 1983;24:845–852.
4. Kimmings AN, van Deventer SJ, Obertop H, Rauws EA, Gouma DJ. Inflammatory and immunologic effects of obstructive jaundice: pathogenesis and treatment. J Am Coll Surg 1995;181:567–581.
5. Padillo J, Puente J, Gomez M et al. Improved cardiac function in patients with obstructive jaundice after internal biliary drainage: hemodynamic and hormonal assessment. Ann Surg 2001;234:652–656.
6. Whipple AO, Parsons WB, Mullins CR. Treatment of carcinoma of the ampulla of vater. Ann Surg 1935;102:763–779.
7. Hatfield AR, Tobias R, Terblanche J et al. Preoperative external biliary drainage in obstructive jaundice. A prospective controlled clinical trial. Lancet 1982;2:896–899.
8. McPherson GA, Benjamin IS, Hodgson HJ, Bowley NB, Allison DJ, Blumgart LH. Pre-operative percutaneous transhepatic biliary drainage: the results of a controlled trial. Br J Surg 1984;71:371–375.
9. Pitt HA, Gomes AS, Lois JF, Mann LL, Deutsch LS, Longmire WP Jr. Does preoperative percutaneous biliary drainage reduce operative risk or increase hospital cost? Ann Surg 1985;201:545–553.
10. Velanovich V, Kheibek T, Khan M. Relationship of postoperative complications from preoperative biliary stents after pancreaticoduodenectomy. A new cohort analysis and meta-analysis of modern studies. JOP 2009;10:24–29.
11. Wang Q, Gurusamy KS, Lin H, Xie X, Wang C. Preoperative biliary drainage for obstructive jaundice. Cochrane Database Syst Rev 2008;CD005444.
12. Heslin MJ, Brooks AD, Hochwald SN, Harrison LE, Blumgart LH, Brennan MF. A preoperative biliary stent is associated with increased complications after pancreatoduodenectomy. Arch Surg 1998;133:149–154.
13. Povoski SP, Karpeh MS Jr., Conlon KC, Blumgart LH, Brennan MF. Association of preoperative biliary drainage with postoperative outcome following pancreaticoduodenectomy. Ann Surg 1999;230:131–412.
14. Bhati CS, Kubal C, Sihag PK et al. Effect of preoperative biliary drainage on outcome of classical pancreaticoduodenectomy. World J Gastroenterol 2007;13:1240–1242.
15. Hodul P, Creech S, Pickleman J, Aranha GV. The effect of preoperative biliary stenting on postoperative complications after pancreaticoduodenectomy. Am J Surg 2003;186:420–425.
16. Jagannath P, Dhir V, Shrikhande S, Shah RC, Mullerpatan P, Mohandas KM. Effect of preoperative biliary stenting on immediate outcome after pancreaticoduodenectomy. Br J Surg 2005;92:356–361.
17. Lermite E, Pessaux P, Teyssedou C, Etienne S, Brehant O, Arnaud JP. Effect of preoperative endoscopic biliary drainage on infectious morbidity after pancreatoduodenectomy: a case-control study. Am J Surg 2008;195:442–446.
18. Limongelli P, Pai M, Bansi D et al. Correlation between preoperative biliary drainage, bile duct contamination, and postoperative outcomes for pancreatic surgery. Surgery 2007;142:313–318.
19. Sohn TA, Yeo CJ, Cameron JL, Pitt HA, Lillemoe KD. Do preoperative biliary stents increase postpancreaticoduodenectomy complications? J Gastrointest Surg 2000;4:258–267. discussion 67–68.
20. Conlon KC, Labow D, Leung D et al. Prospective randomized clinical trial of the value of intraperitoneal drainage after pancreatic resection. Ann Surg 2001;234:487–493. discussion 93–94.
21. Grobmyer SR, Pieracci FM, Allen PJ, Brennan MF, Jaques DP. Defining morbidity after pancreaticoduodenectomy: use of a prospective complication grading system. J Am Coll Surg 2007;204:356–364.
22. DeOliveira ML, Winter JM, Schafer M et al. Assessment of complications after pancreatic surgery: a novel grading system applied to 633 patients undergoing pancreaticoduodenectomy. Ann Surg 2006;244:931–937. discussion 7–9.
23. Vin Y, Sima CS, Getrajdman GI et al. Management and outcomes of postpancreatectomy fistula, leak, and abscess: results of 908 patients resected at a single institution between 2000 and 2005. J Am Coll Surg 2008;207:490–498.
24. Pisters PW, Hudec WA, Hess KR et al. Effect of preoperative biliary decompression on pancreaticoduodenectomy-associated morbidity in 300 consecutive patients. Ann Surg 2001;234:47–55.
25. Povoski SP, Karpeh MS Jr., Conlon KC, Blumgart LH, Brennan MF. Preoperative biliary drainage: impact on intraoperative bile cultures and infectious morbidity and mortality after pancreaticoduodenectomy. J Gastrointest Surg 1999;3:496–505.
26. Cortes A, Sauvanet A, Bert F et al. Effect of bile contamination on immediate outcomes after pancreaticoduodenectomy for tumor. J Am Coll Surg 2006;202:93–99.
27. Sudo T, Murakami Y, Uemura K et al. Specific antibiotic prophylaxis based on bile cultures is required to prevent postoperative infectious complications in pancreatoduodenectomy patients who have undergone preoperative biliary drainage. World J Surg 2007;31:2230–2235.
28. van der Gaag NA, de Castro SM, Rauws EA et al. Preoperative biliary drainage for periampullary tumors causing obstructive jaundice; drainage vs. (direct) operation (DROP-trial). BMC Surg 2007;7:3.

J Gastrointest Surg (2009) 13:2170–2175
DOI 10.1007/s11605-009-0991-7

2009 SSAT POSTER PRESENTATION

Surgical Gastrostomy for Pancreatobiliary and Duodenal Access Following Roux en Y Gastric Bypass

Jessica M. Gutierrez · Howard Lederer · Jon C. Krook · Timothy P. Kinney · Martin L. Freeman · Eric H. Jensen

Received: 15 June 2009 / Accepted: 10 August 2009 / Published online: 24 September 2009

Abstract
Background Pancreatobiliary access following Roux-en-Y gastric bypass (RYGBP) is challenging. We reviewed 32 cases of surgical gastrostomy for complex transgastric upper gastrointestinal endoscopy.
Methods Retrospective review of prospectively collected database of patients with history of RYGBP that had surgical gastrostomy for pancreatobiliary and duodenal access at a single institution from 2004–2008. Indication for procedure, surgical findings, successful cannulation, and complications are reported.
Results Thirty patients (25 female), with age ranging from 27 to 72, underwent 32 procedures. The indications to access the gastric remnant were sphincter of Oddi dysfunction (13), pancreatitis (six), common bile duct stone/obstruction (five), cholangitis (three), pancreatic mass evaluation (two), gastrointestinal bleed (two), and cystic duct leak after cholecystectomy (one). Mean operative time was 200 min (98–338) and estimated blood loss (mean) 85 cc (10–500). Laparoscopic gastrostomy was attempted in 28 cases with one conversion to open (3.6%). Four planned open procedures were also performed. All 30 patients underwent successful endoscopy and 28 had an endoscopic retrograde cholangiopancreatography, all with successful cannulation of the pancreatobiliary tree (100%).
Conclusions Surgical gastrostomy is an effective means to gain access to the upper GI tract and pancreatobiliary tree following RYGBP. This technique should be considered when traditional endoscopic approaches are impossible.

Keywords Roux-en-Y · Gastric bypass · Gastrostomy · ERCP · Endosopy

This data was presented in poster form at the 50th annual meeting for surgery of the alimentary tract/ digestive diseases week in Chicago, IL, May 2009.

J. M. Gutierrez · H. Lederer · J. C. Krook · E. H. Jensen
Department of Surgery, Hennepin County Medical Center and University of Minnesota Medical Center, Minneapolis, MN, USA

T. P. Kinney · M. L. Freeman
Department of Gastroenterology, Hennepin County Medical Center and University of Minnesota Medical Center, Minneapolis, MN, USA

E. H. Jensen (✉)
Department of Surgery, University of Minnesota Medical Center, 420 Delaware Street SE, MMC 195, Minneapolis, MN 55455, USA
e-mail: jense893@umn.edu

Background

Roux-en-Y gastric bypass (RYGBP) as a treatment for morbid obesity has increased in popularity in recent years, producing lasting weight loss in appropriately selected patients.[1]

Morbidly obese patients have multiple comorbidities, which make them high-risk surgical candidates. In addition, procedures such as RYGBP may entail specific complications related to the surgery, such as cholelithiasis, choledocholithiasis, stomal ulceration, bleeding ulcers, anastomotic strictures, and difficult pancreatobiliary access.[2–6] Shiffman et al.[6] report up to 50% of patients develop sludge in the gallbladder after RYGBP. Due to this high incidence, some centers advocate the use of ursodiol or cholecytectomy at the time of the bypass. Alterations in biliary physiology and the resulting pathology may increase the need to obtain pancreatobiliary access postoperatively.

Since RYGBP creates bypassed structures, including gastric remnant, duodenum, proximal jejunum, and the pancreatobiliary tree, endoscopic access to these areas for diagnosis and therapy is severely limited. Traditional push enteroscopy allows retrograde access up the afferent limb after RYGB inconsistently, particularly following long limb bypasses as is the case with weight loss procedures. Newer deep enteroscopy systems, such as single balloon enteroscopy, double balloon enteroscopy, and spiral endoscopy, allow consistent endoscopic access to the afferent limb but have limited therapeutic options because of the small caliber working channel and very long length and forward-viewing nature of the endoscopes employed.[7] In addition, push enteroscopy can be technically challenging in similar cases, with a perforation rate as high as 10%.[7–9]

Our aim in this study is to report our experience with surgical access to the upper gastrointestinal tract following RYGBP at a single institution. We present the largest series to date, evaluating 32 cases of surgical gastrostomy for transgastric endoscopic access in patients with a previous RYGBP.

Methods

We performed a retrospective chart review of a prospectively collected database on patients with history of previous RYGBP who had laparoscopic or open gastrostomy for pancreatobiliary and duodenal access at a single institution [Hennepin County Medical Center (HCMC)] between 2004 and 2008. Patient demographics, indications for surgery, operative findings, and short-term outcomes are reported. The study was approved by the institutional review board at HCMC (protocol 08-1804X).

Description of Procedure

The gastrostomy was done either laparoscopic or open depending on surgeon preference with consideration for previous surgical history, etc. In general, the laparoscopic approach was preferred and was used in the majority of our cases. If it was deemed that the patient was likely to require more than one intervention, a gastrostomy tube was left in place following the initial surgical/endoscopic intervention.

Laparoscopic Gastrostomy

We first established a carbon dioxide pneumoperitoneum to a pressure of 12–15 mm using either a veres needle or visiport in the left upper quadrant. Additional ports were placed at the umbilical level, upper midline, and right lateral abdomen (Fig. 1). The port placement may require some variation depending on the patient's anatomy and previous surgeries. Diagnostic laparoscopy is performed in all cases, and any open hernia defects are corrected. The gastric remnant is then dissected, and an appropriate site for gastrostomy is chosen. A small anterior gastrotomy is then made to allow passage of the left upper quadrant 15 mm port directly into the gastric remnant lumen. The anterior gastric wall is then circumferentially tacked to the abdominal wall. Endoscopy is performed through the secure gastric access. In open cases, the endoscope can be passed directly into the lumen of the gastric remnant. Following the completion of the endoscopic intervention, the gastrostomy is either closed or a gastrostomy tube is placed at the site to allow for additional future endoscopies.

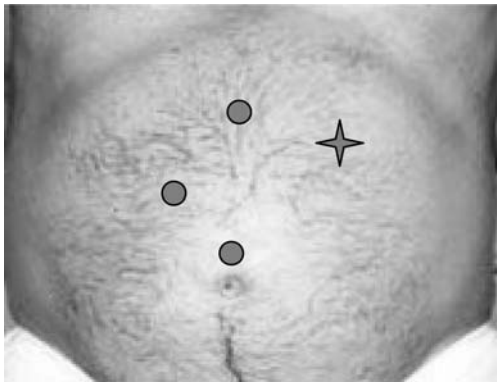


Figure 1 *Star* indicates position of gastrostomy tube.

Results

We identified 30 patients who underwent surgical gastrostomy for upper gastrointestinal endoscopic access between 2004 and 2008. Women made up 83% of the cohort (n=25). Median age was 46, with an age range from 25 to 72. A total of 32 procedures were performed. Two patients had repeat gastrostomy placement after closure of the initial gastrostomy due to recurrence of symptoms and need for repeat endoscopic retrograde cholangiopancreatography (ERCP). Table 1 summarizes demographics, indications, procedures performed, operative findings, and postoperative complications for this group of patients.

The indications for endoscopic intervention were as follows: sphincter of Oddi dysfunction (SOD, n=13), acute pancreatitis (n=6), common bile duct stone/obstruction (n=5), cholangitis (n=3), pancreatic mass evaluation (n=2), upper gastrointestinal bleed (n=2), and cystic duct leak after cholecystectomy (n=1).

For individuals requiring ERCP, mean time from RYGBP to ERCP was 3.4 years (range, 1–10 years). Mean operative time was 200 min (range, 98–338), mean estimated blood loss

Table 1 Summary of Patients with RYGBP that had Gastrostomy for Pancreatobiliary and Duodenal Access

Patient	Age (year)	Gender	Indication	Procedure	Findings	Complications
1	35	F	Cholangitis	Lap gastro, ERCP, Chole	Cholecystitis, no CBD stone	
2	51	F	Pancreatitis	Lap gastro, ERCP	Biliary papillary stenosis	Gastrostomy site infection
3	45	F	SOD	Open gastro	SOD	
4	71	M	CBD Stone	Lap gastro, ERCP	CBD stone	
5	27	M	Pancreatitis	Lap gastro, ERCP	Biliary and pancreatic sphincter dysfunction	
6	52	F	Pancreatitis	Lap gastro, ERCP	Papillary stenosis	
7	31	F	SOD	Lap gastro, ERCP	Peterson's defect, Biliary papillary stenosis, pancreatic sphincter dysfunction	
8	58	F	Pancreatitis	Lap gastro, ERCP	Peterson's defect, Biliary sphincter dysfunction	Converted to open
9	45	F	SOD	Lap gastro, ERCP	Peterson's defect, Pancreatic sphincter dysfunction, Biliary sphincter dysfunction	
10	42	F	SOD	Lap gastro, ERCP	Small bowel mesenteric defect, Biliary sphincter dysfunction	
11	50	F	SOD	Lap gastro, ERCP	Biliary papillary stenosis	
12	37	F	CBD stone	Lap gastro, ERCP, chole	CBD stone	
13	45	F	SOD	Lap gastro, ERCP	Pancreatic sphincter dysfunction	
14	62	F	CBD stone	Open gastro, ERCP	CBD stone	
15	48	F	Pancreatitis	Lap gastro, ERCP	No stones, no abnormalities	
16	44	F	Pancreatic cyst	Lap gastro, EUS	Small pancreatic cyst, ulcer in gastric remnant	
17	30	F	SOD	Lap gastro, ERCP	Biliary sphincter dysfunction	Re-operation (leak after g-tube removal)
18	68	F	Cholangitis	Lap gastro, ERCP	Peterson's defect, No CBD stone	
19	45	F	SOD	Lap gastro x2, ERCP	Biliary and pancreatic sphincter dysfunction	
20	38	F	SOD	Open gastro, ERCP	Small bowel defect, Biliary sphincter dysfunction, Pancreatic duct stricture	Re-operation (pancreatitis)
21	72	F	CBD stone	Lap gastro, ERCP	CBD stone	
22	31	F	SOD	Lap gastro x2, ERCP	Pancreatic duct stricture, Biliary sphincter disfunction	
23	61	M	Cystic duct leak	Open gastro, ERCP	Bile leak	
24	56	F	CBD obstruction	Lap gastro, ERCP	Peterson's defect, Distal biliary obstruction due to pancreatic cancer	
25	37	F	Pancreatic mass	Lap gastro, ERCP, Lap U/S	Small bowel mesenteric defect, Biliary sphincter dysfunction, No pancreatic mass	
26	34	M	SOD	Lap gastro, ERCP	Stenotic pancreatic and biliary orifices	
27	63	F	Cholangitis	Lap gastro, ERCP	Papillary stenosis	
28	31	F	Recurrent GI bleed	Lap gastro, EGD	Petersen's defect, Small bowel mesenteric defect, Jejunal bleed	
29	34	F	Pancreatitis	Lap gastro, ERCP	Small bowel mesenteric defect, transverse colon mesenteric defect, peterson's defect, pancreatic papillary stenosis, pancreatic duct stricture	Re-operation (suspected gastrostomy leak)
30	34	M	GI bleeding	Lap gastro, EGD, Chole	Gastric ulcer, chronic cholelithiasis	

Lap gastro Laparoscopic gastrostomy, *open gastro* open gastrostomy, *SOD* sphincter of Oddi dysfunction, *CBD* common bile duct, *EGD* esophagogastroduodenoscopy, *ERCP* endoscopic retrograde cholangiopancreatography, *EUS* endoscopic ultrasound, *chole* cholecystectomy

was 85 ml (range,10–500). Twenty-eight patients had attempted laparoscopic gastrostomy with one conversion to open (3.6%) due to inability to visualize the gastric remnant. In addition, we performed four planned open procedures, all due to patients with multiple previous open surgeries.

All 30 patients underwent successful endoscopic access; 28 had an ERCP, two patients had an esophagogastroduodenoscopy, and two patients had endoscopic ultrasound (EUS). For cases requiring ERCP, successful cannulation of the pancreatobiliary tree was performed in all cases (100%). In addition to endoscopic access, during surgical exploration, 13 internal hernias were found in ten patients: seven Peterson hernias, five small bowel mesenteric defects, and one transverse mesocolic defect. In all cases, the defects were closed at the time of the gastrostomy. Operative findings are included in Table 1.

Surgical complications occurred in four patients. One patient developed a superficial wound infection at the gastrostomy tube (g-tube) site, which was resolved with antibiotics and no further intervention. Three patients were re-explored. The first was due to peritonitis and suspected intra-abdominal leak, ultimately determined to be pancreatitis secondary to ERCP, with no leak identified. One patient developed free air following removal of the gastrostomy tube (47 days after initial placement) and was found to have an intra-abdominal leak at the gastrostomy site. Our final patient developed significant subcutaneous air following repeat transgastric ERCP (performed 44 days after initial gastrostomy tube placement). The existing gastrostomy was taken down and re-sited due to concern for leak. There were no mortalities in our series.

Discussion

Obtaining access to the duodenum for pancreatobiliary endoscopy and other endoscopic interventions after RYGBP is a difficult problem. Gaining access to the duodenum via a gastrostomy tube for the sole purpose of reaching the papilla was first described in 1998 by Baron and Vickers.[10] Since then, there have been multiple techniques reported to obtain transgastric access.[11–16] Purely endoscopic access to the ampulla after Roux-en-Y bypass can be achieved in some cases using pediatric colonoscopes and/or conventional duodenoscopes. Our group has previously reported a series of 15 patients in which successful ERCP was possible in 67% of cases.[17] Several other techniques have also been described to obtain pancreatobiliary and duodenal access: direct percutaneous transgastric, surgical gastrostomy, percutaneous transhepatic instrumentation of the common bile duct, and surgical transenteric endoscopy.[11,15,18,19]

In the current series, surgical gastrostomy allowed universal success for ERCP at a single step with cannulation and therapy. We did elect to leave gastrostomy tube in 83% of our patients due to possible need of further intervention. Ceppa et al. reported their experience with ten patients in which they had successful endoscopic access to gastric remnant. Five patients required ERCP, and they were successful in four of the five (80%) patients. In one patient, ERCP was unsuccessful due to an impacted stone, which required open common bile duct exploration.[15] They elected to close all their gastrostomies after the procedure.

The indications for intervention described in previous reports are varied. Forty percent of our patients required an ERCP for suspected SOD, 18% due to pancreatitis, these being the most common two indications. This patient population is reflective of referral patterns at our institution for complex ERCP. SOD was suspected in individuals who presented with refractory, recurrent, focal right upper quadrant or epigastric pain in association with elevated pancreatic or hepatic enzymes on at least two separate occasions. For individuals who had an intact gallbladder, ultrasound, and cholecystokinin stimulation hepatobiliary iminodiacetic acid scans were performed. If evidence of stones, sludge, or dyskinesia were identified, laparoscopic cholecystetomy was performed prior to ERCP for SOD. All patients underwent CT scan prior to gastrostomy. The majority also had MRCP to rule out other potential pathology. Our patient selection was based on previous experience with predictors of outcome after biliary and pancreatic sphincterotomy for SOD.[20] In this series, all patients underwent sphincterotomy.

The complexity and high risk of ERCP for suspected SOD, including sphincter of Oddi manometry, placement of a pancreatic stent, and biliary plus often pancreatic sphincterotomy require access to the papilla with a duodenoscope rather than the small caliber forward viewing endoscopes that can be used with deep enteroscopy systems. In addition, such maneuvers are not possible via a percutaneous transhepatic approach. Given these factors, direct endoscopy through the gastric remnant provides optimal access in these cases.

While diagnostic endoscopy of the afferent limb can be performed using deep enteroscopy, one of the two patients undergoing “”EGD also underwent cholecystectomy at the same setting, justifying the laparoscopy over the push enteroscopy approach. In addition, EUS was performed in two patients, which cannot, as of yet, be performed via deep enteroscopy.

In addition to the preoperatively suspected pathology, we found 13 internal hernias in ten patients. This is a known complication of RYGBP that could have contributed to chronic abdominal pain in these patients.[2] These

hernias would have been missed if the gastrostomy would have been placed via CT or US guidance or if deep push enteroscopy had been performed. Internal hernias are more common after laparoscopic than open RYGBP with an incidence between 2.5% and 3%. Higa et al.[21] reported that 40% of cases presented with abdominal pain. We believe therefore that it is crucial to identify and repair them.

In this series, we had a 10% re-exploration rate, with no mortalities. One of our patients had pancreatitis after ERCP. Pancreatitis is a known complication of ERCP. Wang et al.[22] reviewed 2,691 patients undergoing ERCP and found an incidence of pancreatitis in 4.31%. In the setting of morbid obesity, it is still challenging to rule a possible surgical complication in the setting of acute abdominal findings without abdominal exploration.

Complications related to the gastrostomy tube accounted for our other two re-explorations in our series. Both of these occurred in the early half of our experience with this technique. We have tried various methods of securing the gastric remnant to the abdominal wall, including T-tacks and absorbable suture. We currently prefer 2-0 silk suture to ensure a secure gastrostomy, which will stand up to multiple endoscopic interventions if necessary. It is possible that closing the gastrostomy after the first ERCP could have prevented the need for both re-explorations, but due to the high likelihood of repeat ERCP in both patients, a gastrostomy tube was felt to be necessary. Both of our patients had a first attempt at laparoscopic re-exploration; however, for safety reasons, both had to be converted to open. These cases demonstrate a major difficulty facing morbidly obese patients who require invasive procedures. Others have shown that postoperative complications after revisional bariatric surgery either for inadequate weight loss or for complications are higher than primary operation with morbidity rates up to 20%.[23] We continue to recommend initial attempts at laparoscopic re-exploration whenever feasible.

In this report, we present the largest series to date to utilize a surgical gastrostomy as an effective means to gain access to the upper GI tract following RYGBP. The main advantage of this approach for ERCP and other complex upper gastrointestinal endoscopy is the ability to perform ERCP in a single step procedure and to perform complex procedures requiring side viewing duodenoscopes, which are not possible via a deep enteroscopic approach. We had successful ERCP cannulation in 100% of patients, indicating that this approach provides excellent access for pancreatobiliary and proximal gastrointestinal disorders. In addition, we identified additional unsuspected hernias in 33% of our cases. In the absence of significant past surgical history, the laparoscopic approach is feasible and can be performed in the majority of patients.

References

1. Pories WJ. Bariatric surgery: risks and rewards. J Clin Endocrinol Metab 2008;93(11 Suppl 1):S89–S96.
2. Byrne TK. Complications of surgery for obesity. Surg Clin North Am 2001;81(5):1181–1193. vii-viii.
3. Lord RV, Edwards PD, Coleman MJ. Gastric cancer in the bypassed segment after operation for morbid obesity. Aust N Z J Surg 1997;67(8):580–582.
4. Macgregor AM, Pickens NE, Thoburn EK. Perforated peptic ulcer following gastric bypass for obesity. Am Surg 1999;65(3):222–225.
5. Printen KJ, LeFavre J, Alden J. Bleeding from the bypassed stomach following gastric bypass. Surg Gynecol Obstet 1983;156(1):65–66.
6. Shiffman ML, Sugerman HJ, Kellum JH, Brewer WH, Moore EW. Gallstones in patients with morbid obesity. Relationship to body weight, weight loss and gallbladder bile cholesterol solubility. Int J Obes Relat Metab Disord 1993;17(3):153–158.
7. Koornstra JJ. Double balloon enteroscopy for endoscopic retrograde cholangiopancreaticography after Roux-en-Y reconstruction: case series and review of the literature. Neth J Med 2008;66(7):275–279.
8. Cicek B, Parlak E, Disibeyaz S, Koksal AS, Sahin B. Endoscopic retrograde cholangiopancreatography in patients with Billroth II gastroenterostomy. J Gastroenterol Hepatol 2007;22(8):1210–1213.
9. Faylona JM, Qadir A, Chan AC, Lau JY, Chung SC. Small-bowel perforations related to endoscopic retrograde cholangiopancreatography (ERCP) in patients with Billroth II gastrectomy. Endoscopy 1999;31(7):546–549.
10. Baron TH, Vickers SM. Surgical gastrostomy placement as access for diagnostic and therapeutic ERCP. Gastrointest Endosc 1998;48(6):640–641.
11. Stein EG, Cynamon J, Katzman MJ, Goodman E, Rozenblit A, Wolf EL, Jagust MB. Percutaneous gastrostomy of the excluded gastric segment after Roux-en-Y gastric bypass surgery. J Vasc Interv Radiol 2007;18(7):914–919.
12. Pimentel RR, Mehran A, Szomstein S, Rosenthal R. Laparoscopy-assisted transgastrostomy ERCP after bariatric surgery: case report of a novel approach. Gastrointest Endosc 2004;59(2):325–328.
13. Goitein D, Gagne DJ, Papasavas PK, McLean G, Foster RG, Beasley HS, Caushaj PF. Percutaneous computed tomography-guided gastric remnant access after laparoscopic Roux-en-Y gastric bypass. Surg Obes Relat Dis 2006;2(6):651–655.
14. Mori A, Ohashi N, Maruyama T, Tatebe H, Sakai K, Inoue H, Takegoshi S, Okuno M. Endoscopic retrograde cholangiopancreatography through a gastric stoma using an ultrathin endoscope: a novel approach. Endoscopy 2007;39(Suppl 1):E323.
15. Ceppa FA, Gagne DJ, Papasavas PK, Caushaj PF. Laparoscopic transgastric endoscopy after Roux-en-Y gastric bypass. Surg Obes Relat Dis 2007;3(1):21–24.
16. Martinez J, Guerrero L, Byers P, Lopez P, Scagnelli T, Azuaje R, Dunkin B. Endoscopic retrograde cholangiopancreatography and gastroduodenoscopy after Roux-en-Y gastric bypass. Surg Endosc 2006;20(10):1548–1550.
17. Wright BE, Cass OW, Freeman ML. ERCP in patients with long-limb Roux-en-Y gastrojejunostomy and intact papilla. Gastrointest Endosc 2002;56(2):225–232.
18. Ahmed AR, Husain S, Saad N, Patel NC, Waldman DL, O'Malley W. Accessing the common bile duct after Roux-en-Y gastric bypass. Surg Obes Relat Dis 2007;3(6):640–643.
19. Mergener K, Kozarek RA, Traverso LW. Intraoperative transjejunal ERCP: case reports. Gastrointest Endosc 2003;58(3):461–463.

20. Freeman ML, Gill M, Overby C, Cen YY. Predictors of outcomes after biliary and pancreatic sphincterotomy for sphincter of Oddi dysfunction. J Clin Gastroenterol 2007;41 (1):94–102.
21. Higa KD, Ho T, Boone KB. Internal hernias after laparoscopic Roux-en-Y gastric bypass: incidence, treatment and prevention. Obes Surg 2003;13(3):350–354.
22. Wang P, Li ZS, Liu F, Ren X, Lu NH, Fan ZN, Huang Q, Zhang X, He LP, Sun WS, Zhao Q, Shi RH, Tian ZB, Li YQ, Li W, Zhi FC. Risk factors for ERCP-related complications: a prospective multicenter study. Am J Gastroenterol 2009;104(1):31–40.
23. Calmes JM, Giusti V, Suter M. Reoperative laparoscopic Roux-en-Y gastric bypass: an experience with 49 cases. Obes Surg 2005;15(3):316–322.

J Gastrointest Surg (2009) 13:2176–2182
DOI 10.1007/s11605-009-1043-z

2009 SSAT QUICK SHOT PRESENTATION

Murine Functional Liver Mass is Reduced Following Partial Small Bowel Resection

Zhaohua Qiu · Shannon W. Longshore · Brad W. Warner · David A. Rudnick

Received: 28 May 2009 / Accepted: 4 September 2009 / Published online: 23 September 2009

Abstract
Introduction Liver mass is regulated in precise proportion to body mass in health and is restored by regeneration following acute injury. Despite extensive experimental analyses, the mechanisms involved in this regulation have not been fully elucidated. Previous investigations suggest that signals from the bowel may play an important role. The purpose of the studies reported here was to determine the effect of proximal partial small bowel resection on liver mass in a murine model.
Methods Mice were subjected to a 50% proximal small bowel resection or sham surgery followed by primary anastomosis, then sacrificed at serial times for determination of liver:body mass ratio and analyses of liver tissue.
Results Liver:body weight ratio was significantly decreased 72 h after small bowel resection, and this decrease correlated with reduced functional liver mass as assessed by determination of total hepatic tissue protein and alanine transaminase (ALT) activity. Liver from bowel-resected animals demonstrated increased expression of LC3-II, a marker of autophagy, and also of pro-apoptotic Bax compared to anti-apoptotic Bcl-2.
Conclusion These data support a role for signals from the intestine in liver mass regulation, and they have potential implications regarding the pathogenesis of liver injury following small bowel resection.

Zhaohua Qiu and Shannon W. Longshore contributed equally to this work.

These studies were supported by grants from National Institutes of Health (RO1 DK52712 (DAR), DK53234 (BWW); T32-54294C (SWL)) and CDHNF/TAP (DAR), and by the Digestive Disease Research Core Center at Washington University School of Medicine (P30DK052574).

Presented at 2009 SSAT Annual Meeting, June 3, 2009, Chicago, IL

Z. Qiu · D. A. Rudnick
Department of Pediatrics,
Washington University School of Medicine,
St. Louis, MO, USA

D. A. Rudnick
Department of Developmental Biology,
Washington University School of Medicine,
St. Louis, MO, USA

S. W. Longshore · B. W. Warner
Department of Surgery,
Washington University School of Medicine,
St. Louis, MO, USA

S. W. Longshore
Department of Surgery, University of California,
Davis Medical Center,
Sacramento, CA, USA

D. A. Rudnick (✉)
Department of Pediatrics,
Developmental Biology Unit,
Washington University School of Medicine,
660 S Euclid Avenue, Box 8208, St. Louis, MO 63110, USA
e-mail: rudnick_d@kids.wustl.edu

Keywords Liver regeneration · Small bowel resection · Autophagy · Apoptosis

Introduction

Liver mass is regulated in precise proportion to body mass in health, and this ratio (liver:body weight) is specifically restored by regeneration following acute injury.[1,2] Although extensive analyses have been conducted investigating the mechanisms that regulate liver mass and regeneration, the precise nature of the signals involved has not yet been fully elucidated. We hypothesize that signals derived from the intestine and delivered via the portal circulation contribute to the regulation of liver:body mass. This possibility has previously been suggested. For example, in a prior study from our group, we demonstrated that resection of the proximal 50% of the small intestine was associated with significantly decreased total liver weight.[3] Furthermore, the role of the small intestine in regulating recovery of liver mass after injury, i.e. regeneration, has also been investigated with some studies suggesting that the intestinal tract is the source of a humoral factor essential for normal hepatic regeneration after partial hepatectomy,[4,5] and others indicating that the small intestine may not be required for this regenerative response.[6,7] Finally, recent analyses demonstrating the farnesoid X receptor (FXR)-dependent effects of enterally absorbed bile acids on regulation of liver mass and recovery from injury [8] provide additional support for the role of the small intestine in liver mass regulation. Based on our hypothesis and these data, in the studies reported here we used a mouse experimental model of partial small bowel resection (SBR) to more carefully elucidate the temporal pattern of change in the liver:body mass ratio and investigate the molecular signaling events associated with such change.

Materials and Methods

Animal Husbandry and Surgery Male, 7–9-week old, 20–30 g C57Bl/6J mice (Jackson Laboratory, Bar Harbor, ME, USA) were maintained on 12 h dark–light cycles with ad libitum access to standard rodent chow and water, allowed to acclimate to their new environment for at least 7 days prior to surgery, and placed on a preoperative complete liquid diet (Micro-stabilized Rodent Liquid Diet LD101; Purina Mills, St. Louis, MO, USA) 1 day prior to surgery. Proximal partial small bowel resection or sham surgeries were performed as previously described.[3,9] Briefly, SBR was performed by transecting the small bowel in two places, 12 cm proximal to the cecum and immediately distal to the duodenum, and removing the ~12 cm of intervening small bowel (jejunum). Intestinal continuity was subsequently restored with an end-to-end, single-layered, interrupted jejuno-ileal anastomosis using 9–0 monofilament suture. A sham operation was performed by a simple transection of the bowel 12 cm proximal to the cecum and immediately restoring intestinal continuity with a similar anastomosis. After the operation, animals received only water for the first 24 h, followed by the complete liquid diet until sacrifice. Some mice were individually housed to permit quantification of post-operative intake of the liquid diet. Animals were sacrificed at serial times including 1, 2, 3, and 7 days after surgery. At the time of sacrifice, which was by subcutaneous injection of ketamine:xylazine:acepromazine (4:1:1) followed by cervical dislocation, the liver was rapidly removed and weighed, and the left lobe was sectioned with one portion placed in formalin for histology and other portions snap frozen in liquid nitrogen and saved at −80 C for subsequent analysis. In a separate series of experiments, mice were subjected to distal SBR by transecting the small bowel 12 cm proximal to the cecum and at the ileo-cecal junction, removing ~12 cm of intervening distal small bowel (ileum), and performing a primary jejuno-colonic anastomosis. Three to ten animals were examined at each time point in each surgical group. Animals that appeared ill (pilorection, lethargy) or obstructed (dilated bowel proximal to the anastomosis) at the time of sacrifice and tissue harvest (three out of 54 animals) were excluded from further analysis. No animals died prior to sacrifice. All experiments were approved by the Animal Studies Committee of Washington University and conducted in accordance with institutional guidelines and the criteria outlined in the "Guide for Care and Use of Laboratory Animals" (NIH publication 86–23).

Total Hepatic Protein and Transaminase Activity Determination Whole tissue lysates were made from snap frozen liver as previously described.[10–13] Protein determination was performed on lysates using the BCA Protein Assay Kit (Thermo Scientific, Rockford, IL, USA) and the results used to quantify total protein content in harvested liver. Alanine (ALT) and aspartate (AST) transaminase activity in the liver lysate were determined by the St. Louis Children's Hospital Clinical Laboratory and the results used to quantify total activity of each transaminase in harvested liver.

Histology, Immunohistochemistry, and Cell Size Measurements Formalin-fixed, paraffin-embedded liver tissue was stained with hematoxylin and eosin. MicroSuite Five Biological Suite (Olympus, Center Valley, PA, USA) was used to quantify hepatocyte cross-sectional area by examination of six different images from each liver, which were obtained with a Nikon Eclipse 80i microscope using a video-assisted computer program (Metamorph, UIC, Dowington, PA, USA). TUNEL staining was performed by the Digestive Disease Research

Center Histology Core using the ApopTag Peroxidase In Situ Apoptosis Detection Kit (Chemicon International/Millipore, Billerica, MA, USA).

Protein Expression Analysis Forty micrograms aliquots of protein lysate, made as previously described,[10–13] were subjected to sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), followed by electrophoretic transfer to nitrocellulose. Filters were probed with primary antibody (LC3B, Bax, Bcl-2, Caspases 3, 9, 12, PARP, Cell Signaling Technology, Danvers, MA, USA) followed by either a horseradish peroxidase- or fluorophore-conjugated secondary antibody, and then developed using ECL (Amersham, Piscataway, NJ, USA) or the Odyssey Infra-Red Imaging System (LI-COR BioSciences, Lincoln, NE, USA). Densitometric analysis was performed with Scion Image data analysis software (Scion Corporation, Frederick, MD, USA) or with Odyssey System software.

Gene Expression Analysis Total RNA was analyzed for expression of specific genes of interest using real-time reverse-transcriptase polymerase chain reaction with standardization to the expression of β2-microglobulin as described previously.[14] Target-specific forward and reverse primers, from Primer Bank (http://pga.mgh.harvard.edu/primerbank) or published literature,[15] include: Bax, forward: 5'-GCT AGC AAA CTG GTG CTC AA-3', reverse: 5'-TCT TGG ATC CAG ACA AGC AG-3'; Bcl-2 forward: 5'-GTC ACA GAG GGG CTA CGA GT-3', reverse: 5'-TCA GGC TGG AAG GAG AAG AT-3'; XIAP, forward: 5'-CGA GCT GGG TTT CTT TAT ACC G-3', reverse: 5'-GCA ATT TGG GGA TAT TCT CCT GT-3'; cIAP1, forward: 5'-TGT GGC CTG ATG TTG GAT AAC-3', reverse: 5'-GGT GAC GAA TGT GCA AAT CTA CT-3'; cIAP2, forward: 5'-ACG CAG CAA TCG TGC ATT TTG-3', reverse: 5'-CCT ATA ACG AGG TCA CTG ACG G-3'; survivin, forward: 5'-GAG GCT GGC TTC ATC CAC TG-3', reverse: 5'-CTT TTT GCT TGT TGT TGG TCT CC-3'; BRUCE, forward: 5'-CGC GGG ACC ATC AAA GTC AT-3', reverse: 5'-GCA GTG TCT AGC AAC AAG ATC C-3'.

Statistical Analyses Data were analyzed using SigmaStat software (SPSS, Chicago, IL, USA). Unpaired Student's *t* test for pair-wise comparisons was used to compare liver:body mass, dietary intake, cell size, and mRNA and protein expression levels between experimental groups, with significance (alpha) set at 0.05. Data are reported as mean+ standard error.

Results

Functional Liver Mass is Reduced after Proximal and Distal Partial Small Bowel Resection

We have previously reported that liver size is reduced in a murine model of partial small bowel resection (SBR) in which the proximal 50% of mouse small intestine is

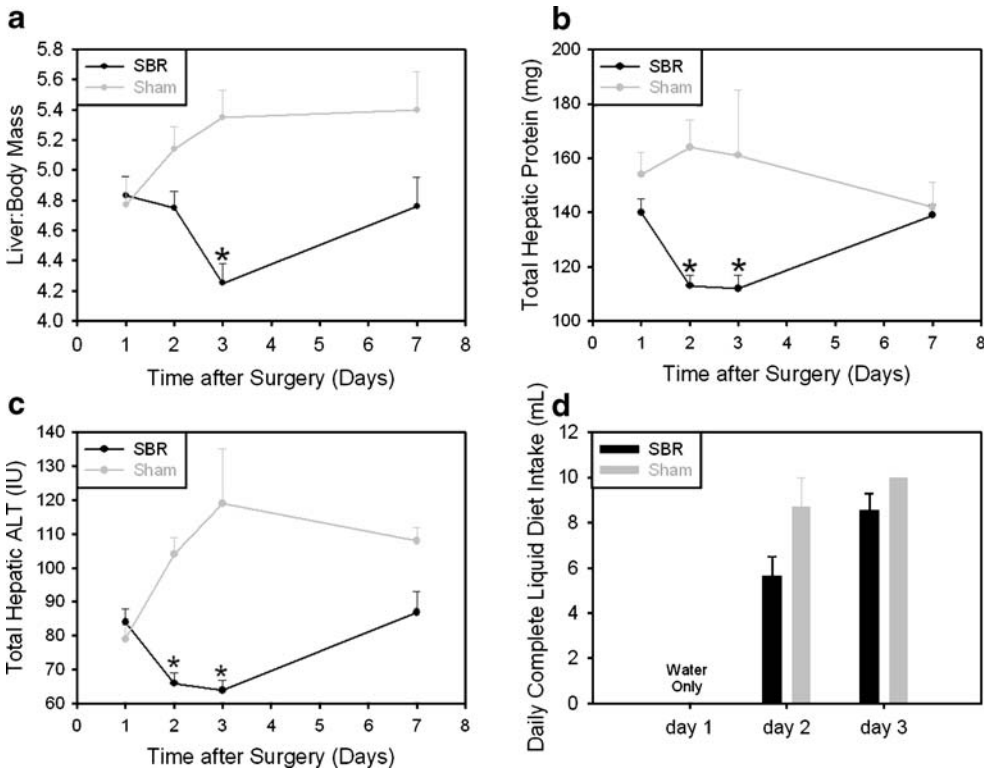


Figure 1 Change in liver:body mass after small bowel resection. **a** Liver:body mass ratio after proximal and distal small bowel resection (*SBR*) and sham surgery (*$p<0.03$). **b** Total hepatic protein (*$p<0.02$) and **c** total hepatic ALT (*$p<0.003$) after proximal SBR and sham surgery. **d** Daily complete liquid diet intake after proximal SBR or sham surgery (day 2, $p=0.1$; day 3, $p=0.3$).

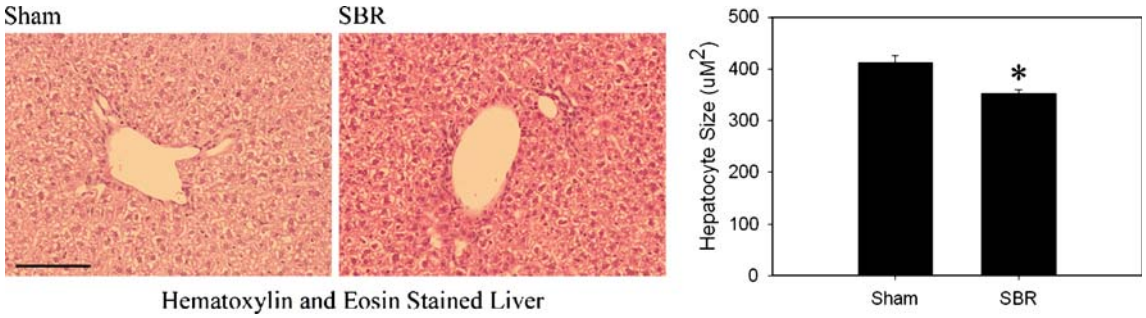


Figure 2 Hepatocyte size after small bowel resection. Hematoxylin and eosin stained sections of mouse liver after sham (*left*) or SBR surgery (*middle*) and summary of hepatocellular cross sectional area measurement (*right*) after proximal SBR and sham surgery (*$p<0.02$). A 100 μm *bar* is shown in lower left corner of left panel.

resected followed by primary anastomosis.[3] Based on this study, we wanted to further characterize the temporal regulation of changes in liver mass after SBR. The results of this analysis showed that liver:body mass is unchanged at 24 h after SBR, then declines significantly reaching a nadir 72 h after surgery, and subsequently recovers to near normal by 7 days (Fig. 1a). In order to determine whether this decreased liver mass represented loss of functional hepatic parenchyma, we quantified total protein and alanine transaminase activity (ALT) content in the hepatic tissue recovered at the serial times after surgery. In each case the results showed a significant decrease following SBR compared to sham-operated animals (Fig. 1b and c), indicating that metabolically active liver mass was reduced specifically in response to intestinal resection. Comparable changes were also seen in total hepatic aspartate transaminase activity (AST) after proximal SBR (data not shown). As in the case of liver:body weight, total tissue protein, and transaminase activity demonstrated recovery by 7 days after intestinal resection. Finally, we investigated the effect of a distal 50% SBR on liver weight. The results showed comparable decline in liver: body mass 72 h after surgery (data not shown), indicating that the influence of SBR on liver mass was not dependent upon the site of bowel resected.

Dietary Intake is not Significantly Reduced in Mice Subjected to SBR Compared to Control Animals In order to address the possible contribution of differences in enteral intake between SBR and sham-operated mice to changes in liver:body mass, a subset of operated animals were individually housed for determination of daily liquid diet intake. The results showed a trend towards modestly reduced complete liquid diet intake in SBR versus sham-operated animals on post-operative day 2, which did not achieve statistical significance ($p=0.1$), and comparable intake between SBR and sham-operated animals on day 3 ($p=0.3$, Fig. 1d).

Hepatocyte Size is Reduced After SBR

Morphometric analysis showed a significant reduction in average hepatocellular cross-sectional area in SBR versus sham-operated animals without any apparent differences in liver histology (Fig. 2), suggesting that at least some of the decrease in liver mass results from decreased hepatocyte size.

LC3-II is Activated in Liver After SBR

Based on the SBR-induced changes in hepatocyte size, we next examined whether autophagic signaling is

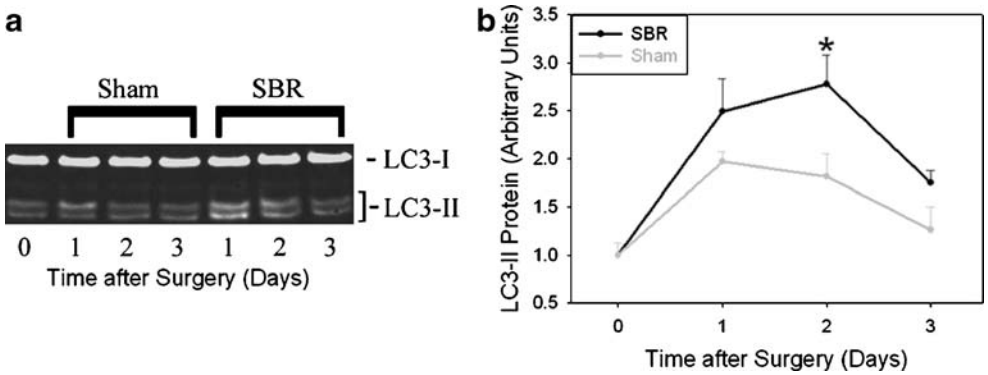


Figure 3 Increased hepatic expression of LC3-II, an autophagic marker, after small bowel resection. **a** Representative protein immunoblot and **b** summary of densitometric analysis showing relative LC3-II expression in liver after proximal SBR and sham surgery (*$p<0.03$).

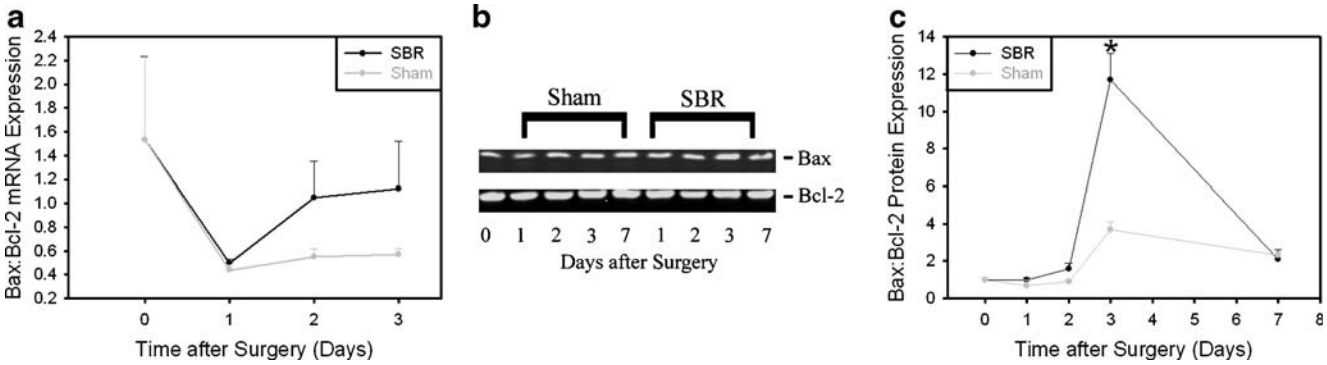


Figure 4 Increased Bax:Bcl-2 expression after small bowel resection. **a** mRNA expression analysis, **b** representative protein immunoblot, and **c** summary of densitometric analysis of protein expression showing relative Bax:Bcl-2 expression in liver after proximal SBR and sham surgery (*$p<0.001$).

activated in livers from mice subjected to partial bowel resection. Autophagy is a process by which eukaryotic cells degrade and remove redundant or defective proteins and organelles.[16,17] This pathway can be stimulated by nutrient deprivation [17] and is a central regulator of cell growth and size.[18] Autophagic activation can be detected by protein immunoblot analysis of LC3, a component of the autophagic machinery that undergoes lipidation during such activation.[19] This modification results in a change in electrophoretic mobility of LC3 on denaturing SDS-PAGE analysis from the slower migrating parent molecule (LC3-I) to the faster migrating modified form (LC3-II). Immunoblot analysis of whole protein lysates of liver recovered at serial times after SBR showed significantly increased levels of LC3-II at 48 h after surgery compared to sham-operated animals (Fig. 3a and b). These data suggest that hepatic autophagy may be activated after resection of the proximal small bowel.

The Ratio of Bax:Bcl-2 Expression is Increased After SBR

Apoptosis represents another mechanism by which organ size can be regulated;[20] therefore, we investigated whether hepatic apoptotic signaling is activated in liver after SBR. First we examined expression of pro-apoptotic Bax and anti-apoptotic Bcl-2 mRNA and protein expression. The results showed a significant increase in the ratio of Bax:Bcl-2 protein expression 72 h after proximal SBR (Fig. 4a–c). Despite this significant change in expression favoring increased apoptosis, we did not observe any corresponding increase in hepatic TUNEL staining, Caspase 3, 9, or 12 activation, or PARP cleavage (data not shown). Together, these observations raise the possibility that apoptotic progression may be inhibited in liver by specific mechanisms after SBR, for example by induction of expression of inhibitor of apoptosis (IAP) family members.[21,22] To address this possibility, we quantified hepatic mRNA expression of several IAPs. The results showed that hepatic expression of the IAPs XIAP, cIAP1, cIAP2, survivin, or BRUCE was not significantly increased after SBR versus sham surgery, though several showed a trend towards increased expression after SBR (Fig. 5).

Discussion

The precision with which the liver:body mass ratio is regulated in health and restored by regeneration after injury has been recognized for thousands of years, as indicated by the legend of Prometheus from ancient Greek mythology,[23] and extensive experimental analyses have been conducted to identify the responsible mechanisms. Nevertheless, the specific signals that regulate liver:body mass with such remarkable fidelity have not been fully elucidated, and further studies are needed before the potential benefits that such understanding might offer towards clinical management of patients with liver diseases are fully realized.

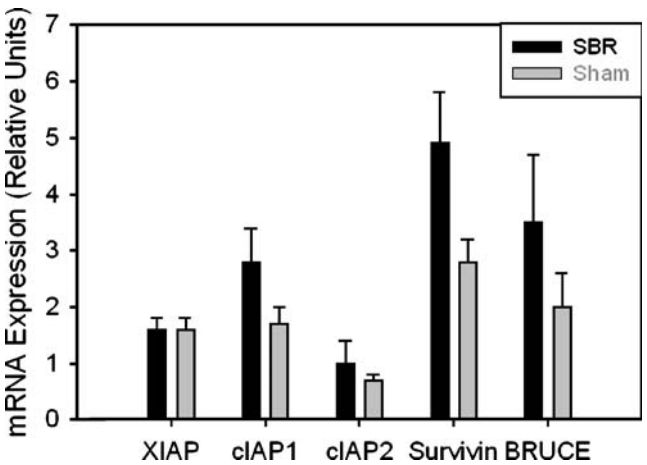


Figure 5 Hepatic mRNA expression of XIAP, cIAP1, and cIAP2, survivin, and BRUCE after small bowel resection. Expression is shown in proportion to expression in liver from unoperated animals.

Several lines of evidence suggest that important signals involved in regulating liver mass may come from the small intestine. For example, some studies have shown that hepatic regeneration is impaired after extensive SBR,[4,5] and we have previously reported that liver mass is decreased after proximal SBR.[3] Based on these observations, the studies reported here were conducted in order to further characterize the changes that occur in liver:body mass after partial small bowel resection, including determination as to whether such changes involve both physical and functional liver mass and identification of candidate mechanistic mediators of this effect. The results showed that following proximal SBR, liver:body mass is significantly decreased with comparably decreased total hepatic tissue protein and transaminase activity, indicating that SBR results in loss of functional, metabolically active liver tissue. A similar decrease in liver:body mass was noted after distal SBR, indicating that the mechanisms responsible for decreased liver mass in this model do not depend on region-specific functions of the small intestine. For example, these mechanisms are not likely to depend on bile-acid-dependent regulation of FXR activity, which has been shown to regulate liver mass [8] but depends primarily on active reabsorption of bile acids in the distal small intestine.[24] Our data also showed that by 7 days after SBR liver:body mass, total hepatic transaminase activity, and total hepatic protein had recovered. This timing of recovery correlates with, and may result from, signals derived from the intestinal adaptive response, whose onset is detectable as early as 24 h after SBR and which plateaus 7 days after such surgery.[25,26]

Our studies also identified a molecular marker of autophagic activation (LC3-II) increased in liver tissue recovered from mice subjected to bowel resection, raising the possibility that autophagy may contribute to loss of liver tissue in this model. Autophagy is an ancient, evolutionarily conserved mechanisms by which eukaryotic cells degrade and remove redundant, senescent, or defective proteins and organelles.[16,17] This pathway has been shown to regulate cell size,[18] which is intriguing in light of our observation that partial bowel resection also results in decreased hepatocellular cross-sectional area. Autophagy is increasingly being studied because of emerging links between its dysregulation and human diseases, including liver diseases. For example α1-antitrypsin deficiency associated liver disease has been associated with increased hepatocellular autophagy.[27] In addition, autophagy has recently been implicated as a candidate mediator of acute liver cell damage in patients with anorexia nervosa.[28] Given the established link between nutritional deprivation and autophagic activation,[17] these data highlight the possibility that, despite comparable post-operative dietary intake in SBR versus sham-operated mice, the bowel resected animals may suffer from some degree of relative nutritional deprivation related to reduced small bowel absorptive capacity. Alternatively, the small bowel may be the source of a non-nutritive signal that regulates autophagy. Based on the data presented here, future studies should investigate the impact of pharmacological or genetic interventions that disrupt autophagy on regulation of liver:body mass after SBR.

Finally, our studies also showed increased hepatic expression of the pro-apoptotic protein Bax in proportion to the anti-apoptotic protein Bcl-2 after partial bowel resection. However, our inability to detect evidence of hepatic activation of downstream markers of apoptotic activation, such as caspase 3 and 9 activation, PARP cleavage, or TUNEL staining raised the possibility that hepatic apoptotic progression may be specifically inhibited in this setting. To address this we investigated hepatic mRNA expression of several IAP family members. None of these was identified as significantly up-regulated after SBR. It is intriguing to note that hepatocellular apoptosis was not identified in anorexia nervosa patients with acute liver injury.[28] Nevertheless, the functional role that apoptosis plays in the changes that occur in functional liver mass after small bowel resection remains to be further defined, and future analyses investigating the effects of genetic or pharmacological disruption of apoptotic pathways on changes in liver mass after SBR may provide additional insight.

Conclusion

The data presented here define the temporal pattern of change in functional liver mass after SBR in an experimental mouse model, and identify autophagy and, perhaps, apoptosis as candidate mediators of this effect. These data raise the interesting possibility that similar signaling events may effect hepatic mass and function after partial bowel resection in human patients, which could contribute to liver dysfunction after extensive small bowel resection, for example in neonates with necrotizing enterocolitis.

Acknowledgements The authors thank Dr. Dennis Dietzen for his assistance with transaminase activity determinations on mouse liver lysates.

References

1. Michalopoulos GK, DeFrances MC. Liver regeneration. Science 1997;276:60–66.
2. Michalopoulos GK. Liver regeneration. J Cell Physiol 2007;213:286–300.
3. Nelson LA, O'Brien DP, Kemp CJ, Williams JL, Dunke-Jacobs E, Erwin CR, Warner BW. Intestinal and hepatic response to

combined partial hepatectomy and small bowel resection in mice. Am J Surg 2002;183:435–440.
4. Fisher B, Szuch P, Levine M, Fisher ER. A portal blood factor as the humoral agent in liver regeneration. Science 1971;171:575–577.
5. Fisher B, Szuch P, Levine M, Saffer E, Fisher ER. The intestine as a source of a portal blood factor responsible for liver regeneration. Surg Gynecol Obstet 1973;137:210–214.
6. Bucher NL, Swaffield MN. Regeneration of liver in rats in the absence of portal splanchnic organs and a portal blood supply. Cancer Res 1973;33:3189–3194.
7. Poirier RA, Cahow CE. Role of the small intestine in liver regeneration. Am Surg 1974;40:555–557.
8. Huang W, Ma K, Zhang J, Qatanani M, Cuvillier J, Liu J, Dong B, Huang X, Moore DD. Nuclear receptor-dependent bile acid signaling is required for normal liver regeneration. Science 2006;312:233–236.
9. Helmrath MA, Erwin CR, Warner BW. A defective EGF-receptor in waved-2 mice attenuates intestinal adaptation. J Surg Res 1997;69:76–80.
10. Rudnick DA, Perlmutter DH, Muglia LJ. Prostaglandins are required for CREB activation and cellular proliferation during liver regeneration. Proc Natl Acad Sci U S A 2001;98:8885–8890.
11. Liao Y, Shikapwashya ON, Shteyer E, Dieckgraefe BK, Hruz PW, Rudnick DA. Delayed hepatocellular mitotic progression and impaired liver regeneration in early growth response-1-deficient mice. J Biol Chem 2004;279:43107–43116.
12. Clark A, Weymann A, Hartman E, Turmelle Y, Carroll M, Thurman JM, Holers VM, Hourcade DE, Rudnick DA. Evidence for non-traditional activation of complement factor C3 during murine liver regeneration. Mol Immunol 2008;45:3125–3132.
13. Turmelle YP, Shikapwashya O, Tu S, Hruz PW, Yan Q, Rudnick DA. Rosiglitazone inhibits mouse liver regeneration. The FASEB Journal 2006;20:2609–2611.
14. Shteyer E, Liao Y, Muglia LJ, Hruz PW, Rudnick DA. Disruption of hepatic adipogenesis is associated with impaired liver regeneration in mice. Hepatology 2004;40:1322–1332.
15. Dziarmaga A, Hueber PA, Iglesias D, Hache N, Jeffs A, Gendron N, Mackenzie A, Eccles M, Goodyer P. Neuronal apoptosis inhibitory protein is expressed in developing kidney and is regulated by PAX2. Am J Physiol Renal Physiol 2006;291: F913–F920.
16. Hussey S, Terebiznik MR, Jones NL. Autophagy: healthy eating and self-digestion for gastroenterologists. J Pediatr Gastroenterol Nutr 2008;46:496–506.
17. Yin XM, Ding WX, Gao W. Autophagy in the liver. Hepatology 2008;47:1773–1785.
18. Vellai T, Bicsak B, Toth ML, Takacs-Vellai K, Kovacs AL. Regulation of cell growth by autophagy. Autophagy 2008;4:507–509.
19. Tanida I, Ueno T, Kominami E. LC3 and autophagy. Methods Mol Biol 2008;445:77–88.
20. Stanger BZ, Tanaka AJ, Melton DA. Organ size is limited by the number of embryonic progenitor cells in the pancreas but not the liver. Nature 2007;445:886–891.
21. Srinivasula SM, Ashwell JD. IAPs: what's in a name? Mol Cell 2008;30:123–135.
22. Schimmer AD. Inhibitor of apoptosis proteins: translating basic knowledge into clinical practice. Cancer Res 2004;64:7183–7190.
23. Rosenthal N. Prometheus's vulture and the stem-cell promise. N Engl J Med 2003;349:267–274.
24. Hofmann AF. The enterohepatic circulation of bile acids in mammals: form and functions. Front Biosci 2009;14:2584–2598.
25. Helmrath MA, VanderKolk WE, Can G, Erwin CR, Warner BW. Intestinal adaptation following massive small bowel resection in the mouse. J Am Coll Surg 1996;183:441–449.
26. Warner BW, Erwin CR. Critical roles for EGF receptor signaling during resection-induced intestinal adaptation. J Pediatr Gastroenterol Nutr 2006;43(Suppl 1):S68–S73.
27. Teckman JH, Perlmutter DH. Retention of mutant alpha(1)-antitrypsin Z in endoplasmic reticulum is associated with an autophagic response. Am J Physiol Gastrointest Liver Physiol 2000;279:G961–G974.
28. Rautou PE, Cazals-Hatem D, Moreau R, Francoz C, Feldmann G, Lebrec D, Ogier-Denis E, Bedossa P, Valla D, Durand F. Acute liver cell damage in patients with anorexia nervosa: a possible role of starvation-induced hepatocyte autophagy. Gastroenterology 2008;135:840–848.

J Gastrointest Surg (2009) 13:2183–2188
DOI 10.1007/s11605-009-1041-1

2009 SSAT QUICK SHOT PRESENTATION

Selective Management of Patients with Acute Biliary Pancreatitis

Dana A. Telem · Kimberly Bowman · John Hwang · Edward H. Chin · Scott Q. Nguyen · Celia M. Divino

Received: 8 July 2009 / Accepted: 2 September 2009 / Published online: 25 September 2009

Abstract
Background Detection of common bile duct (CBD) stones in patients with acute biliary pancreatitis (ABP) proves challenging. We hypothesized that grouping clinically significant predictors would increase reliability of detection.
Methods A retrospective review was performed of 144 consecutive patients who presented to a single tertiary care institution from 2002 to 2007 with ABP.
Results Of the 144 patients, 32 had a persistent CBD stone. Following multivariate analysis, admission CBD size on ultrasound, gamma glutamyl transferase (GGT), alkaline phosphatase (AP), total bilirubin (TB), and direct bilirubin (DB) significantly correlated with persistent CBD stone. Receiver operator curve analysis and linear regression were applied to obtain optimal and equitable predictive values, and variables combined. Optimal values were: CBD≥9 mm; AP≥250 U/l; GGT≥350 U/l; TB≥3 mg/dl; and DB≥2 mg/dl. Presence of five variables had an associated odds ratio (OR) of 53.1 ($p<0.001$) and four variables an OR of 8.97 ($p=0.004$) for presence of persistent CBD stone. Zero variables conferred a significantly decreased probability of CBD stone, OR 0.15 ($p<0.001$). Presence of one to three variables did not predict presence of CBD stone.
Conclusion Presence of four or five variables significantly correlated with persistent CBD stone. Biliary evaluation by endoscopic retrograde cholangiopancreatography is suggested, as initial magnetic resonance cholangiopancreatography (MRCP) may only increase cost and delay time to intervention. In the absence of any variable, biliary evaluation by intraoperative cholangiogram may be sufficient. Decisions regarding patients with one to three variables should occur on a case-to-case basis. Initial biliary evaluation by MRCP is likely preferable, however, as no increased probability of CBD stone was identified, thus not warranting risks associated with intervention.

Keywords Gallstone pancreatitis · Choledocholithiasis · ERCP · MRCP · Laparoscopic cholecystectomy · Common bile duct

Presented as a quickshot at the 2009 annual SSAT meeting.

D. A. Telem · K. Bowman · J. Hwang · E. H. Chin · S. Q. Nguyen · C. M. Divino (✉)
Department of Surgery, Division of General Surgery,
The Mount Sinai Medical Center,
5 E. 98th St. Box 1259, 15th floor,
New York, NY 10029, USA
e-mail: Celia.Divino@mountsinai.org

Introduction

Acute biliary pancreatitis (ABP) accounts for 40% of pancreatitis cases diagnosed worldwide.[1,2] Proposed mechanisms for ABP pathogenesis include reflux of bile into the pancreatic duct or transient obstruction of the ampulla of Vater by biliary sludge or stone.[2,3] The majority of biliary stones pass spontaneously; however, risk of persistent ampullary obstruction increases with advanced patient age and stone size less than 5 mm.[3] Complications of persistent common bile duct (CBD) stone include sepsis, hemorrhage, and necrotizing pancreatitis, and occur with increased frequency when duct obstruction persists greater than

48 h.[3–6] Persistent CBD stones may also increase ABP mortality rate. Autopsy studies demonstrate CBD stones in up to 60% of patients with mortality secondary to ABP.[5]

Detection of persistent CBD stones in patients presenting with ABP remains challenging, as no reliable predictive parameters exist.[7–9] Proper identification of ABP patients with CBD stone is central for selective biliary evaluation, prevention of disease progression, and assistance with perioperative planning.[10–16] The purpose of this study was to increase reliability of CBD stone detection in patients presenting with ABP. We hypothesized that grouping clinically significant predictors, as opposed to individual values, would increase reliability of detection. Identifying the subset of patients with a high probability of persistent stone will facilitate appropriate selection of biliary evaluation modality, potentially decreasing negative imaging and intervention.

Methods

Following approval by the Mount Sinai School of Medicine Institutional Review Board, a retrospective review was performed of 144 consecutive patients with ABP who presented to The Mount Sinai Medical Center from 2002 to 2007. Patients were identified through an administrative database by use of ICD-9 577.0 identification code for acute pancreatitis alone and in conjunction with ICD-9 codes for cholecystectomy (51.2, 51.21, 51.22, 52.23, and 51.24). Clinical diagnosis of ABP was confirmed by elevated pancreatic enzymes and ultrasound findings of cholelithiasis at time of hospital admission. Minors, patients with history of alcohol abuse, known history of pancreatitis secondary to hereditary or medical factors, patients with cholangitis, and patients with history of cholecystectomy were excluded from the study. Standard of care at our institution is performance of cholecystectomy during same hospital admission for ABP when feasible.

Patient demographics, medical, social, and surgical history, and physical exam on admission were assessed. Ranson's score was determined from presentation laboratory values. Hospital course including laboratory values, radiographic studies (ultrasound, computed tomography scan, and magnetic resonance cholangiopancreatography [MRCP]), interventions (endoscopic retrograde cholangiopancreatography [ERCP] and cholecystectomy), pathology report, length of hospital stay, morbidity, and mortality were reviewed. Laboratory values were trended daily from admission to discharge. Decisions regarding preoperative biliary evaluation, choice of ERCP versus MRCP for biliary assessment, and time to laparoscopic cholecystectomy were determined by the individual physician.

Statistical Evaluation

Univariate analysis by unpaired Student *t* test with two-tail distribution was used for quantitative variables and chi-square test for categorical variables. Multivariate logistic regression models were used to estimate odds ratios and an associated 95% confidence interval. Final multivariate models were created by elimination of non-significant variables from univariate analysis. Once significant values were identified, "cut-off" points were determined. Receiver operator curves (ROC) were plotted and linear regression applied to obtain optimum predictive values. Optimum values were determined as data points that provided the most favorable and equitable combination of sensitivity and specificity between variables. Significant variables were grouped and odds ratio with 95% confidence interval calculated for patients based on total variables present on admission. PRISM 2.0 software (San Diego, CA, USA; 2003) was used for all analysis and statistics were reviewed with a statistician.

Results

From 2002 to 2007, 144 patients with ABP qualified for the study. Analysis of initial management demonstrated 69 (48%) patients underwent biliary evaluation, 29 patients by MRCP, and 40 ERCP. All biliary evaluation occurred within 72 h of admission. Of the 29 patients who underwent MRCP, 11 (38%) patients had CBD stone. Of the 11 patients with positive MRCP, 100% had CBD stone on subsequent ERCP. One subsequent ERCP failed secondary to anatomical difficulty and the patient required CBD exploration. Forty patients underwent initial ERCP of which 16 (40%) were positive for CBD stone. All ERCP were successful. Twelve patients underwent sole sphincterotomy, two sole stent placement, two both sphincterotomy and stent placed, and three patients had neither.

Of the 144 patients, 100 (69%) underwent cholecystectomy on same admission. Mean time to cholecystectomy was 7.6 days (range 4–22 days). Sixty-one (61%) patients underwent cholangiogram at time of cholecystectomy, of which five patients had incidental discovery of CBD stone. All five patients did not undergo preoperative biliary evaluation and were successfully managed by postoperative ERCP.

A total of 32 patients (22%) were identified with a CBD stone. Table 1 demonstrates univariate comparison of patients with and without persistent CBD stone. Patients were well matched by age, gender, comorbidity, history of pancreatitis, and severity of ABP as assessed by Ranson's score on presentation. Following univariate analysis of admission variables, multivariate logistic regression models

Table 1 Univariate Analysis of Patients with ABP with and without CBD Stone

Parameter	(+) CBD stone	(−) CBD stone	*p* value
	(*n*=32)	(*n*=112)	
Mean age (years)	58	58	0.84
Gender			
M	15 (47%)	57 (51%)	0.66
F	17 (53%)	54 (49%)	0.66
History of pancreatitis	5 (15%)	18 (16%)	0.94
Symptom duration	(*n*=23)	(*n*=75)	
<24 h	5 (22%)	32 (43%)	0.07
24–48 h	4 (17%)	20 (26%)	0.33
>48 h	14 (61%)	23 (31%)	0.009
Admission ultrasound	(*n*=30)	(*n*=109)	
CBD size (mm)	10.0	6.2	<0.0001
Mean admission values	(*n*=32)	(*n*=112)	
AP (U/l)	315.3	158.9	<0.0001
GGT (U/l)	548.7	320.9	0.031
TB (mg/dl)	4.3	2.2	0.002
DB (mg/dl)	3.2	1.4	0.006
AST (U/l)	222.3	233.5	0.88
ALT (U/l)	229.4	201.4	0.61
LDH (U/l)	350.3	450.2	0.20
Amylase (U/l)	1,057.2	1,079.7	0.64
Lipase (U/l)	12,458.2	13,012.5	0.48
WBC ($\times 10^3/mm^3$)	10.1	10.7	0.51
Admission Ranson's score	(*n*=22)	(*n*=80)	
0–1	16 (73%)	43 (54%)	0.11
2	4 (18%)	24 (30%)	0.27
3	2 (9%)	11 (14%)	0.56
4	0	1 (1%)	0.60
5	0	1 (1%)	0.60

were created by elimination of non-significant univariate variables. Increased CBD size on admission ultrasound (US), increased admission alkaline phosphatase (AP), total bilirubin (TB), direct bilirubin (DB), and gamma glutamyl transferase (GGT) significantly correlated with presence of persistent stone. Significant variables with associated odds ratio (OR) and 95% confidence interval (CI) are presented in Table 2.

Table 2 Significant Variables Following Multivariate Analysis of Significant Univariate Variables

Parameter	OR	95%CI	*p* value
CBD≥10.0 mm	6.6	[2.1–20.71]	0.0014
AP≥315 U/l	22.43	[5.7–88.8]	<0.0001
TB≥4.3 mg/dl	5.7	[1.7–19.7]	0.0025
DB≥3.2 mg/dl	3.2	[1.1–9.0]	0.03
GGT≥548 U/l	4.3	[1.6–12]	0.003

Receiver operator curves were plotted and linear regression applied to determine optimum cut-off values. Optimal values were those that maintained the most equitable and favorable balance of sensitivity and specificity between variables and are demonstrated by Fig. 1 and Table 3. Optimal values were determined as admission ultrasound CBD≥9 mm, AP≥250 U/l, GGT≥350 U/l, TB≥3 mg/dl, and DB≥2 mg/dl. Selected cut-off points had comparable sensitivity and specificity for correlation with CBD stone, which allowed for equal weighting when variables were grouped. Table 4 demonstrates results after variable grouping and application to our patient population. Patients with five clinical variables present on admission had an OR of 53.1 ($p<0.001$) for presence of persistent CBD stone. Patients with any four clinical variables had an OR of 8.97 ($p=0.004$) for presence of CBD stone. No increased correlation with persistent CBD stone was demonstrated in patients with any combination of one to three variables.

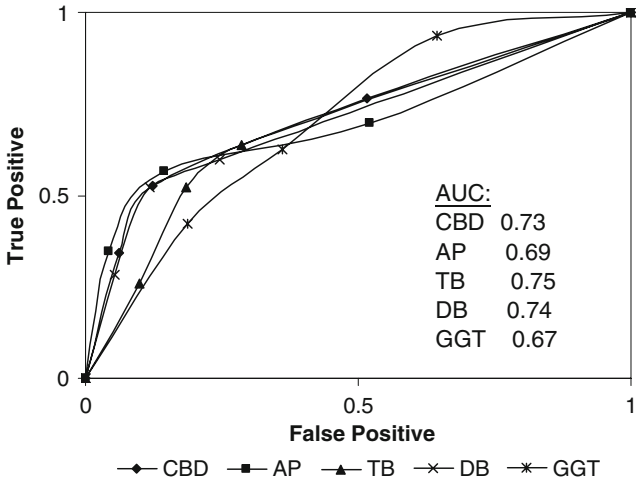


Figure 1 ROC analysis area under the curve (*AUC*) calculation for individual clinical predictors of CBD stone in patients with acute biliary pancreatitis.

Retroactive application of grouped variables to the 69 patients who underwent preoperative biliary evaluation demonstrated 78% of patients with one to three variables had negative biliary evaluation (variables present [negative evaluation]=0 [78%], 1 [71%], 2 [57%], 3 [63%]). For patients with four to five variables, 92% had CBD stone on biliary evaluation.

Discussion

Our study identified five clinical variables on hospital presentation: CBD size on ultrasound, AP, GGT, TB, and DB, which significantly correlated with presence of persistent CBD stone. Several studies have also identified individual clinical parameters that correlate with persistent CBD stone.[7–9,17] Lin et al. identified initial CBD size on ultrasound and AST as significant predictors of CBD stone in patients with ABP.[18] A study by Chang et al. demonstrated TB, ALT, and AP as significant clinical variables, with hospital day 2 TB as the most accurate predictor.[7] Cohen et al. demonstrated rise in any serum chemistry within 24–48 h of hospital admission correlated with a persistent CBD stone in 31% of patients.[8] To date, however, no individual laboratory value or trend has proven to reliably identify ABP patients at high risk of persistent CBD stone. As the majority of CBD stones pass spontaneously within 48 h, it is not surprising that a significant proportion of biliary evaluation in patients with abnormal

Table 3 Determination of Optimal Clinical Values Based on Sensitivity and Specificity with 95% Confidence Interval [CI] of Clinical "Cut-Off" Values

	"Cut-off"	Sensitivity	95% CI	Specificity	95% CI
Admission CBD on ultrasound					
<5 mm	5 mm	0.35	0.26–0.46	0.94	0.88–0.97
5.1–8.9 mm	9 mm	0.49	0.41–0.57	0.87	0.79–0.94
9–11 mm	11 mm	0.77	0.71–0.82	0.49	0.39–0.59
>11 mm					
Admission AP					
<150 U/l	150 U/l	0.36	0.30–0.43	0.96	0.92–0.98
151–250 U/l	250 U/l	0.51	0.47–0.56	0.84	0.78–0.89
251–350 U/l	350 U/l	0.71	0.68–0.74	0.49	0.4–0.56
>351 U/l					
Admission GGT					
<150 U/l	150 U/l	0.42	0.31–0.52	0.82	0.75–0.86
151–350 U/l	350 U/l	0.62	0.57–0.74	0.64	0.59–0.72
351–450 U/l	450 U/l	0.93	0.88–0.96	0.45	0.39–0.42
>451 U/l					
Admission TB					
<2 mg/dl	2 mg/dl	0.27	0.17–0.38	0.9	0.83–0.94
2.1–3 mg/dl	3 mg/dl	0.49	0.39–0.59	0.8	0.75–0.85
3.1–4 mg/dl	4 mg/dl	0.65	0.55–0.73	0.72	0.65–0.77
>4 mg/dl					
Admission DB					
<1 mg/dl	1 mg/dl	0.29	0.21–0.38	0.95	0.91–0.98
1.1–1.9 mg/dl	2 mg/dl	0.47	0.4–0.54	0.87	0.81–0.91
2.0–2.9 mg/dl	3 mg/dl	0.61	0.54–0.67	0.75	0.69–0.82
>3.0 mg/dl					

Table 4 Combined Variables and Associated Positive Predictive Value (PPV), Odds Ratio (OR), and 95% Confidence Interval (CI)

No. of variables	(+) CBD stone (n=32)	(−) CBD stone (n=112)	PPV	OR±95% CI	p value
0	18%	60%	0.09	0.15 [0.04–0.48]	0.0007
1	14%	21%	0.19	0.61 [0.16–2.4]	0.47
2	13%	6%	0.43	2.3 [0.5–11.4]	0.36
3	5%	10%	0.14	0.43 [0.1–6.4]	0.44
4	23%	3%	0.71	8.97 [1.6–50.4]	0.004
5	27%	0%	1.0	53.1 [6.8–581.2]	0.0002

liver function tests result in negative studies. We hypothesized that the combined predictive ability of significant admission clinical variables would be more reliable at identifying patients with persistent, rather than passed, CBD stone.

Based on this hypothesis, cut-off points with comparable sensitivity and specificity were selected to allow variables to be equally weighted and grouped. Assessment of our study population demonstrated that patients with four or five clinical variables were at significantly increased risk for persistent CBD stone. Patients with five variables had an OR of 53.1 ($p<0.001$) with 100% PPV for presence of CBD stone and for those with four variables, a calculated OR of 8.97 ($p=0.004$) with 71% PPV. In addition, 92% of patients with four or five variables on admission who underwent preoperative biliary evaluation were found to have persistent CBD stone. While the retrospective nature of this paper precludes definitive recommendations, this finding strongly supports biliary evaluation by ERCP for patients in whom four or five variables are present, as MRCP may only delay time to intervention. Endoscopic ultrasound (EUS) is recommended prior to ERCP where available. Within the past several years, EUS has emerged as a highly sensitive and specific modality for detection of biliary stones.[19] Studies demonstrate that the use of EUS prior to ERCP decreases negative ERCP rates in up to 75% of patients with ABP.[20,21] Performance of EUS prior to ERCP adds minimal procedural time and precludes performance of unnecessary intervention.[19–21]

Patients in whom any one to three clinical variables were present demonstrated no significantly increased probability of persistent CBD stone. However, when retroactively assessed, 22% of patients were found to have persistent CBD stone on biliary evaluation. While decisions regarding biliary evaluation for this patient subset should occur on a case-to-case basis, preoperative biliary imaging by MRCP is likely preferable with subsequent ERCP in patients with positive imaging. MRCP has a 91% sensitivity and 98% specificity for detection of choledocholithiasis and is advantageous as it is a non-invasive procedure with negligible complication rate.[22,23] MRCP is preferential as many studies will likely be negative, not warranting the 5–10% morbidity rate associated with ERCP.[10,15]

Of note, patients with zero clinical variables were at significantly decreased risk for persistent CBD stone. For this subset of patients, our study suggests biliary evaluation by cholangiogram (IOC) at time of cholecystectomy may be sufficient. Although debated within the literature, at our institution biliary, evaluation with IOC at time of cholecystectomy in patients with ABP remains the standard of care.[9] The authors strongly recommend performance of cholangiogram, in the absence of preoperative biliary imaging, as a means to ensure patients with asymptomatic choledocholithiasis are identified.

The necessity for improved reliability of persistent CBD stone detection in patients with ABP is emphasized by the significant rate of negative MRCP and ERCP reported within literature, varying from 50% to 80% and 40% to 70%, respectively.[8,17,18,21] Our institution is no exception. Sixty-two percent of patients underwent negative MRCP and 60% negative ERCP which is disconcerting as biliary evaluation for ABP patients is not standard and based on physician assessment. This finding further highlights the inaccuracy of current evaluation criteria utilized to identify persistent CBD stones in patients with ABP. Grouping clinical variables may facilitate appropriate selection of initial biliary evaluation in patients presenting with ABP. While future prospective application is necessary, this study identified a combination of clinical variables which significantly correlated with presence of persistent CBD stone. In addition, we identified a subset of patients with a significantly negligible risk. Although methodological limitations preclude conclusive recommendations, this study suggests that evaluation by ERCP for patients with four or five clinical variables and cholangiogram for patients with zero variables is appropriate. For patients presenting with one to three variables, individual assessment is necessary; however, initial evaluation by MRCP, rather than ERCP, appears preferable.

References

1. Riela A, Zinsmeister AR, Melton LJ, DiMagno EP. Etiology, incidence, and survival of acute pancreatitis in Olmsted County, Minnesota. Gastroenterology 1991;100:A296.
2. Frossard JL, Steer ML, Pastor CM. Acute pancreatitis. Lancet 2008;371(9607):143–152.
3. Wilson C, Imrie CW, Carter DC. Fatal acute pancreatitis. Gut 1988;29(6):782–788.
4. Corfield AP, Cooper MJ, Williamson RC. Acute pancreatitis: a lethal disease of increasing incidence. Gut 1985;26(7):724–729.
5. Wilson C, Imrie CW, Carter DC. Fatal acute pancreatitis. Gut 1988;29(6):782–788.
6. Acosta JM, Rubio Galli OM, Rossi R, Chinellato AV, Pellegrini CA. Effect of duration of ampullary biliary obstruction on severity of lesions of acute pancreatitis. J Am Coll Surg 1997;184(5):499–505.
7. Chang L, Lo SK, Stabile BE, Lewis RJ, de Virgilio C. Biliary pancreatitis: a prospective study on the incidence of cholangitis and clinical predictors of retained common bile duct stones. Am J Gastroenterol 1998;93(4):527–531.
8. Cohen ME, Slezak L, Wells CK, Andersen DK, Topazian M. Prediction of bile duct stones and complications in biliary pancreatitis using early laboratory trends. Am J Gastroenterol 2001;96(12):3305–3311.
9. Roston AD, Jacobson IM. Evaluation of the pattern of liver tests and yield of cholangiography in symptomatic choledocholithiasis: a prospective study. Gastrointest Endosc 1997;45(5):394–399.
10. Moretti A, Papi C, Aratari A, Festa V, Tanga M, Koch M, et al. Is early endoscopic retrograde cholangiopancreatography useful in the management of acute biliary pancreatitis? A meta-analysis of randomized controlled trials. Dig Liver Dis 2008;40(5):379–385.
11. Petrov MS, van Santvoort HC, Besselink MG, van der Heijden GJ, van Erpecum KJ, Gooszen HG. Early endoscopic retrograde cholangiopancreatography versus conservative management in acute biliary pancreatitis without cholangitis: a meta-analysis of randomized trials. Ann Surg 2008;247(2):250–257.
12. Diagnosis and treatment of common bile duct stones (CBDS). Results of a consensus development conference. Scientific Committee of the European Association for Endoscopic Surgery (E.A.E.S.). Surg Endosc 1998;12(6):856–864.
13. Vitale GC. Early management of acute biliary pancreatitis. Ann Surg 2007;245(1):18–19.
14. Folsch UR, Nitsche R, Lüdtke R, Hilgers RA, Creutzfeld W. Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis. N Engl J Med 1997;336:237–242.
15. de Virgilio C, Verbin C, Chang L, Linder S, Stabile BE, Klein S. Biliary pancreatitis. The role of preoperative endoscopic retrograde cholangiopancreatography. Arch Surg 1994;129(9):90912.
16. Acosta JM, Katkhouda N, Debian KA, Groshen SG, Tsao-Wei DD, Berne TV. Early ductal decompression versus conservative management for biliary pancreatitis with ampullary obstruction: a prospective randomized clinical trial. Ann Surg 2006;243(1):33–40.
17. Chan T, Yaghoubian A, Rosing D, Lee E, Lewis RJ, Stabile BE, De Virgilio C. Total bilirubin is a useful predictor of persisting common bile duct stone in gallstone pancreatitis. Am Surg 2008;74(10):977–980.
18. Lin G, Halevy A, Girtler O, Gold-Deutch R, Zisman A, Scapa E. The role of endoscopic retrograde cholangiopancreatography in management of patients recovering from acute biliary pancreatitis in the laparoscopic era. Surg Endosc 1997;11(4):371–375.
19. Chak A, Hawes R, Cooper GS, et al. Prospective assessment of the utility of EUS in the evaluation of gallstone pancreatitis. Gastrointest Endosc 1999;49:599–604.
20. Liu CL, Fan ST, Lo CM, et al. Comparison of early endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography in the management of acute biliary pancreatitis: a prospective randomized study. Clin Gastroenterol Hepatol 2005;3:1238–1244.
21. Moon JH, Cho YD, Cha SW, et al. The detection of bile duct stones in suspected biliary pancreatitis: comparison of MRCP, ERCP, and intraductal US. Am J Gastroenterol 2005;100:1051–1057.
22. Varghese JC, Liddell RP, Farrell MA, Murray FE, Osborne H, Lee MJ. The diagnostic accuracy of magnetic resonance cholangiopancreatography and ultrasound compared with direct cholangiography in the detection of choledocholithiasis. Clin Radiol 2000;55(7):579.
23. Mofidi R, Lee AC, Madhavan KK, Garden OJ, Parks RW. The selective use of magnetic resonance cholangiopancreatography in the imaging of the axial biliary tree in patients with acute biliary pancreatitis. Pancreatology 2008;8(1):55–60.

J Gastrointest Surg (2009) 13:2189–2200
DOI 10.1007/s11605-009-1055-8

2009 SSAT QUICK SHOT PRESENTATION

Angiotensin II Regulates the Expression of Monocyte Chemoattractant Protein-1 in Pancreatic Cancer Cells

Navdeep Chehl · Qiaoke Gong · Galina Chipitsyna · Tamer Aziz · Charles J. Yeo · Hwyda A. Arafat

Received: 26 May 2009 / Accepted: 22 September 2009 / Published online: 9 October 2009

Abstract
Introduction Pancreatic ductal adenocarcinoma (PDA) is one of the most lethal cancers with an overall median survival of less than 9 months and a 5-year survival rate of less than 5%. Increasing evidence indicates that inflammation facilitates PDA growth. *Discussion* Angiotensin II (AngII), the principal hormone of the renin–angiotensin system, is actively generated in the pancreas and has been proposed as a key mediator of inflammation. Monocyte chemoattractant protein (MCP)-1 is a chemokine that plays an important role in the recruitment of mononuclear cells into sites of inflammation. In this study, we investigated the potential proinflammatory role of AngII in PDA through studying its effect on MCP-1. AngII significantly increased the expression of MCP-1 mRNA and protein in PDA cells and induced its promoter activity. Constitutive and AngII-induced MCP-1 transcription was inhibited by an AngII type 1 receptor (AT1R) blocker, but was unchanged by an AT2R blocker. AngII activated the phosphorylation of extracellular signal-regulated kinase (ERK)1/2, but not p38 or c-Jun NH2-terminal mitogen-activated protein kinases. Inhibition of ERK1/2 activation reduced the AngII-induced MCP-1 synthesis. AngII induced the activation and nuclear translocation of nuclear factor-κB (NF-κB), an effect that was inhibited by AT1R blockade. Inhibition of NF-κB by pyrrolidine dithiocarbamate decreased the AngII-mediated increase in MCP-1 mRNA. Our data provide a novel insight into an AngII-initiated signal transduction pathway that regulates MCP-1 as a possible inflammatory mechanism in PDA and suggest that AngII blockade may regulate chemokine-induced signal transduction to prevent or reduce inflammation in PDA.

Keywords Pancreatic cancer · Angiotensin II · Inflammation · Monocyte chemoattractant protein-1

Introduction

Pancreatic ductal adenocarcinoma (PDA) is the fourth leading cause of cancer-related death in the USA[1] and is characterized by rapid disease progression, highly invasive tumor phenotype, and resistance to chemotherapy. Patient prognosis is extremely grim, with an overall 1-year survival rate of just 10% and only a 5% chance of surviving beyond 5 years.[2] These facts stress the need to elucidate the mechanisms underlying PDA carcinogenesis and to find new treatments.

An increased incidence of PDA in patients with chronic pancreatitis has been observed,[3–7] and various inflammatory cytokines in chronic pancreatitis have been linked to pancreatic carcinogenesis. Hereditary pancreatitis, which accounts for less than 1% of all cases of pancreatitis, is also associated with increased risk of PDA,[8,9] especially with longer duration of the disease process.[10] In human PDA and in animal models that recapitulate the disease progression, an intense fibroinflammatory reaction composed of mesenchymal fibroblasts and inflammatory cells accompanies the progression from normal histology to

Presented as a quick shot oral presentation at the 50th Annual Meeting of the Society for Surgery of the Alimentary Tract, May 30, 2009–June 04, 2009, Chicago, IL, USA.

N. Chehl · Q. Gong · G. Chipitsyna · T. Aziz · C. J. Yeo · H. A. Arafat (✉)
Department of Surgery, Jefferson Pancreatic, Biliary & Related Cancer Center, Thomas Jefferson University, 1015 Walnut Street, Philadelphia, PA 19107, USA
e-mail: hwyda.arafat@jefferson.edu

PDA.[11–13] Inflammatory cells secrete cytokines and other factors that constitute a tumor microenvironment favoring angiogenesis, anti-apoptosis, cell migration, and metastasis and, thus, potentially contribute to cancer development and progression.[14,15]

Monocyte chemoattractant protein-1 (MCP-1) is a member of the C–C chemokines that accumulate and influence macrophages/monocytes and lymphocytes and has been suggested to be involved in tumor progression and metastasis.[16] The expression of MCP-1 has been reported in several tumor types including human melanoma, ovarian cancer, and esophageal cancer[17–19] and has been shown to be involved in the recruitment of mast cells and survival of pancreatic islet tumors.[20] These observations suggest that MCP-1 produced by cytokine-stimulated tumor cells is involved in the recruitment and activation of stromal immune cells. However, the upstream effector molecules and the signaling cascades involved in its regulation in PDA cells have not been elucidated.

The circulating renin–angiotensin system (RAS) is well known to play important roles in the cardiovascular and renal systems. The RAS cascade contains several key components including the bioactive octapeptide angiotensin II (AngII), as well as multiple G-protein-coupled receptor subtypes including AngII receptors 1 and 2 (AT1R, AT2R).[21] AngII signaling through AT1R activates nuclear factor-κB (NF-κB) and increases the expression of NF-κB-dependent genes.[22] NF-κB triggers the expression of proinflammatory genes such as MCP-1 in several cell types.[23,24]

The pancreas possesses its own AngII-generating system[23–26] that may finely tune specific functions via paracrine/autocrine actions.[25,26] Recent data from our lab have demonstrated that the RAS cascade may play a significant role in PDA cell survival and angiogenesis.[27,28] In this study, we tested the hypothesis that AngII may contribute to PDA inflammation through induction of MCP-1 in PDA cells. We analyzed its effect on MCP-1 synthesis and protein production in two human pancreatic cancer cell lines—HS766T and BxPC-3—and evaluated the signaling mechanisms involved.

Materials and Methods

Materials Angiotensin II was purchased from AnaSpec Inc. (San Jose, CA, USA). Losartan was from Merck (Whitehouse Station, NJ, USA), and PD123319 was from Sigma (St. Louis, MO, USA). MEK1/2 inhibitor U0126 and rabbit polyclonal antibodies for total and phospho-extracellular signal-regulated kinase (ERK)1/2 (Thr^{185}/Tyr^{189}), total and phospho-c-jun NH2-terminal protein kinase (JNK; Ser^{473}), and total and phospho-p38 (Thr^{180}/Tyr^{182}) were purchased from Cell Signaling Technology, Inc. (Beverly, MA, USA). Anti-p65 NF-κB and anti-IκBα were purchased from Santa Cruz Biotechnology (Santa Cruz, CA, USA), and anti-actin was purchased from Chemicon (Temecula, CA, USA). Human-specific MCP-1 ELISA kit was from Assay Design (Ann Arbor, MI, USA). Horseradish peroxidase-conjugated donkey antigoat and antirabbit IgG were from Vector Laboratories Inc. (Burlingame, CA, USA).

Cell Lines and Culture We used the HS766T and BxPC-3 cells, generously donated by Dr. Scott Kern, Johns Hopkins University School of Medicine, Baltimore, MD, USA. Cells were cultured at 1×10^4 to near confluence in 96-well plates and maintained in Dulbecco's modified Eagle medium supplemented with 10% fetal bovine serum in a humid atmosphere of 5% CO_2/95% air. Cells were treated with AngII (10^{-8}–10^{-6} mol/L) for 3 h then collected and examined for MCP-1 mRNA expression. To examine MCP-1 protein secretion in the media, cells were treated with AngII for 48 h, after which the media were harvested and analyzed. We then examined the detailed signaling involved in the AngII-mediated increase in MCP-1 in HS766T cells. To evaluate the effect of AngII blockade on MCP-1 production, cells were preincubated for 1 h with or without an AT1R blocker, losartan (10–100 μM) before stimulation with AngII. Cells were also preincubated with the AT2R blocker, PD123319 (10–100 μM). To evaluate the role of NF-κB signaling in the AngII-MCP-1 activation, cells were preincubated with NF-κB inhibitor, pyrrolidine dithiocarbamate (PDTC; 1–100 μM) before adding AngII. The concentrations used were based upon our preliminary concentration studies with reference to the values of MCP-1 mRNA expression and based upon our previous studies.[24,27,28]

RNA Extraction and Real-Time Reverse Transcription Polymerase Chain Reaction Total RNA was isolated from cells using Trizol reagent (Life Technologies, Gaithersburg, MD, USA), according to the manufacturer's protocol. RNAs were quantified and input amounts were optimized for each amplicon. Primers and probes were designed with the help of Primer Express Software (Applied Biosystems; Foster City, CA, USA). The specificities of the primers were validated using semiquantitative polymerase chain reaction (PCR). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as the housekeeping gene. MCP-1 and GAPDH were purchased as "assays on demand" (Applied Biosystems) and were utilized according to the manufacturer's instructions. cDNA was prepared, diluted, and subjected to real-time PCR using the TaqMan technology (7500 Sequence Detector; Applied Biosystems). The mRNA level of each sample for each gene was normalized to that of the GAPDH mRNA. The relative mRNA levels were presented as unit

values of $2 \wedge \left[C_{T(GAPDH)} - C_{T(MCP-1)}\right]$, where C_T is the threshold cycle value defined as the fractional cycle number at which the target fluorescent signal passes a fixed threshold above baseline.

ELISA MCP-1 concentration in the media was measured using a human-specific ELISA kit (Assay Design, Ann Arbor, MI, USA). Spectrophotometric evaluation of MCP-1 levels was made by Synergy HT multidetection Microplate reader (BioTeck, Winooski, VT, USA).

MTT Assay To examine the effect of AngII on in vitro cell growth, cells were plated in quintuplicate in 96-well plates and incubated in full growth media at 37°C and 5% CO_2. Cells were treated with or without AngII (10^{-8}–10^{-6} mol/L) for 72 h. Cell viability was examined using the 3-(4, 5-methylthiazol-2-yl)-2, 5-diphenyl-tetrazolium bromide (MTT) conversion assay. MTT (Sigma) was added (50 μg/well) for 4 h. Formazan products were solubilized with acidic isopropanol, and the optical density was measured at 570 nm. Optical density is directly correlated with cell quantity. Experiments were made in triplicate and repeated three times.

Transient Transfection and Promoter Studies To evaluate the effect of AngII and losartan on MCP-1 and NFκB transcription, we used the MCP-1 gene promoter (GenBank™ accession number AF079313) and NFκB gene promoter (GenBank™ accession number in progress) in luciferase expression vector pGL_3 basic (Promega). To evaluate the involvement of NF-κB in the AngII-induced activity of the MCP-1 promoter in vitro, we used MCP-1 promoter that was mutated at NF-κB binding site position −2,276. All promoter constructs were kindly provided by Dr. Decio Ezirik, Free University Brussels, Belgium.[23] Cells were seeded into 24-well culture plates (10^5). At ~80% confluence, they were cotransfected by TransFast reagent (Promega) and 0.5 μg of pGL_3 vectors containing the luciferase-labeled MCP-1/mut MCP-1 or NF-κB promoters and 0.1 μg of green fluorescence protein as transfection control. Two hours later, serum-containing medium was overlaid and the cells were incubated for additional 24 h. The cells then were incubated with serum-free medium for 18 h after which AngII or losartan or PD123319 were added for 3 h. Luciferase activities were assayed with the Dual-Luciferase Reporter Assay System (Promega) in a Veritas Microplate Luminometer (Turner Designs, Sunnyvale, CA, USA). Transfection efficiency was normalized using the total protein concentration of the cell lysates. The results for losartan-treated cells were expressed as a fold induction of the luciferase activity of the same construct in the control condition, taking the control (no treatment) value as 100.

Western Immunoblotting Western blot analysis was performed as described previously.[28] Cells were lysed in modified radioimmunoprecipitation assay lysis buffer, and the protein concentrations in the supernatant were determined using the bicinchoninic acid protein assay reagent (Pierce; Rockford, IL, USA). Equal protein concentrations (50 μg) were denatured in a gel loading buffer at 100°C for 5 min and then loaded onto 10% sodium lauryl sulfate (SDS)-polyacrylamide slab gels and transferred to polyvinylidene difluoride membranes and incubated at 4°C overnight with primary antibodies diluted in phosphate buffered saline plus Tween 20: antitotal and antiphospho-ERK1/2 mitogen-activated protein kinase (MAPK), antitotal and antiphospho-p38 MAPK, and antitotal and antiphospho-stress-activated protein kinases (SAPK)/JNK (Cell Signaling Technology, Beverly, MA, USA), anti-IκBα (Santa Cruz Biotechnology, Santa Cruz, CA, USA), and anti-actin (Chemicon, Temecula, CA, USA). The blots were washed and incubated with horseradish peroxidase-conjugated secondary antibodies. The protein bands were visualized with enhanced chemiluminescence reagents (ECL Plus Western Blotting Detection System; Amersham Pharmacia Biotech).

NF-κB Activation Assay NF-κB activation was analyzed using quantification of nuclear translocation using NF-κB/p65 ActivELISA kit to detect the active form of the p65 subunit (Imgenex; San Diego, CA, USA). Briefly, whole-cell extracts were prepared from 5×10^5 cells that were subjected to AngII (10–7 mol/L) for 30 min, followed by 1 h incubation with losartan (100 μM). In some experiments, cells were treated with tumor necrosis factor (TNF)-α (25 ng/mL) as a positive control. Cytoplasmic and nuclear extracts were prepared according to the manufacturer's instructions. Briefly, the cytoplasmic fraction was collected in the supernatant of the whole cell lysates after centrifugation for 30 s at 28,487×*g* in a cold microcentrifuge. Nuclear fraction was collected in the supernatant of the nuclear pellet after its resuspension in 100 μl nuclear lysis buffer, incubation at 4°C for 30 min, and centrifugation in a microcentrifuge at 28,487×*g* for 10 min at 4°C. Nuclear fractions were subjected to ELISA using specific, anti-NF-κB antibodies, according to the manufacturer's instructions. Absorbance was read at 405 nm wavelength using a Synergy HT multidetection microplate reader (BioTeck, Winooski, VT, USA).

Immunohistochemical Staining of PDA Cells Cells were grown in chamber slides (lab-tech, Nunc, Thermo Fisher Scientific, Rochester, NY, USA). To study the localization of p65 NF-κB subunit, cells were treated with AngII (10^{-7} mol/L) for 30 min before adding losartan (100 μM) for 1 h, after which they were washed with Hanks balanced

salt solution, pH 7.4, at 37°C after aspiration of the culture medium. Cells were then fixed in 4% formaldehyde in PBS at room temperature for 10 min and were then treated with 0.1% Triton X-100 for 30 s to permeabilize nuclear membranes. Following blocking nonspecific reaction with normal donkey serum, the cells were incubated overnight with antirabbit p65 IgG (400 ng/mL) at 4°C. Cells were then washed three times for 5 min each with PBS and incubated for 30 min at room temperature with biotinylated goat antirabbit IgG, diluted 1:200 in PBS (Vector Laboratories, Inc., Burlingame, CA, USA), as the secondary antibody. 3,3′-Diaminobenzidine tetrahydrochloride chromogenic substrate (Vector Laboratories Inc.) was used according to the manufacturer protocol to visualize the chromogenic reaction. Cells were rinsed three times for 5 min each with PBS, counterstained with hematoxylin, mounted on glass slides, and viewed by light microscopy (Nikon), and images were analyzed with Image Pro analysis Image analysis software. The number of clearly stained nuclei in ten fields was averaged, and the data were calculated as the percentage of nuclear staining/total number of nuclei.

Statistical Analyses All experiments were performed four to six times. Data were analyzed for statistical significance by analysis of variance (ANOVA) with post hoc Student's *t* test analysis. Data are presented as mean ± standard error of the mean (SEM). Continuous normally distributed variables were analyzed by Student's *t* test. These analyses were performed with the assistance of a computer program (JMP 5 Software SAS Campus Drive; Cary, NC, USA). Differences were considered significant at $p \leq 0.05$.

Results

AngII-Induces MCP-1 mRNA Accumulation and Protein Secretion in Cultured PDA Cells To investigate whether AngII can directly increase MCP-1 mRNA accumulation in PDA cells, HS766T and BxPC-3 cells were treated with or without AngII (10^{-8} and 10^{-7} mol/L) for 3 and 24 h. Significant induction of MCP-1 mRNA expression was seen with a maximum increase at 24 h at 10^{-7} mol/L of AngII in HS766T cells (Fig. 1a). In BxPC-3 cells, the increase in MCP-1 mRNA levels could be detected after 3 h of AngII stimulation, and levels were reduced after 72 h of AngII treatment (Fig. 1b). To examine whether the increase in MCP-1 mRNA levels in response to AngII is associated with MCP-1 production, MCP-1 protein levels in the media were determined by ELISA. Extracellular MCP-1 protein concentration increased markedly from 1.2 to 5.5 and 51.75 pg/mL after 24 and 48 h of AngII stimulation in HS766T cells, respectively (Fig. 2a). In BxPC-3 cells, MCP-1 levels were increased from 11.23 to 17.2 and 101.35 pg/mL after 48 and 72 h of AngII stimulation, respectively (Fig. 2b). These data indicate that while basal MCP-1 levels may vary between PDA cell lines, MCP-1 induction by AngII is a general phenomenon seen in the tested PDA cells lines.

Since AngII has been shown to increase cellular proliferation in smooth muscle and cardiac muscle cells,[29,30] we tested whether it has similar effect in PDA cells. MTT assay was performed on HS766T cells treated with or without AngII (10^{-8}–10^{-6} mol/L) for 24 and 72 h. Addition of AngII did not affect cellular proliferation when compared to control values (data not shown). These data suggest that the AngII-mediated increase in MCP-1 is independent of cellular proliferation.

AngII Induces MCP-1 Promoter Activity in PDA Cells H766T cells were transfected with MCP-1 promoter/luciferase gene construct. After 24 h of transfection, the cells were incubated with AngII (10^{-7}) for 1–2 h, after which the luciferase activity in the cell lysates was measured. A significant increase in MCP-1 promoter activation is seen after incubation with AngII (Fig. 3). These data show that the MCP-1 promoter responds directly to AngII.

AngII-Induced MCP-1 Transcription in PDA Cells Is Blocked by an AT1R Antagonist To determine the receptor that mediates the AngII-induced MCP-1 gene expression in PDA cells, the AT1R blocker, losartan, and the AT2R blocker PD123319 were added for 1 h prior to addition of AngII to the cells. Losartan at 100 μM inhibited the constitutive and AngII-mediated increase in MCP-1 promoter activity. Interestingly, pretreatment of the cells with PD123319 significantly increased the constitutive and AngII-mediated increase in MCP-1 promoter activity (Fig. 3). These data suggest that the induction of MCP-1 gene expression by AngII is mediated through AT1R in PDA cells. These data also suggest a contrasting role for AT2R in PDA cells that might mediate signaling pathways opposite to those of AT1R.

AngII-Induced MCP-1 Gene Expression Requires ERK1/2 MAP Kinase Activity AngII signaling through AT1R activates members of the MAPK family, ERK1/2, p38 MAPK, and JNK/SAPK in different tissues.[29,30] We tested whether AngII-induced MCP-1 mRNA expression involves activation MAP kinase in PDA cells. After washing, the HS766T cells were lysed and 40-μg protein aliquots were subjected to Western blot analysis. We probed the blots with antibodies specific for phosphorylated ERK1/2

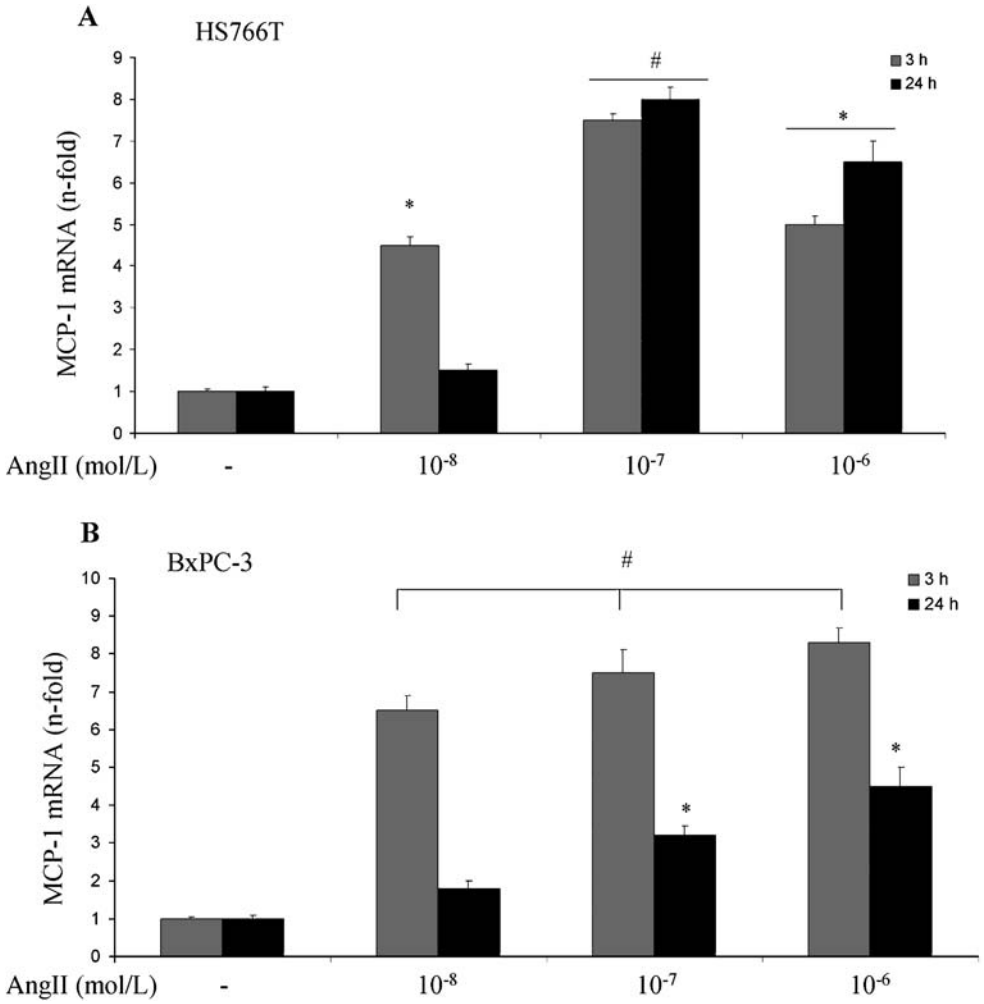


Figure 1 AngII-induced MCP-1 accumulation in PDA cells. **a** Hs766T and **b** BxPC-3 cells were treated with AngII (10^{-8}–10^{-6} mol/L) for 3 and 24 h. Significant induction of MCP-1 mRNA expression is seen with the maximum induction after 3 h at 10^{-7} mol/L of AngII. Values are expressed as mean ± SEM of three experiments Values are expressed as mean ± SEM of three experiments. *$p<0.05$, #$p<0.02$ vs. control untreated cells using one-way repeated ANOVA with subsequent all pairwise comparison procedure by Student's *t* test.

(Thr183/Tyr185), phosphorylated p38 (Thr180/Tyr182), and phosphorylated JNK/SAPK (Thr183/Tyr185).

AngII increased ERK1/2 phosphorylation within 5 min of treatment (Fig. 4a), but not p38 or JNK or (data not shown). Preincubation of the cells with the MEK1/2 selective inhibitor U0126 reduced the AngII-induced MCP-1 gene expression (Fig. 4b). This suggests that specific activation of ERK1/2 kinase may play an important role in AngII-induced MCP-1 expression in PDA cells.

AngII-Induced MCP-1 Gene Expression Requires Activation of NF-κB Activation of the transcription factor NF-κB is an essential step for activating the transcription of MCP-1.[23] We investigated whether for AngII to mediate its MCP-1-regulatory effect requires the activation of NF-κB. Incubation of HS766T cells with NF-κB inhibitor, PDTC, dose-dependently decreased the AngII-mediated increase in MCP-1 mRNA (Fig. 5a, left panel). To further evaluate the role of NF-κB in the induction of MCP-1 by AngII, we transfected the cells with MCP-1 promoter that was mutated at NF-κB binding site position −2,276. As seen in Fig. 5a (right panel), AngII failed to enhance mutMCP-1 promoter activity, suggesting an essential role for NF-κB in the regulation of MCP-1 by AngII in PDA cells.

AngII Activates NF-κB Signaling in PDA Cells We investigated whether activation of MCP-1 transcription by AngII is mediated through regulation of NF-κB activity and/or transcription. We also explored whether AT1R blockade by losartan could reverse these effects. First, we used Western blotting analysis to analyze the degradation of the IκBα protein, which is a requisite for the binding of NF-κB to κB sites in the promoter region. As seen in Fig. 5b, AngII induced IκBα protein degradation, an effect that was inhibited by losartan. Losartan did not affect the TNF-α-mediated IκBα degradation.

Next, using immunohistochemical staining with antirabbit p65 IgG, we analyzed the nuclear translocation of NF-κB after pretreatment with AngII alone or with subsequent treatment with losartan. The number of clearly stained nuclei in ten fields was averaged, and the data were calculated as the percentage of nuclear staining/total number of nuclei. In the control untreated cells, a diffuse

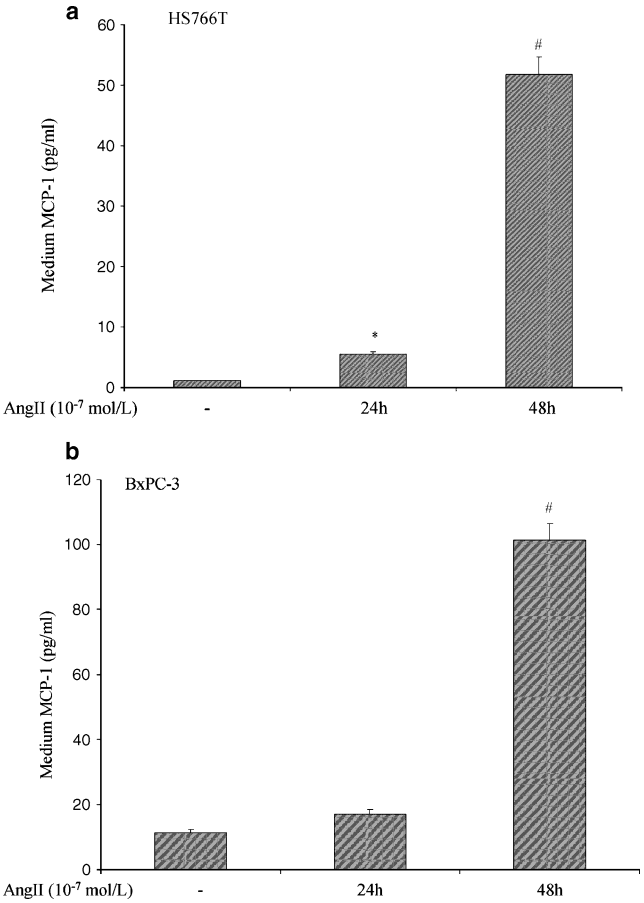


Figure 2 MCP-1 protein in culture media was measured using human-specific ELISA kit. Significant induction of MCP-1 protein secretion is seen in HS766T (**a**) and BxPC-3 cells (**b**) with a maximum at 48 h. Each experiment was repeated three times for reproducibility. Values are expressed as mean ± SEM of three experiments. *$p<0.05$, #$p<0.005$ vs. control levels, using one-way repeated ANOVA with subsequent all pairwise comparison procedure by Student's *t* test.

cytoplasmic staining was observed, while cells treated with AngII had a clear nuclear staining, indicating nuclear translocation of p65. Adding losartan to the cells significantly ($p<0.02$) prevented the AngII-induced nuclear translocation of p65 in HS766T cells (Fig. 5c; control 8± 0.8 stained nuclei/10^5 nuclei; +TNF-α 94±21; +AngII 65± 20 stained nuclei/10^5 nuclei; +AngII + losartan 15±0.4 stained nuclei/10^5 nuclei).

To analyze the effect of AngII and losartan on NF-κB activation, cells were pretreated with AngII (10^{-7} mol/L) for 30 min and then treated with losartan (10–100 μM) for 1 h. Cells were analyzed for the presence of the active forms of NF-κB p65 using the ActivELISA kit (Imgenex; San Diego, CA, USA). The anti-p65 antibody coated plate captures free p65 and the amount of active p65 is detected by colorimetric detection at OD 405 after adding a second anti-p65 antibody followed by alkaline phosphatase-conjugated secondary antibody. AngII increased the activation of NF-κB by 1.54-fold, an effect that was dose dependently and significantly reduced by losartan (Fig. 5d). Losartan alone also significantly ($p<0.005$) reduced the constitutive activity of NF-κB in HS766T cells. These findings suggest that AngII, through activation of NF-κB, could be responsible for mediating inflammation in PDA, an effect that can be potently inhibited by AT1R blockade.

AT1R Blockade by Losartan Dose Dependently Reduces the Constitutive and AngII-Induced Activation of NF-κB Promoter To further elucidate the effect of AngII and its blockade on NF-κB, we investigated whether AngII or losartan has a direct effect on NF-κB transcription. Cells were transfected with luciferase-labeled NF-κB promoter, then treated with AngII (10^{-7} mol/L) alone or with subsequent treatment with losartan (10–100 μM). As seen in Fig. 5e, AngII induced an approximate 1.3-fold increase in NF-κB promoter activity, an effect that was dose dependently blocked by losartan. Losartan alone induced a dose-dependent reduction in the endogenous activity of NF-κB promoter. These data suggest that AngII regulates not only the activity of NF-κB but also its transcription. AngII blockade by losartan reverses these effects.

Discussion

The molecular and cellular mechanisms that contribute to the insidious nature of PDA are poorly understood. MCP-1 is probably the CC chemokine most frequently found in tumors.[31] Human tumors shown to express MCP-1 in vivo include sarcomas, gliomas, lung tumors, carcinomas of the breast, cervix, ovary,[16–19,32] and pancreas.[33] Several investigations have provided recent evidence for the potential contribution of monocyte chemoattractants to cancer progression.[34–36] However, only a few studies have investigated the upstream effector molecules and the signaling cascades involved in the regulation of MCP-1 in PDA cells. In the present study, we introduce AngII as a novel trigger for MCP-1 expression in PDA cells and propose a previously undescribed role for AT1R as a novel participant in PDA progression and inflammation

We previously reported the presence of constitutive AngII generating system in PDA tissue and showed significant elevation of the mRNA and protein levels of the enzyme responsible for AngII generation, ACE, when compared to matching control tissue levels.[27] We show here that AngII is a potent stimulator of MCP-1 expression in PDA cells. AngII induced MCP-1 accumulation rapidly in PDA cells and with significant magnitude, a process that

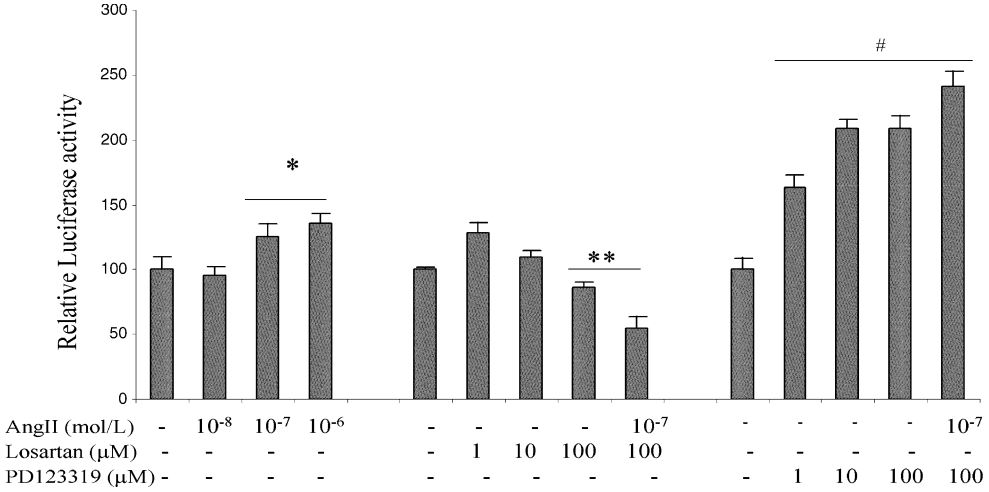


Figure 3 AngII induces MCP-1 promoter activity in HS766T cells. After 24 h of transfection, the cells were incubated with AngII (10^{-7} mol/L) for 2 h with or without adding losartan (1–100 μM) or PD123319 (1–110 μM). After incubation, the luciferase activity in the cell lysates was measured. AngII causes a dose-dependent increase in MCP-1 promoter activity. Losartan dose dependently reduced the constitutive and the AngII-mediated activation of MCP-1 promoter. Relative luciferase activity was calculated after deduction of the activity levels with pGL3 vector alone. Results represent mean ± SEM of triplicate determinations. All experiments were repeated at least three times to confirm the reproducibility of the observations.

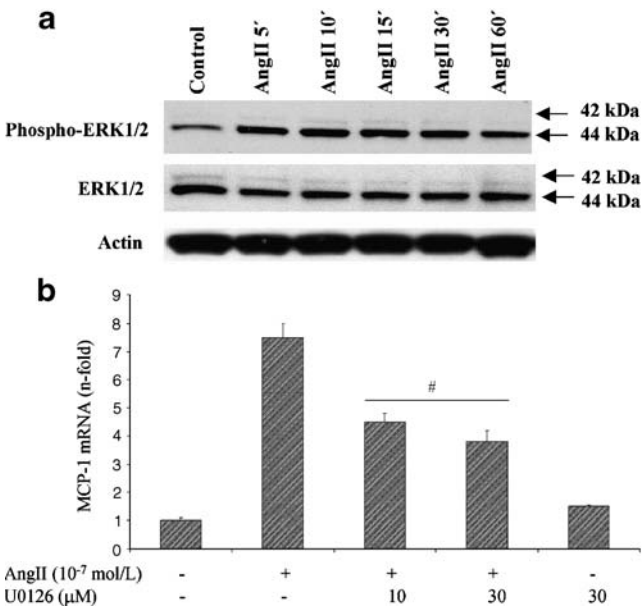


Figure 4 AngII-induced MCP-1 gene expression requires ERK1/2 MAP kinase activity. **a** Time-dependent activation of ERK1/2 MAP kinase signaling pathway by AngII in HS766T cells. Representative Western blot probed with phospho-antibody against the activated from of ERK1/2 showing increased phosphorylation of ERK1/2 after incubation of AngII (10^{-7} mol/L) 5–60 min. Blots were stripped and developed with antitotal ERK1/2 and beta-actin as controls for equal protein loading. **b** Effect of MEK1/2 inhibitor, U0126, on AngII induced increase in MCP-1 mRNA. Cells were pretreated with the inhibitor (10–30 μM) for 10 min before incubation with AngII (10^{-7} mol/L) for 3 h. Data represent three independent experiments. *$p<0.05$ vs. AngII treated cells using one-way repeated ANOVA with subsequent all pairwise comparison procedure by Student's t test.

was independent of cell proliferation, since the same doses that induced MCP-1 failed to increase cell proliferation. Dose–response studies demonstrated a significant induction of MCP-1 mRNA and protein levels at a physiological concentration of AngII (10^{-7} mol/L). Although it is not known whether the circulating levels of AngII would match its tissue levels, the maximal effect concentration at 10^{-7} mol/L is similar to other AngII actions that have been reported.[37,38] It is yet to be determined, however, whether the levels of circulating MCP-1 in PDA patients are correlated with both ACE and MCP-1 tissue levels. Studies in this regard are currently ongoing in our laboratory.

We also show that AngII-induced MCP-1 gene expression occurs through an AT1R-mediated mechanism and through induction of its promoter activity, as demonstrated by our promoter studies (Fig. 3). Our data show that MCP-1 promoter was induced significantly as early as after 1 h of stimulation. The implications of this acute response to AngII could be critical in conditions where pancreatic AngII generation is increased. Further studies are required to analyze the AngII-specific response elements on MCP-1 promoter. Studies in this regard are currently ongoing in our lab.

The addition of losartan, an AT1R antagonist, prevented the AngII-MCP-1 transcription, an effect that was not observed when PD123319, an AT2R antagonist, was added. As a matter of fact, AT2R blockade leads to activation of MCP-1 transcription (Fig. 3). AT1R and AT2R belong to the heterotrimeric G-protein-coupled receptor superfamily. Our lab and others have shown that increased expression of AT1R mRNA results in elevation of the functional response to AngII.[28,39] Thus, it is possible that AngII induces MCP-1

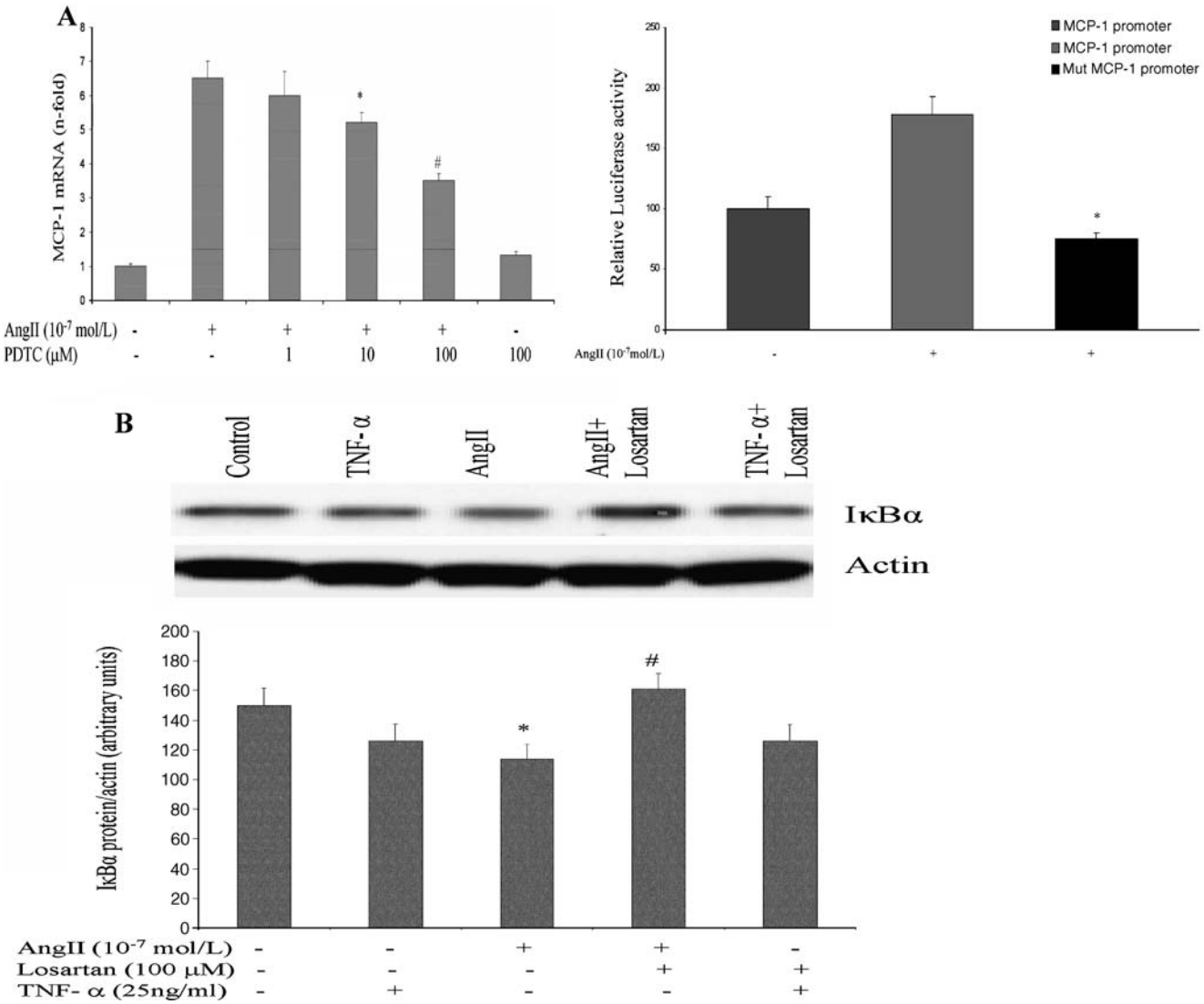
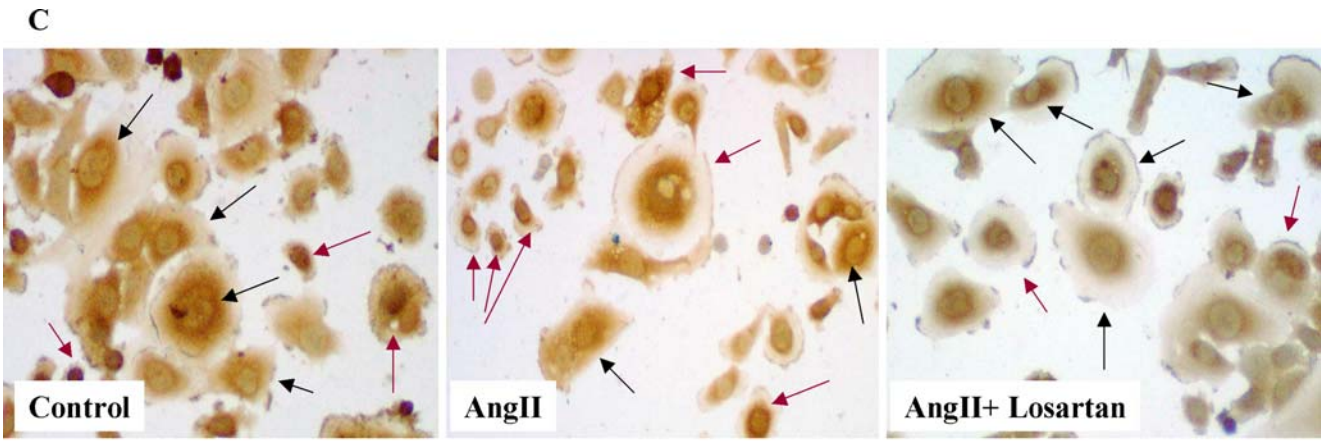
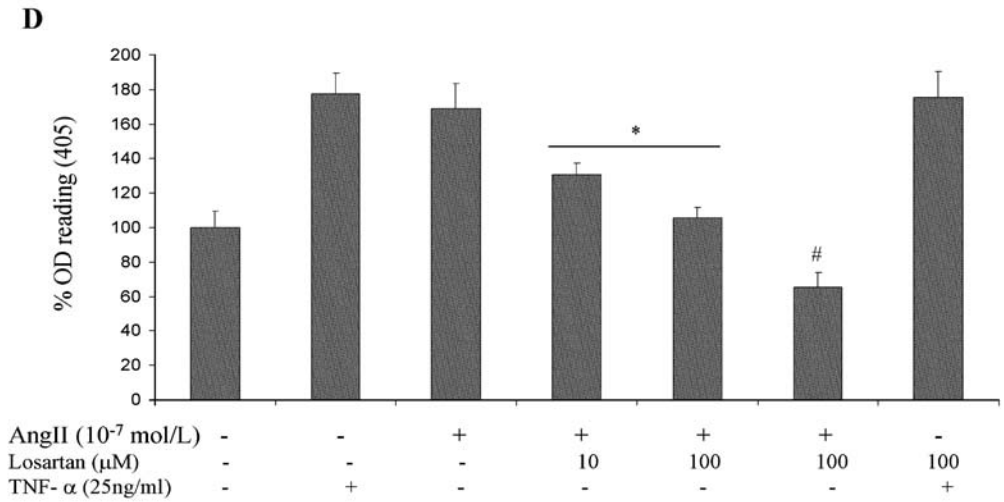


Figure 5 **a** AngII-induced MCP-1 gene expression requires activation of NF-κB. *Left panel*: Incubation of HS766T cells with NF-κB inhibitor, PDTC, dose dependently decreased the AngII-mediated increase in MCP-1 mRNA. Data represent three independent experiments. *$p<$ 0.05, #$p<0.02$ vs. AngII treated cells using one-way repeated ANOVA with subsequent all pairwise comparison procedure by Student's t test. *Right panel*: After 24 h of transfection with nonmutated and mutMCP-1 promoters at site 2-276, cells were incubated with or without AngII (10^{-7} mol/L) for 2 h. After incubation, the luciferase activity in the cell lysates was measured. The AngII-mediated increased in MCP-1 promoter activity was significantly inhibited in the mutMCP-1 promoter transfected cells. Relative luciferase activity was calculated after deduction of the activity levels with pGL3 vector alone. Results represent mean ± SEM of triplicate determinations. All experiments were repeated at least three times to confirm the reproducibility of the observations. $p<0.05$ vs. non-mutMCP-1 transfected cells using one-way repeated ANOVA with subsequent all pairwise comparison procedure by Student's t test. **b** AngII stimulates NF-κB signaling in PDA cells. Hs766T cells were treated with losartan (100 μM) without 30 min pretreatment with AngII (10^{-7} mol/L) or TNF-α (25 ng/mL) as a positive control. Total cellular proteins (25 μg) were separated on 8% SDS-PAGE and the levels of IκBα protein (37 kDa) were measured by Western blot analysis. Equal loading of protein was verified by probing the same blot for actin (43 kDa). Losartan reversed the AngII-mediated IκBα protein degradation. **c** Immunohistochemical staining for p65 NF-κB subunit showing mostly cytoplasmic staining in the control cells (*black arrows*). Cells treated with AngII show intense nuclear staining (*red arrows*). Losartan-treated cells show inhibition of the AngII-induced nuclear translocation in most of the cells (*black arrows*), while few cells retained their nuclear staining (*red arrows*). **d** Losartan inhibits the constitutive and AngII-mediated activation of NF-κB. Lysates from HS766T cells treated with losartan (100 μM) with or without pretreatment with AngII were analyzed for the presence of the active forms of NF-κB p65 using the ActivELISA kit. TNF-α (25 ng/mL) was added as a positive control AngII-mediated and constitutive NFκB p65 activations were potently inhibited by losartan. Values are expressed as mean ± SEM of three experiments. *$p\leq0.05$ vs. control untreated values; #$p<0.02$ vs. control untreated values, using one-way repeated ANOVA with subsequent all pairwise comparison procedure by Student's t test. **e** Losartan dose dependently reduces the constitutive and AngII-induced activation of the NF-κB promoter. HS766T cells were transfected with luciferase-labeled NF-κB promoter. Relative luciferase activity was calculated after deduction of the activity levels with pGL3 vector alone. Results represent mean ± SEM of triplicate determinations. *$p\leq0.05$, #$p<0.02$ vs. AngII-treated values; **$p\leq0.05$, ## $p<0.02$ vs. control untreated values vs. control untreated values, using one-way repeated ANOVA with subsequent all pairwise comparison procedure by Student's t test.





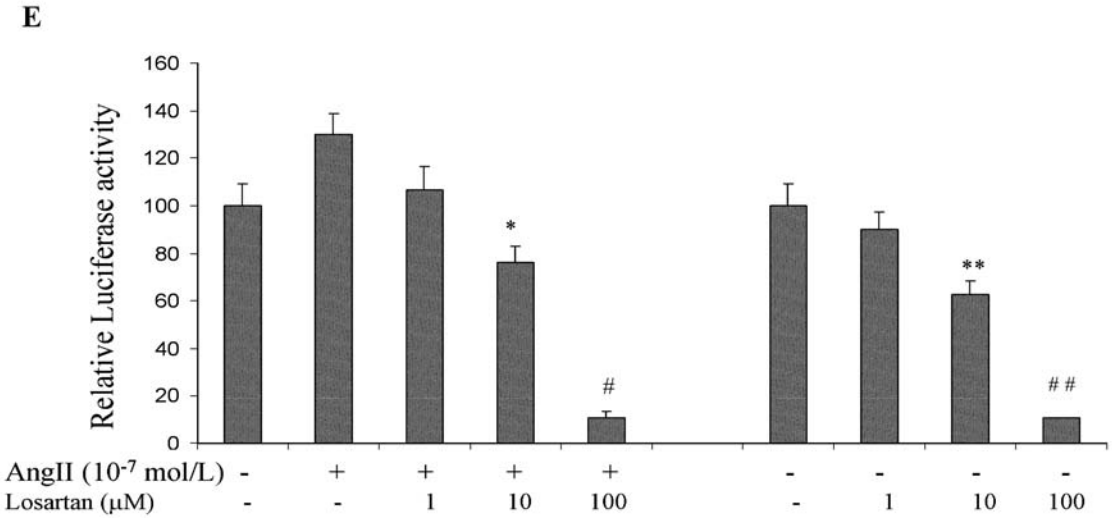


Figure 5 (continued).

transcripts in PDA cells directly through acting on its promoter and indirectly through AT1R upregulation. Nonetheless, the exact role of AT2R in PDA is not clear at this point and its contribution to mediating an opposing anti-inflammatory effect for AngII is yet to be determined. Studies to elaborate on the role of AT2R in PDA are currently ongoing in our laboratory.

MAP kinases encoded by the ERK genes are a family of serine/threonine protein kinases activated as early responses to a variety of stimuli involved in cell growth, transforma-

tion, and differentiation.[40] They are also involved in the activation of AP-1 and NF-kB.[41] Two isoforms of ERK (referred to as p44 (ERK1) and p42 (ERK2)) are activated by phosphorylation of threonine and tyrosine residues by MAP kinase kinase (MEK).[42,43] AngII rapidly activates MAP kinases, particularly ERK1 and ERK2, in vascular smooth muscle cells[40,44] and in pancreatic cancer cells.[28] Using a selective inhibitor for MEK activation, U0126, we demonstrated that AngII-induced MCP-1 mRNA occurs through a MEK-sensitive mechanism (Fig. 4b). AngII had no effect within this time period on the phosphorylation of either P38 or SAPK/JNK. Further studies are now required to fully delineate the specific signaling pathway by which AngII ultimately modulates MCP-1 synthesis in PDA cells.

The differential induction and binding of activated transcription factors to the promoter region of the MCP-1 gene provide a critical regulatory step, allowing expression of the chemokine in a cell- and stimulus-specific manner.[45] Studies on models of inflammation-associated cancer have implicated NF-κB in cancer progression.[46,47] The NF-κB pathway may have dual effects in tumor progression: first by preventing the death of cells with malignant potential and second by stimulating the production of proinflammatory cytokines by inflammatory cells in the tumor microenvironment.[46] Constitutive activation of NF-κB has been observed in a number of different PDA cell lines,[48,49] in animal models of pancreatic cancer,[49] and in human pancreatic tissue.[50] NF-κB activation also may contribute to the characteristic resistance of pancreatic tumor cells to the apoptotic effect of chemotherapeutic agents.[51,52] Thus, inhibiting the activation of NF-κB could be a useful adjunct in the treatment of the disease. In our data here, we show the specificity of NF-κB to mediating the AngII-MCP-1 induction, first through using a specific NF-κB inhibitor, PDTC, and second through using MCP-1 promoter where an NF-κB binding site has been mutated. In both studies, AngII failed to induce MCP-1 transcription (Fig. 5a).

Our data also demonstrate, for the first time, that blocking AT1R by losartan inhibits the constitutive and AngII-induced activation of NF-κB (Fig. 5b, d) and inhibits the translocation of NF-κB to the nucleus in PDA cells (Fig. 5c). Most interestingly, AngII stimulated the transcription of NF-κB through increasing its promoter activity (Fig. 5e), an effect that was potently inhibited by losartan. Thus, AngII may have a dual stimulatory effect, the first through triggering the NF-κB signaling pathway and the second through activating its transcription. The details of the mechanism by which losartan downregulates NF-κB promoter activity are still unclear. Losartan may induce binding of transcription factors to the promoter or to a suppressor region. Alternatively, losartan may induce changes in the secondary and tertiary structure of the promoter. Studies addressing transcription factor binding are ongoing in our laboratory.

Our study demonstrates that AngII elicits a proinflammatory response in PDA cells by stimulation of MCP-1 production through an AT1R-ERK1/2–NF-κB-dependent mechanism. It is not clear from this study that AngII regulates MCP-1 in vivo. However, the existence of AngII as a potential endogenous trigger for MCP-1 in PDA is unique and suggests that targeting AngII could be used as a novel target for prevention of monocyte recruitment and as a preventive and therapeutic strategy in PDA and in chronic pancreatitis.

Acknowledgments This work is supported by a grant from the American Cancer Society (RSG CSM-113191).

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer statistics, 2008. CA Cancer J Clin 2008;58(2):71–96.
2. Sohn TA, Yeo CJ, Cameron JL, Koniaris L, Kaushal S, Abrams RA, Sauter PK, Coleman J, Hruban RH, Lillemoe KD. Resected adenocarcinoma of the pancreas—616 patients: results, outcomes, and prognostic indicators. J Gastrointest Surg 2000;4:567–579.
3. Seo Y, Baba H, Fukuda T, Takashima M, Sugimachi K. High expression of vascular endothelial growth factor is associated with liver metastasis and a poor prognosis for patients with ductal pancreatic adenocarcinoma. Cancer 2000;88:2239–2245.
4. Rocca G, Gaia E, Iuliano R. Increased incidence of cancer in chronic pancreatitis. J Clin Gastroenterol 1987;9:175–179.
5. Otsuki M. Chronic pancreatitis in Japan: epidemiology, prognosis, diagnostic criteria, and future problems. J Gastroenterol 2003;38:315–326.
6. Maisonnneuve P, Lowenfels AB. Chronic pancreatitis and pancreatic cancer. Dig Dis 2002;20:32–37.
7. Queneau PE, Adessi GL, Thibault P. Early detection of pancreatic cancer in patients with chronic pancreatitis; diagnostic utility of a Kras point mutation in the pancreatic juice. Am J Gastroenterol 2001;96:700–704.
8. Lowenfels AB, Maisonneuve P, DiMagno EP, Elitsur Y, Gates LK Jr, Perrault J, Whitcomb DC. Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. J Natl Cancer Inst 1997;90:442–446.
9. Ghadrian P, Liu G, Gallinger S, Schmocker B, Paradis A, Lal G, Brunet JS, Foulkes WD, Narod SA. Risk of pancreatic cancer among individuals with a family history of cancer of the pancreas. Int J Cancer 2002;97:807–810.
10. Whitcomb DC, Applebaum S, Martin SP. Hereditary pancreatitis and the risk of pancreatic carcinoma. Ann NY Acad Sci 1999;880:1433–1437.
11. Hingorani SR, Petricoin EF, Maitra A, Rajapakse V, King C, Jacobetz MA, Ross S, Conrads TP, Veenstra TD, Hitt BA, Kawaguchi Y, Johann D, Liotta LA, Crawford HC, Putt ME, Jacks T, Wright CV, Hruban RH, Lowy AM, Tuveson DA. Preinvasive and invasive ductal pancreatic cancer and its early detection in the mouse. Cancer Cell 2003;4:437–450.
12. Leach SD. Mouse models of pancreatic cancer: the fur is finally flying!. Cancer Cell 2004;5:7–11.
13. Pikarsky E, Porat RM, Stein I, Abramovitch R, Amit S, Kasem S, Gutkovich-Pyest E, Urieli-Shoval S, Galun E, Ben-Neriah Y. NF-kappaB functions as a tumor promoter in inflammation-associated cancer. Nature 2004;431:461–466.

14. Balkwill F. Cancer and the chemokine network. Nat Rev Cancer 2004;4:540–550.
15. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001;357:539–545.
16. Oppenheim JJ, Zachariae CO, Mukaida N, Matsushima K. Properties of the novel proinflammatory supergene "intercrine" cytokine family. Annu Rev Immunol 1991;9:617–648.
17. Graves DT, Barnhill R, Galanopoulos T, Antoniades HN. Expression of monocyte chemotactic protein-1 in human melanoma in vivo. Am J Pathol 1992;140:9–14.
18. Negus RP, Stamp GW, Relf MG, Burke F, Malik ST, Bernasconi S, Allavena P, Sozzani S, Mantovani A, Balkwill FR. The detection and localization of monocyte chemoattractant protein-1 (MCP-1) in human ovarian cancer. J Clin Invest 1995;95:2391–2396.
19. Koide N, Nishio A, Sato T, Sugiyama A, Miyagawa S. Significance of macrophage chemoattractant protein-1 expression and macrophage infiltration in squamous cell carcinoma of the esophagus. Am J Gastroenterol 2004;99:1667–1674.
20. Soucek L, Lawlor ER, Soto D, Shchors K, Swigart LB, Evan GI. Mast cells are required for angiogenesis and macroscopic expansion of Myc-induced pancreatic islet tumors. Nat Med 2007;13:1211–1218.
21. De Gasparo M, Catt KJ, Inagami T, Wright JW, Unger TH. The angiotensin II receptors. Pharmacol Rev 2000;52:415–472.
22. Amaya K, Ohta T, Kitagawa H, Kayahara M, Takamura H, Fujimura T, Nishimura G, Shimizu K, Miwa K. Angiotensin II activates MAP kinase and NF-kappaB through angiotensin II type I receptor in human pancreatic cancer cells. Int J Oncol 2004;4:849–856.
23. Kutlu B, Darville MI, Cardozo AK, Eizirik D. Molecular regulation of monocyte chemoattractant protein-1 expression in pancreatic beta-cells. Diabetes 2003;2:348–355.
24. Chipitsyna G, Gong Q, Gray CF, Haroon Y, Kamer E, Arafat HA. Induction of monocyte chemoattractant protein-1 expression by angiotensin II in the pancreatic islets and beta-cells. Endocrinology 2007;148:2198–2208.
25. Tahmasebi M, Puddefoot JR, Inwang ER, Vinson GP. The tissue renin–angiotensin system in human pancreas. J Endocrinol 1999;161:317–322.
26. Leung PS, Chappell MC. A local pancreatic renin–angiotensin system: endocrine and exocrine roles. Int J Biochem Cell Biol 2003;35:838–846.
27. Arafat HA, Gong Q, Chipitsyna G, Rizvi A, Saa CT, Yeo CJ. Antihypertensives as novel antineoplastics: angiotensin-I-converting enzyme inhibitors and angiotensin II type 1 receptor blockers in pancreatic ductal adenocarcinoma. J Am Coll Surg 2007;204:996–1005.
28. Anandanadesan R, Gong Q, Chipitsyna G, Witkiewicz A, Yeo CJ, Arafat HA. Angiotensin II induces vascular endothelial growth factor in pancreatic cancer cells through an angiotensin II type 1 receptor and ERK1/2 signaling. J Gastrointest Surg 2008;12:57–66.
29. Menard J, Clauser E, Bouhnik J, Corvol P. Angiotensinogen: biochemical aspects. In Robertson JIS, Nichollas MS, eds. The Renin Angiotensin System. London: Gower Medical, 1993, pp 8.1–8.10.
30. Kim S, Iwao H. Stress and vascular responses: mitogen-activated protein kinases and activator protein-1 as promising therapeutic targets of vascular remodeling. J Pharmacol Sci 2003;9:177–181.
31. Bottazzi B, Polentarutti N, Acero R, Balsari A, Boraschi D, Ghezzi P, Salmona M, Mantovani A. Regulation of the macrophage content of neoplasms by chemoattractants. Science (Wash. DC) 1983;220:210–212.
32. Coussens LM, Werb Z. Inflammation and cancer. Nature (Lond.) 2002;420:860–867.
33. Monti P, Leone BE, Marchesi F, Balzano G, Zerbi A, Scaltrini F, Pasquali C, Calori G, Pessi F, Sperti C, Di Carlo V, Allavena P, Piemonti L. The CC chemokine MCP-1/CCL2 in pancreatic cancer progression: regulation of expression and potential mechanisms of antimalignant activity. Cancer Res 2003;63:7451–7461.
34. Ueno T, Toi M, Saji H, Muta M, Bando H, Kuroi K, Koike M, Inadera H, Matsushima K. Significance of macrophage chemoattractant protein-1 in macrophage recruitment, angiogenesis, and survival in human breast cancer. Clin Cancer Res 2000;6:3282–3289.
35. Goede V, Brogelli L, Ziche M, Augustin HG. Induction of inflammatory angiogenesis by monocyte chemoattractant protein-1. Int J Cancer 1999;82:765–770.
36. Salcedo R, Ponce ML, Young HA, Wasserman K, Ward JM, Kleinman HK, Oppenheim JJ, Murphy WJ. Human endothelial cells express CCR2 and respond to MCP-1: direct role of MCP-1 in angiogenesis and tumor progression. Blood 2000;96:34–40.
37. Chen XL, Tummala PE, Olbrych MT, Alexander RW, Medford RM. Angiotensin II induces monocyte chemoattractant protein-1 gene expression in rat vascular smooth muscle cells. Circ Res 1998;83:952–959.
38. Funakoshi Y, Ichiki T, Shimokawa H, Egashira K, Takeda K, Kaibuchi K, Takeya M, Yoshimura T, Takeshita A. Rho-kinase mediates angiotensin II-induced monocyte chemoattractant protein-1 expression in rat vascular smooth muscle cells. Hypertension 2001;38:85–84.
39. Nickenig G, Sachinidis A, Michaelsen F, Bohm M, Seewald S, Vetter H. Upregulation of vascular angiotensin II receptor gene expression by low-density lipoprotein in vascular smooth muscle cells. Circulation 1997;95:473–478.
40. Duff JL, Marrero MB, Paxton WG, Schieffer B, Bernstein KE, Berk BC. Angiotensin II signal transduction and the mitogen-activated protein kinase pathway. Cardiovasc Res 1995;30:511–517.
41. Hirano M, Osada S, Aoki T, Hirai S, Hosaka M, Inoue J, Ohno S. MEK kinase is involved in tumor necrosis factor alpha-induced NF-kappaB activation and degradation of IkappaB-alpha. J Biol Chem 1996;271:13234–13238.
42. Crews CM, Alessandrini A, Erikson RL. The primary structure of MEK, a protein kinase that phosphorylates the ERK gene product. Science 1992;258:478–480.
43. Cobb MH, Goldsmith EJ. How MAP kinases are regulated. J Biol Chem 1995;270:14843–14846.
44. Duff JL, Berk BC, Corson MA. Angiotensin II stimulates the pp44 and pp42 mitogen-activated protein kinases in cultured rat aortic smooth muscle cells. Biochem Biophys Res Commun 1992;188:257–264.
45. Roebuck KA, Carpenter LR, Lakshminarayanan V, Page SM, Moy JN, Thomas LL. Stimulus-specific regulation of chemokine expression involves differential activation of the redox-responsive transcription factors AP-1 and NF-κB. J Leukoc Biol 1999;65:291–298.
46. Greten FR, Eckmann L, Greten TF, Park JM, Li ZW, Egan LJ, Kagnoff MF, Karin M. IKKbeta links inflammation and tumorigenesis in a mouse model of colitis-associated cancer. Cell 2004;118:285–296.
47. Chandler NM, Canete JJ, Callery MP. Increased expression of NF-KB subunits in human pancreatic cancer cells. J Surg Res 2004;118:9–14.
48. Liptay S, Weber CK, Ludwig L, Wagner M, Adler G, Schmid RM. Mitogenic and antiapoptotic role of constitutive NF-KB/Rel activity in pancreatic cancer. Int J Cancer 2003;105:735–746.

49. Wang W, Abbruzzese JL, Evans DB, Larry L, Cleary KR, Chiao PJ. The nuclear factor-KB RelA transcription factor is constitutively activated in human pancreatic adenocarcinoma cells. Clin Cancer Res 1999;5:119–127.
50. Fujioka S, Sclabas GM, Schmidt C, Frederick WA, Dong QG, Abbruzzese JL, Evans DB, Baker C, Chiao PJ. Function of nuclear factor kappaB in pancreatic cancer metastases. Clin Cancer Res 2003;9:345–354.
51. Fahy BN, Schliemann MG, Virudachalam S, Bold JG. Inhibition of AKT abrogates chemotherapy-induced NF-KB survival mechanisms: implications for therapy in pancreatic cancer. J Am Coll Surg 2004;198:591–599.
52. Arlt A, Gehrz A, Muerkoster S, Vorndamm J, Kruse M, Folsch UR, Schäfer H. Role of NF-kappaB and Akt/PI3K in the resistance of pancreatic carcinoma cell lines against gemcitabine-induced cell death. Oncogene 2003;22:3243–3251.

J Gastrointest Surg (2009) 13:2201–2211
DOI 10.1007/s11605-009-1004-6

PANCREAS CLUB

Summary of Proceedings at the 43rd Annual Pancreas Club Meeting

William R. Schiller

Received: 21 July 2009 / Accepted: 14 August 2009 / Published online: 9 September 2009

Abstract The 43rd Meeting of the Pancreas Club was held on May 30 and 31, 2009 at Northwestern University coincident to the meetings of the Society for Surgery of the Alimentary Tract and Digestive Disease Week. For the first time, the Pancreas Club meeting was extended to 1.5 days. There were 115 abstract submissions of which 42 were chosen for oral presentation, and 67 were assigned to the poster category. Within the oral category, 30 were allowed 10 min for presentation and 5 min for discussion, while 12 were assigned to 3-min presentations followed by 2 min for discussion. In the poster group, 20 abstracts were selected for "Professor Rounds" discussion by senior pancreatologists during the formal poster viewing sessions.

Keywords Pancreatic cancer · Pancreatitis · Diseases of the pancreas

Session I, held on Saturday afternoon May 30, 2009 concerned topics related to both clinical and basic science aspects of pancreatic cancer. The first paper, "Targeted Nanotherapy of a Suicide Gene (Diphtheria Toxin DNA) Effectively Kills Pancreatic Cancer Cells" by Showalter et al, reported efforts to target mesothelin (MSLN) overexpression in pancreatic cancer cells using a proven nanoparticle technique to deliver Diphtheria toxin A (DT-A) to human pancreatic cancer cell lines in vitro. This suicide gene was transfected to the cancer cell lines using a previously described technique. One dose of DT-A nanotherapy kills over 85% of pancreatic cancer cells in 6 days. There was some discussion following the presentation concerning the reason for the survival of the remaining cells. It was proposed that either the cells were MSLN negative, or there was a failure of DT-A transfection. The overall result of this experiment revealed that high MSLN-expressing pancreatic cancer cells responded to a nanoparticle suicide gene delivery system by a greater than 95% inhibition of protein translation as a marker for cell death. The investigators concluded that these findings might be used as a therapeutic technique against pancreatic cancers.

The next paper, "Heat Shock Factor-1 is Critical for the Survival of Pancreatobiliary Tumors" explored a previous finding that because HSF1 (a transcription factor for multiple cell survival proteins such as HSP70) is overexpressed in pancreatobiliary cancer cell lines compared to normal, it might be possible to produce cancer cell apoptosis by inhibition of expression of HSF1. Cancer and normal cell lines were studied by western blot and human pancreatic cancer specimens by immunohistochemistry. The authors, including Dudeja et al., confirmed the overexpression of both HSF1 and HSP70 in cancer cell lines and cancer specimens. Inhibition of both HSF1 by HSF1siRNA and of HSP70 by Tripotolide significantly reduced the viability of pancreatic and cholangiocarcinoma cell lines. This effect seemed related to activation of caspase-3, cell apoptosis, increased annexin V staining, and cell death. The authors proposed development of this technique as a new therapeutic modality against pancreatic cancer.

The following paper, "Beta-Lapachone Induces NQO1 Dependent Pancreatic Cancer Death" explored another mode of chemotherapy against human pancreatic cancer. Beta-lapachone (β-lap) is a cancer-selective agent that kills cells that overexpress NAD(P): quinone oxidoreductase (NQO1). Since NQO1 is overexpressed in pancreatic cancer by a factor of 20 compared to normal cells, the

W. R. Schiller (✉)
PMB 300 223 N. Guadalupe,
Santa Fe, NM 87501, USA
e-mail: wrschiller@hughes.net

authors, including Bey et al., hypothesized that pancreatic cancers would be killed in an NQO1-dependent manner when exposed to β-lap. Laboratory induced expression of NQO1 in both human and murine pancreatic cancer cell lines was used in vitro to provide an experimental target for varying concentrations of β-lap for 2 h to determine the LD50 of the drug. They reported in this preclinical model that β-lap is lethal in an NQO1 dependent manner in both murine and human pancreatic cancer cells. They proposed further refinement of this modality to produce a nontoxic chemotherapeutic agent.

In the next paper entitled "Perioperative Mortality after Pancreatectomy: A Simple Risk Score," Hill et al. used a national dataset to create a risk score to predict in-hospital mortality after pancreatic resection for benign and malignant disease. Logistic regression and bootstrap methods were used to analyze 16,116 records for variables such as age, gender, comorbidities, diagnosis, type of resection, and hospital volume. Coefficients from these analyses were used to create integer scores for each variable and calculate an additive risk score. They described stratification into low-, medium-, and high-risk groups with observed mortality of 1.3%, 4.9%, and 14.3%, respectively; $p<$ 0.001. The additive scores were constructed so that 0–9 was assigned to the low-risk group, 10–17 to the medium-risk group, and 18–28 to the high-risk group. They described this predictive tool as disease-specific and able to account for differences in procedure type. They proposed that a score greater than 17 might indicate prohibitive risk.

Poultsides et al. reported their experience with mucinous neoplasms of the pancreas in a presentation entitled "Malignancy in Intraductal Papillary Mucinous Neoplasms of the Pancreas: Does Size Matter?" The objective of this study was to test the validity of the International Association of Pancreatology guidelines for the management of IPMNs. They described their experience with 303 resected IMPNs, where preoperative imaging data had classified as main duct neoplasms in 12%, branch duct neoplasms in 46%, and combined lesions in 42%. The incidence of invasive and in situ carcinoma was 58% and 22% in main duct lesions and 56% and 21%, respectively, in combined IPMNs. Branch-duct IPMNs harbored invasive carcinoma in 27% and in situ carcinoma in 20% of cases. Branch-duct IPMNs with invasive carcinoma were radiographically larger (5.2 vs. 2.7 cm, $p<0.001$) than branch duct IPMNs without invasive carcinoma. Additionally, the incidence of invasive and in situ carcinoma in branch duct IPMNs with a solid compartment was 58%, and only 13% in branch duct IPMNs without a solid component. Furthermore, in branch duct IPMNs without a solid component, the incidence of in situ carcinoma (25%) did not correlate with size greater than 3 cm or the presence of symptoms. Discussants following the presentation indicated their predominant opinion that symptomatic lesions should be resected. Dr. Sushanth Reddy was the presenter of this study and received the Kenneth Warren Research Foundation Award.

The next paper by Correa-Gallego et al. was entitled "Incidental Pancreatic Cysts: Do We Really Know What We are Watching?" The management of asymptomatic cystic neoplasms of the pancreas, usually discovered incidentally is still being debated since a specific preoperative diagnosis is often inaccurate. The authors reviewed the records of 330 such patients whose lesions had been discovered by radiographic or ultrasound techniques. Of the 330 patients, 136 were operated upon at the time of diagnosis. The majority of the patients were female (62%) and of the 136, the mean age was 61 years and the mean cyst size was 37 mm. Among the lesions presumed to be main duct or combined IPMNs, 15 of 16 were confirmed after resection, as were 11 of 12 lesions preoperatively throught to be serous cystadenomas. However, in 50 lesions thought to be branch duct IPMNs, only 32 were confirmed as such by histopathology. Ten of this remainder group revealed main duct extension while eight others were categorized as a variety of neoplastic and benign pancreatic cysts. In those patients not treated surgically, 79% were believed to have branch duct IPMNs.The authors summarized by stating that their preoperative diagnosis was incorrect in one third of cases, and 5% of cases were not neoplastic. Their conclusion was that better diagnostic methods are needed in order to formulate more appropriate treatment strategies.

The first of the short presentations was entitled "Histopathologic Basis for the Favorable Survival After Resection of Intraductal Papillary Mucinous Neoplasm-Associated Invasive Adenocarcinoma" by Poultsides et.al. This study was designed to analyze pathological features that could account for improved survival of patients with IPMN as compared to pancreatic duct adenocarcinoma (PDA) after curative resection. Median survival rate was 43 months after resection for IPMN-associated vs 19 months for standard PDA ($p<0.001$). To that end, a single institution's experience of 1,260 consecutive patients was examined using Log rank and Cox regression analysis to identify factors associated with survival. Their presentation revealed that the favorable biologic behavior of IPMN-associated cancer compared to PDA is based on the lower rates of advanced T-stage and lower incidence of five factors: lymph node metastases, high tumor grade, positive resection margin, and perineural and vascular invasion. Further discussion indicated that the increased survival of IPMN-associated tumors was clearly associated with the lower incidence of lymph node metastases. The two types of tumors seem to be biologically different.

The next short session was entitled, "Is It Safe to Observe Asymptomatic Branch Duct or Mixed-Type Intra-

ductal Papillary Mucinous Neoplasms (IPMN) less than 3 cm and Without a Solid Component: The Pathological Findings of 16 Patients Who Underwent Pancreatectomy for this Condition" by Weiss et.al. The international consensus guidelines of 2006 recommended observation of asymptomatic branch duct IPMNs less than 3 cm in diameter and without a solid component. In order to provide additional data regarding the validity of this guideline, this paper concerns a retrospective analysis of 16 patients who underwent pancreatic resection for BD or MT IPMN lesions fitting these criteria prior to the publication of these guidelines. Pathological analysis of these 16 specimens revealed the following: 44% low-grade dysplasia, 38% moderate-grade dysplasia, and 18% carcinoma in situ (CIS). None of the specimens revealed invasive cancer or nodal metastasis. One patient died 95 days postoperatively of preexisting renal failure. Surveillance computed tomography (CT) of the 15 postoperative survivors indicate that 12 patients have no evidence of disease, two have stable disease in the pancreatic remnant, and one has recurrent IPMN in the pancreatic remnant. These findings support the 2006 recommendation that close surveillance alone is appropriate for these IPMN lesions. Whether the lesions with CIS will progress to invasive carcinoma remains uncertain; thus, their overall management is unresolved. The subsequent discussion began with an inquiry regarding the rationale for subjecting these 16 patients to surgical resection. The attending surgeons apparently had concerns regarding malignant potential of the frequently observed cellular atypia commonly observed in these tumors. The audience expressed a lack of confidence in the nonoperative management of patients with tumors of the type in question.

The last short presentation for the first day was entitled "Toward Improving Uniformity and Standardization in the Reporting of Pancreatic Anastomoses: A New Classification System by the International Study Group of Pancreatic Surgery (ISGPS)." A systematic search was performed by the authors Shukla et al. to determine the various factors, either related to the pancreatic remnant after resection or to the types of pancreatic anastomoses that have been shown to influence failure rates of pancreatic anastomoses. Based on multi-institutional data, the authors formulated a new classification that incorporates remnant factors such as duct size, length of mobilization, gland texture, and reconstruction factors such as jejunal or gastric anastomoses with the pancreatic remnant, use of duct-to-mucosa anastomoses, invagination of the remnant, and the use of a stent across the anastomosis. This study is an attempt to standardize future reports on outcomes after pancreatic surgery.

The remainder of this session was devoted to the first of two 1-h poster sessions augmented by poster-side Professor Rounds for a group of preselected abstracts.

The second afternoon session began with a paper by Bausch et al. entitled, "Plectin-1 as a Novel Imaging Biomarker for Pancreatic Cancer." Using immunohistochemical staining methods, the authors assayed the expression of Plectin-1 in patients with normal pancreas, chronic pancreatitis, pancreatic inflammation, and pancreatic cancer. In addition, they used Plectin-1 targeting peptides conjugated to magnetofluorescent nanoparticles (PTP-NP) together with in vivo MRI fluorescence molecular tomography (FMT) in human xenografted pancreatic cancer to test the suitability of Plectin-1 as an imaging biomarker. They detected staining for Plectin-1 in all specimens of pancreatic cancer while being absent in normal pancreas. It was not detectable in the majority of specimens with either chronic or acute pancreatic inflammation, weak staining being observed in a majority of specimens. Plectin-1 staining was present in all metastatic foci which were assayed. In vivo imaging of the xenografted pancreatic cancers by MRI and FMT using PTP-NP resulted in observation of significant accumulation of the targeting probe. These data suggest that Plectin-1 is a sensitive and specific marker for pancreatic cancer and may be used clinically to improve detection and staging. Discussants seemed in agreement that it is unknown as to why Plectin-1 is over-expressed in patients with pancreatic cancer. Dr. Dirk Bausch was the presenter of this paper and recipient of the Pancreatic Cancer Action Network Award for this basic science investigation of pancreatic cancer.

The goal of the next paper entitled, "Somatic Mutations of SMAD4 are Associated with Poor Prognosis in Pancreatic Cancer: Functional Annotation of the 'Pancreatic Cancer Genome' Project" was to correlate the presence of specific mutations in somatic genes with survival following resection for pancreatic adenocarcinoma (PA). The authors, including Serrano et al., sequenced over 750 million base pairs of DNA from 23,219 transcripts in a series of 24 cases of PA. In addition, 39 genes that were mutated in more than one of these 24 cancers were sequenced in an additional panel of 90 well-characterized pancreatic cancers. Of these 114 patients, 91 underwent pancreatoduodectomy, and the somatic mutations in 89 of the 91 cancers were correlated with patient survival. When adjusted for age, lymph node status, margin status, and tumor size, only SMAD4 gene inactivation was significantly associated with shorter survival. Patients with SMAD4 gene inactivation survived a median of 11.5 months, compared to 14.2 months for patients without SMAD4 inactivation ($p=0.006$.) It was observed by the discussants that either intragenic mutation or homozygous deletion may result in SMAD4 inactivation. Evaluation of SMAD4 status might be feasible as a clinical guide as to whether to provide aggressive therapy or not based on predicted effectiveness.

Berger et al. presented "Does the Type of Pancreaticojejunostomy After Pancreaticoduodenectomy Decrease the

Rate of Pancreatic Fistula? A Randomized, Prospective, Multi-Institutional Trial," in which they tested the hypothesis that a duct-to-mucosa pancreaticojejunostomy would reduce the rate of pancreatic fistula (PF). Two institutions performed the trial wherein 197 consented patients were stratified by pancreatic texture then randomized to either invagination or duct-to-mucosa pancreaticojejunal anastomosis by a total of eight experienced pancreatic surgeons. There were 97 patients randomized to the duct-to-mucosa group and 100 patients assigned to the invagination group. The primary endpoint was the PF rate, while secondary endpoints included PF grade, postoperative length of stay (LOS), and other morbidities and mortality. While the overall incidence of PF was 17.8%, there was an incidence of 24% in the duct-to-mucosa group but only 12% in the invagination group ($p<0.05$). The median LOS was similar for both groups. Only 8% of patients with a hard pancreatic texture developed PF, while in those determined to have soft texture, PF developed in 27% of patients. When the PF grade was determined, there were five patients from each reconstructive group in Grade A (mild), 14 duct-to-mucosa patients in Grade B compared to five with invaginated gland, and three duct-to-mucosa compared to two patients in the invagination cohort classified as Grade C. There were two postoperative deaths, both thought to be as a direct consequence of PF following duct-to-mucosa anastomosis. Duct-to-mucosa reconstruction did not improve the pancreatic fistula rate as was hypothesized.

The last paper of the first meeting day was entitled, "Pancreatogastrostomy Versus Pancreaticojejunostomy after Pancreatoduodenectomy—Interim Results of a Single Center Prospective Randomized Trial" by Keck et al. Intraoperatively, 59 patients with diagnoses including pancreatic cancer (45%), chronic pancreatitis (12%), and other pathologies (43%) were randomized to either PG or PJ reconstruction. The pancreatic texture in the total study was classified as hard in 48%, although there were more cases of soft pancreas in the PG group than in the PJ group (63% vs 39%). PF occurred in 31% of patients with Grades B and C fistulas being observed in 12% of the total group. There was no difference of the PF between the PG and PJ group (10% and 14%, respectively). In a subgroup of patients classified as having a soft pancreas ($n=30$), there was a nonsignificant trend for fewer fistulas in the PG group compared to the PJ group (11% vs 36%, $p=0.16$).

The first paper of the Sunday session by Sullivan et al. was entitled "Expression of a Pro-Metastatic Splice Variant of Osteopontin, OPN-C, in Human Pancreatic Ductal Adenocarcinoma." The authors state that their recent studies have revealed a concordant expression of osteopontin (OPN) in primary invasive PDA from patients who are smokers. In this report, they investigated the effect of nicotine on OPN and a splice variant OPN-C in PDA cell lines and related the cellular expression and serum levels of OPN and OPN-C to patient smoking habits. They examined the mRNA and protein expression in PDA tissue and in cell lines treated with and without nicotine. The authors studied invasive PDA ($n=40$, 29 smokers and 11 nonsmokers) and IPMN ($n=6$, two smokers and four nonsmokers). Serum levels of OPN were analyzed in the different patient groups by ELISA. PDA cells expressed variable basal levels of OPN and nicotine treatment increased OPN expression in all cell lines. Nicotine also induced expression of OPN-C in cells and in patient samples. OPN-C was found in 87% of invasive PDA specimens of which 73% were smokers. Levels of OPN-C correlated well with higher expression levels of total OPN in tissue and serum from patients with invasive PDA. Serum levels of OPN seemed not to be a good marker for PDA. The findings of this study suggest that OPN-C may have value as a diagnostic and prognostic marker of invasive PDA, especially in the smoking population.

"Core Signaling Pathways in Human Pancreatic Cancers Revealed by Global Genomic Analysis" by Jones et al. described a comprehensive genetic analysis of 24 pancreatic cancers. They found that pancreatic cancers contain an average of 65 genetic alterations. These alterations consisted of various amplifications, deletions. and point mutations. The changes defined a core set of 12 cellular signaling pathways and processes that were each altered in 67% to 100% of tumors. They reported that 541 genes were at least 10-fold overexpressed in greater than 90% of the 24 cancers in the study. Included were 54 overexpressed genes predicted to be on the cell surface or secreted by the neoplasm. Genetic alterations were found at increased incidence in smokers and in those with family history of pancreatic cancer, compared to those with none of the above-risk factors. They stated that genetically altered core pathways and regulatory processes only became evident once the coding regions of the genome are analyzed in depth. Dysregulation of these core pathways and processes through mutation can explain the major features of pancreatic tumorigenesis.

The next paper was entitled "Obesity Potentiates the Growth and Dissemination of Pancreatic Cancer" by Zyromski et al. who used a novel in vivo model to demonstrate the influence of obesity on pancreatic cancer growth. They studied three strains of mice which included lean animals and adipokine (leptin)-related obese animals, either those with leptin resistance or those in which leptin was absent. These obese mice were of interest because of their lack of satiety control secondary to diminished leptin expression which may increase the risk of pancreatic cancer development. These numerically equal experimental groups were prepared by injection into the flank of murine pancreatic cancer cells with the intent to allow a 5-week

study period. Serum adipokine and insulin levels were also determined. Both obese strains of mice developed larger tumors and had significantly ($p<0.05$) greater metastases and mortality compared to lean mice. Serum adipokine concentrations in all three strains correlated negatively, while serum insulin concentrations correlated positively with tumor proliferation ($p=0.04$ and <0.01, respectively). This study supports the hypothesis that obesity may modulate tumor microenvironment and thereby promote pancreatic cancer growth and dissemination. The pro-inflammatory state associated with obesity appears to result in increased incidence of lymph node metastases and decreased survival times following experimental tumor implantation. The discussants questioned the origin of the increased numbers of adipocytes seen in the tumors of obese mice. These adipocytes might be considered as having originated from the tumor itself or from the host during growth of the implanted tumor.

Hamilton et al. presented a paper entitled, "Targeted Alteration of Peptide Sequence Improves Efficacy of a Pancreas Cancer Vaccine." Mesothelin is an immunogenic protein that is expressed at high levels on pancreatic cancer but at low to nonexistent levels in normal tissues. The authors assume this protein to be a suitable target for immunotherapy. The binding affinity for experimentally optimized mesothelin peptides to mouse MHC Class I molecules was compared to their respective native and unoptimized peptide sequences. Survival was examined by challenging mice with cancer cells injected into the flank 2 weeks following vaccination with optimized mesothelin peptide. Median survival was significantly prolonged in mice receiving vaccination with the optimized peptides for which there was demonstrated increased MHC binding stability. There was no survival benefit observed in groups vaccinated with the peptides that did not have improved MHC stability. The investigators theorized that this same strategy might be used to develop an optimized vaccine for humans. The first paper presented the previous day of the program seemed to confirm the potential use of mesothelin overexpression in pancreatic tumor cells as a basis for targeted therapy.

The next paper by Kennedy et al. was entitled, "HuR Expression Level Dictates Gemcitabine Efficacy Against Pancreatic Cancer and Correlates with Survival After Surgical Resection." Care of patients with PDA includes surgical resection when appropriate and gemcitabine (GEM)-based chemotherapy. GEM is administered as a prodrug which is activated within cells by the enzyme deoxycytidine kinase (dCK) producing two phosphorylated GEM metabolites that inhibit DNA chain elongation and cause cell death. Hu antigen R (HuR) is a stress-related protein that binds RNA and regulates gene expression post-transcriptionally. Because it has been reported that alterations in HuR expression have prognostic significance in a variety of cancers, the investigators studied the consequences of modulating HuR levels in PDA and documented possible chemical value of HuR expression levels in resected PDA patients. HuR cDNA sequence was transfected into several pancreatic cancer cell lines which were then validated for stable overexpression of HuR. These transfected cells were seeded into 96-well plates and treated with various chemotherapeutic agents. They reported that HuR-overexpressing pancreatic cancer cells were up to 30-fold more sensitive to treatment with GEM compared to control cells. They found that HuR overexpression elevates, while HuR silencing reduces dCK protein expression in PDA. In a parallel clinical study, they found a 7-fold increase in risk of mortality in PDA patients with low cytoplasmic HuR levels compared to patients with high HuR levels treated with GEM. Median survival for the low expression group was 15.3 months while the median survival for the high expression group had not yet been reached at 40 months follow-up. Their conclusion was that HuR levels in PDA modulate the therapeutic efficacy of GEM through its activating enzyme dCK and targeted therapeutic HuR up-regulation in pancreatic cancer cells may enhance the current GEM-based treatment strategy.

Another paper regarding the use of Gemcitabine entitled "Does Gemzar Improve Survival in Resected Cancer Patients?" was presented by Androutsopoulos et al. A prospective surgical database identified 579 patients who had undergone resection for PDA. For the entire group, 1-, 3-, and 5-year survival rates were tabulated by whether adjuvant treatment included gemcitabine (G). Patients who received G ($n=199$, 34%) compared to no gemcitabine ($n=379$, 65%) had a significantly improved survival at 1 (80% vs 55%), 3 (35% vs 20%), and 5 (20% vs 12%) years. The addition of gemcitabine as an adjuvant treatment resulted in a statistically significant increase in survival including patients with moderately differentiated tumors, perineural or vascular invasion and those with positive lymph nodes.

A third paper in the session regarding the use of adjuvant Gemcitabine for pancreatic cancer was entitled, "Impact of Gemcitabine-based Neoadjuvant Chemoradiotherapy (NCRT) for Locally Advanced Resectable and Unresectable Pancreatic Adenocarcinoma." The authors, including Kato et al. reported 58 patients with locally advanced pancreatic carcinoma. These patients received radiotherapy over 5 weeks and weekly infusion of gemcitabine preoperatively and then underwent restaging 4 to 6 weeks after completion of NCRT and were taken to surgery. Overall cumulative 1- and 3-year survival rates for all 58 patients were 60.3% and 23.4%. They concluded that NCRT for locally advanced pancreatic carcinoma can select the patients who are likely to benefit from aggressive resection, even if the tumor is determined unresectable due to the involvement of the

major vessels such as celiac and/or superior mesenteric arteries. Discussants inquired concerning the protocol for restaging of treated patients and the potential planning for refining this type of therapy.

A short presentation entitled, "Novel Biomarkers for Pancreas Cancer in the Plasma Peptidome" by DeMeure et al. concerned the search for biomarkers to allow for early detection of pancreatic cancer. Plasma is a complex bodily fluid; therefore, the authors chose to study a low molecular weight fraction which they referred to as plasma peptidome. This plasma fraction is stable over time and contains peptides from 259 different genes and/or proteins. Peptides from QSOX1 and from Serpin F2 genes were detected in the peptidome of 67% and 71% of specimens, respectively, but never in normal healthy donors. These genetically expressed peptides were also observed in 80% of patients with IPMN. When patients with subsequently resected pancreatic cancers were evaluated for these specific peptides, QSOX1 was detected in 60% of these patients and Serpin F2 in 73% of those evaluated. These peptides were also demonstrated by immunohistochemical staining of cancer cells in 12 of 14 operative tumor specimines. The authors summarized by stating that plasma QSOX1 and Serpin F2 warrant further investigation as potential biomarkers in pancreatic cancer.

The last of the morning short presentations was given by Bildzukewicz et al. The paper was entitled, "An Evaluation of a New Chemotherapeutic Strategy: Exogenous Mutant PARP-1 Expression Sensitizes Pancreatic Cancer Cells to Chemically Available Platinum-Based Agents." Poly(ADP-ribose) polymerase-1 (PARP-1) is a nuclear protein that regulates many cell functions including differentiation, proliferation, and apoptosis. It has been shown that cells that are deficient in BRCA-2 and related genes are sensitive to PARP inhibitors. The aim of this study was to determine whether increased expression of the PARP-1 protein and functional mutants would lead to changes in sensitivity against various chemotherapeutic agents and PARP inhibitors. Plasmids containing three different point mutants in various domains of the PARP-1 enzyme were transfected into pancreatic cancer cell lines. These cells were then tested against a panel of chemotherapeutic agents and PARP-1 inhibitors. Although there was no difference in cell viability when treated with PARP inhibitors alone, treatment of the two PARP-mutated overexpressed cell lines with cisplatin and carboplatin resulted in a significant sensitivity to these agents. The experiment showed that mutations in PARP-1 can allow pancreatic cells to become sensitized to chemically available platinums, possibly by interfering with the ability of PARP-1 to bind to DNA. This strategy may be especially applicable to BRCA-2-deficient pancreatic cancers.

The first paper of the second morning session was entitled, "10-Year Follow-up Following Pancreaticoduodectomy (PD) and a Novel Interferon-Based Adjuvant Chemoradiation (IFN-CRTx) for Pancreatic Head Cancer." The authors, including Picozzi et al., presented their 10-year data from a national trial using external beam radiation plus a simultaneous three-drug chemotherapy regimen including 5-FU, cisplatin, and interferon-alpha administered following PD for pancreatic cancer. The report included 43 patients, mean age 62 years, and a history of positive surgical margins in 51%. The follow-up reported was a mean of 64 months. The 1-, 2-, and 5-year overall survival rates were 90.7% (95% confidence interval, 82–99%), 55.8% (41–71%), and 44.2% (29–59%), respectively. This study represents one of the best survival benefits reported to date with resected pancreatic cancer. The discussion included acknowledgement that this regimen is toxic and requires skilled and dedicated care by the oncology team.

The next paper by Fatima et al. was entitled "Pancreatoduodenectomy for Ductal Adenocarcinoma: Implications of Positive Margin on Survival." The goal of this study was to explore the impact on survival of a positive pancreatic resection margin beyond a general concept of it being a poor prognostic factor. A retrospective study of 617 patients who had undergone pancreatoduodenectomy in the time period between 1981 and 2007 was reported of whom 24% had a positive resection margin (R_1 or R_2). Median survivals after R_0 (n=468), R_1 (n=127) and R_2 resections (n=22) were 19, 15, and 10 months, respectively ($p<0.001$). In patients with en-block resection (n=411) vs R_0 resection after re-resection of an initial positive margin (n=57), there was no difference in survival (19 vs 18 months, p=0.28). The presence of a residual positive margin was significantly associated with death (p=0.001). They concluded that while a negative margin is the goal during resection of pancreatic cancer, a similar long-term survival duration can be achieved with intraoperative resection of an initially positive margin.

Naito et al. presented a paper entitled "Patterns of Disease Failure at Autopsy Following Resection for Stage I/II Pancreatic Adenocarcinoma." Despite surgical resection, most patients with Stages I or II disease will develop disease recurrence and eventually die of their disease. This study was designed to compare the clinicopathologic features and genetic status of Dpc4 in pancreatic cancers at diagnosis and after death in 222 patients who had undergone autopsy. The median overall post-surgical survival was 24 months. There were two patterns of recurrence, either local tumor recurrent growth or development of widespread metastases. Gross evidence of recurrent cancer was found in 20 of the 22 patients whereas the remaining two patients had died of other causes. Metastatic recurrence was seen in 85% of patients. Recurrent

carcinoma within the remnant pancreas was seen in 50% of 20 patients who died from their disease, and in three of these patients, it was the sole site of recurrent disease. Local recurrence was seen in 87% of patients with a positive surgical margin but only in 36% of patients with a negative margin ($p=0.07$). There was no relationship between disease burden at death and treatment history. Loss of Dpc4 immunolabeling was observed in 47% of the operative specimens and all patients so identified had metastatic disease, also exhibiting loss of Dpc4 labeling. Conversely, among the remaining patients with intact Dpc4 labeling in the resected specimens, five patients demonstrated intact Dpc4 in the recurrent tumor specimens whereas three showed Dpc4 loss and two patients had no evidence of recurrent tumor at autopsy. A predominant feature of the discussion included the issue of how chemoradiation therapy was administered since it is known that radiation therapy decreases the incidence of local recurrence.

The last paper of the morning entitled "Pancreatectomies Associated with Vascular Resection for Ductal Adenocarcinoma of the Pancreas: A Single Institution Experience" by Del Chiaro et al. documented the effect on survival of vascular resection in association with pancreatic resection. A 20-year retrospective experience with vascular resection plus pancreatectomy for pancreatic cancer yielded 160 patients for further evaluation. Overall, 185 vascular segments were resected in this group on suspicion of being invaded by the pancreatic neoplasm. Pathology confirmed vascular infiltration in 62% of this patient group. They concluded that when these vascular resections were performed, there was a fraction of patients who exhibited prolonged survival and some were able to reach the 5-year survival cohort.

The final hour of the morning was committed to formal viewing of the posters with Professor Rounds poster-side for Posters of Note. These abstracts may be viewed online at www.PancreasClub.com.

The relationship of activated tryspin to acinar cell death was the subject of the first paper of the afternoon session entitled "A New Paradigm of Cell Death during Pancreatitis: Role of Cytosolic Cathepsin B." The aim of this study by Dawra et al. was to elucidate whether tryspin or cathepsin B released during the inflammatory process contributes to apoptotic cell death. Supramaximal stimulation of pancreatic acinar cells with caerulein in vitro resulted in a significant increase in trypsin and cathepsin B activity in the cytosol. This was accompanied by a significant increase in cytochrome c and caspase 3. Inhibition of cathepsin B resulted in a significant decrease in caspase 3 activity. Addition of cathepsin B but not active trypsin to unstimulated permeabilized acinar cells resulted in caspase 3 activation. The results of their experiments showed that release of cathepsin B into the cytosol of pancreatic acinar cells is sufficient to produce apoptotic cell death by means of mitrochondrial changes and that activated trypsin does not directly cause the apoptosis observed during pancreatitis.

The next paper represented an attempt to address the issue of whether early and/or persisting organ failure (OF) outweighs the role of such local complications of acute pancreatitis (AP) as necrosis or pancreatic infection in determining outcome and was entitled "Early and Persisting Organ Failure is a Risk Factor for Pancreatic Infections and Prognosis in Severe Acute Pancreatitis: A Prospective Multicenter Analysis." The authors included Hermeneit et al. from six European surgical referral centers. The study included 188 patients who were enrolled within 96 h of disease onset. Intrapancreatic necrosis was observed in 140 of these patients by means of CT imaging. Sixty-nine patients in the total group developed pancreatic infections, and 27 patients (14%) died. Most instances of OF occurred within the first week of the onset of symptoms, and prognosis seemed consistently related to the type and severity of OF. Pulmonary failure had the lowest impact on mortality, while renal and cardiocirculatory failure were associated with 50% mortality. The presence of intrapancreatic necrosis and pancreatic infections resulted in a mortality rate of 14% and 30%, respectively. In 70% of all pancreatic infections, recurring subsequent intervention or surgery ($n=59$), early and persisting multiple organ dysfunction syndrome (MODS) was evident during the first week of AP, whereas in only 25% of these patients MODS developed as a consequence of the mere presence of infection. Eight patients with FNA-proven infection or necrosis without MODS were successfully treated by conservative means. They concluded that early and persisting OF seems to be of higher prognostic importance than local morphological complications in determining mortality.

Nealon et al. presented "A Follow-up Report: Functional Status is Preserved in Long-Term Follow-up in Patients with Chronic Pancreatitis (CP) Treated with Ductal Decompression Compared to Non-operated Patients: A Prospective Analysis." The authors presented data up to 20 years after enrollment in a prospective study of functional status following pancreatic ductal decompression procedures in patients with CP. They also documented the validation procedure for a revision of their system for stratifying severity in these individuals. Operations for decompression included the Puestow longitudinal pancreatojejunostomy and the Frey procedure. The comparison cohort of nonoperatively treated patients was accumulated due to factors such as patient choice, small ducts, non-debilitating pain and prohibitively poor risk. The total group comprised 491 patients, 138 of whom were enrolled in the non-operative group. The severity staging system

stratified the group into 319 patients with mild to moderate disease while 172 patients were designated as severe. They reported that operative drainage durably delayed the progressive loss of function in CP patients. Pain relief (as defined by being free of narcotic use) was documented in 84%, 77%, and 89% at the 5-, 10-, and 15-year follow-up, respectively. Quality-of-life improvement was reported in 89% of the operated compared to 20% of the nonoperative group. Weight gain was observed in 77% of the operated compared to 26% of the nonoperative group.

The next paper entitled "Spot Urinary IFABP on Admission is Superior to Apache II Scores as a Prognostic Tool in Acute Pancreatitis" was presented by Villatoro et al. Intestinal fatty acid binding protein (IFABP) is a small protein located at the tip of microvilli, which assists in fatty acid absorption. While IFABP excretion is a sensitive marker of shock and intestinal ischemia, this paper addressed the question as to whether spot analysis could reliably replace 24-h urine collections as a technique for performance of this test. Admission urine specimens followed by samples collected at 24, 48, and 72 h post-admission were utilized for this laboratory determination in 56 patients who required urinary catheterization as part of their medical treatment. These specimens were analyzed by ELISA and variables such as daily APACHE II scores, severity and outcome as determined by Atlanta criteria, admission to intensive care and length of hospital stay were collected. There was a significant positive correlation with outcome ($p<0.01$) with APACHE II scores ($p<0.01$), intensive care admission ($p<0.05$), and hospital stay ($p<0.05$). The accuracy of IFABP determinations decreased after 24 and at 72 h and bore no significant correlation with the study variables. This decreased accuracy after the initial 24 h of admission was thought to be a consequence of an IFABP level decrease secondary to fluid resuscitation.

"Predictors of Common Bile Duct Stones during Early Endoscopic Retrograde Cholangiopancreaticography (ERCP) in Acute Biliary Pancreatitis" was presented by van Santvoort et.al. The aim of this study was to evaluate common radiological and biochemical predictors for common bile duct stones (CBDS) in a large prospective cohort of 173 patients in 15 Dutch hospitals with acute biliary pancreatitis (ABP) undergoing early ERCP within less than 72 h after onset of symptoms. Abdominal ultrasound (US) and/or CT were performed on admission and liver biochemistry indices were obtained daily. Patients were stratified according to severity of ABP and the clinical, ratiological and biochemical predictors were assessed by univariate logistic regression. Analysis revealed that 57% of the 173 patients enrolled in the study had predicted severe ABP, 12% exhibited dilated bile ducts and 9% had CBDS on US/CT. When ERCP was performed, CBDS were found in 53% of the group. Only gamma-glutamyltransferase and alkaline phosphatase showed a significant association with CBDS, but both tests proved to have low discriminatory power. They summarized by stating that common predictors for CBDS do not seem valuable in APB and suggested that magnetic resonance imagery might be more selective, especially when choosing patients for ERCP and stone removal.

The next paper assessed whether a proposed TNM-based staging and proliferative activity-based grading has clinical value for pancreatic endocrine tumors (PETs). The study, entitled "Pancreatic Endocrine Tumours: Improved TNM Staging and Histopathological Grading Allow a Clinically Efficient Prognostic Stratification of Patients" by Falconi et al. contained information from 274 patients with PET operated upon from 1991 to 2005. According to the WHO classification, 246 were well-differentiated neoplasms (51 benign, 56 uncertain, and 139 carcinomas), and 28 were poorly differentiated carcinomas. Grading was based on Ki67 immunohistochemistry. The prognostic value of this system was ascertained by survival analysis. This analysis highlighted the fact that in the absence of nodal and distant metastases, infiltration, and tumor dimensions over 4 cm had prognostic significance. The T parameters of the grading system were appropriately modified to reflect this finding. The 5-year survival for the improved TNM stages I, II, III, and IV were 100%, 93%, 65%, and 35%, respectively, and multivariate analysis identified TNM stages as independent predictors of death. Ki67-based grading resulted in independent prediction of survival. They concluded that both the improved TNM grading system and Ki67 index allowed for prognostic stratification of patients.

"Clinical Utility of Secretin MRCP for Pancreatic Diseases" was presented by Kent et.al. This paper represents an effort to define the clinical usefulness of administering secretin to selected patients in whom MRCP is performed (sMRCP) in order to evaluate pancreatic function and ductal anatomy more clearly. Use of sMRCP was reported in 174 patients for five different indications. Overall, use of sMRCP provided additive diagnostic value in 36% of cases. The sMRCP technique produced the highest yield of information in the postoperative setting and in those patients with a history of pancreatitis. It was of little use in situations involving poorly characterized abdominal pain and there was a low yield of additional information in patients with cystic lesions.

The first of the afternoon short sessions, "Nesidioblastosis Following Roux-en-Y Gastric Bypass Surgery: A Difficult Balance," was presented by Morgan et al. Nesidioblastosis has been described in bariatric patients who have undergone Roux-en-Y gastric bypass procedures as a significant cause of hypoglycemia postoperatively. Female patients with this syndrome and documented

elevated serum insulin levels were the subject of this report. Five of the six patients in this study were treated by pancreatic resections, and one of these subsequently required insulin for glucose control. The sixth patient was apparently controlled by an insulin regimen alone. They noted that the optimal volume of pancreatic removal is poorly defined as indicated by the necessity for re-resection in two patients (for persistent hypoglycemia) and the resultant diabetic status of two others. They concluded that additional experience is needed to define the optimal management of this syndrome.

Another short presentation was entitled "Anti-inflammatory Effects of the Nigella Sativa Seed Extract, Thymoquinone, in Pancreatic Cancer Cells." The authors, including Chehl et al. noted that in some patients, pancreatic inflammation is a precursor to the development of pancreatic cancer. In this study, they evaluated the anti-inflammatory properties of thymoquinone (Tq) which is known to cause apoptosis and inhibition of PDA cell proliferation. They found that Tq significantly reduced the PDA cell-culture production of TNF-, IL-1β, IL-8, Cox-2, and MCP-1. Tq also inhibited the intrinsic and TNF-, mediated activation of NF-kB in PDA cells, and reduced the transport of NF-kB from cytosol to the cell nucleus. They summarized by stating that Tq provides a promising strategy that combines anti-inflammatory and proapoptotic modes of action.

Following this paper, the annual "How I Do it" Session entitled "Laparoscopic Pancreatic Resection: Pearls for Open Pancreatic Resection" was presented by Michael L. Kendrick. A video recording of this session is available online.

The final session of the day began with a paper entitled "Predictive Factors for Pancreatic Fistula After Distal Pancreatectomy Using the International Study Group of Pancreatic Fistula (ISGPF) Severity Scale" by Hashimoto, Y. and Traverso, L.W. The aim of this study was to analyze a single institutional experience with distal pancreatectomy (DP) with attention to predictive factors for the development of postoperative PF using the ISGPF severity scale. Their database yielded 215 cases of DP who were operated upon by a single surgeon using suture closure of the pancreatic stump and closed-suction drainage. Drain amylase and volume were measured daily postoperatively. The ISGPF definition of PF was Grade A (asymptomatic for PF), Grade B (any case with evidence of PF), and Grade C (severe symptoms of PF, reoperation, sepsis, or death). For pain management, all patients used patient-controlled epidural anesthesia, and those who failed this technique were managed by intravenous patient controlled analgesia (IV-PCA). Soft gland texture; blood loss >700 ml; and need for IV-PCA were associated with a clinically relevant PF as diagnosed by the ISGPF grading system. The use of IV-PCA was thought to predispose to PF due to a tendency to pharmacologically produce sphincter of Oddi spasm.

Cho et al. presented their paper entitled "Laparoscopic Versus Open Left Pancreatectomy: Can Preoperative Factors Indicate the Safer Technique?" The authors performed a multi-institutional analysis of laparoscopic left pancreatectomy (LLP) and open left pancreatectomy (OLP) to determine if risk factors associated with operative morbidity differed between the two techniques and to develop guidelines for the use of each method. The analysis consisted of 693 cases (439 OLP, 254 LLP) in whom patient age and ASA score were similar. Body mass index was higher in patients undergoing LLP while OLP was more often performed for adenocarcinoma and larger tumors. The OLP patients tended to have greater blood loss and longer operative times. Fistula formation after OLP was associated with splenic preservation, operative time greater than 200 min and operative blood loss greater than 300 ml. Variables associated with significant fistula formation after LLP were obesity (BMI>27) and resection specimen length greater than 8.5 cm. They concluded that lower BMI, non-adenocarcinoma diagnosis, and pancreatic tail lesions would be preoperative factors indicating the safety of LLP as the operative technique. Furthermore, no patient cohorts had higher postoperative complication rates after LLP as compared to OLP. They recommended a more definitive prospective and randomized comparative study of these two techniques.

Keck et al. presented "Morbidity after Distal Pancreatic Resection: Analysis of Pancreatic Leak Using the New ISGPS Classifications." A retrospective analysis of 102 patients undergoing DP for risk of postoperative pancreatic fistulas (POPF) was undertaking using the ISGPS classification. Indications for DP were pancreatic cancer (30%), chronic pancreatitis (CP; 34%), or various other malignant or benign diseases (36%). Abdominal drains were always used and in 82% a splenectomy was also performed. Management of the pancreatic stump was performed in 54% by a jejunal Roux-en-Y anastomosis, by suture closure in 42% and by stapler closure in 4% of the group. According to the ISGPS classification, the POPF were divided into grades A, B, or C. The rate of POPF was 20.6% (n=21) with eight patients exhibiting a grade A, nine with grade B, and four with grade C. Risk factor analysis revealed increased development of POPF with stump closure compared to drainage into the jejunum (32% vs 11%) and with female gender (27% vs 10%). The postoperative mortality for the group was 2% and overall morbidity was 35%. In the series, 40% of POPF occurred without any clinical morbid consequences. There was a higher rate of POPF after stump closure; however, the relative frequency of severe leak was higher after pancreatojejunostomy. While other factors such as pancreatic

consistency, BMI or renal function were important in their experience after pancreaticoduodenectomy, they seemed not to influcence POPF rates after distal resection.

The next paper "Delay in Diagnosis of Pancreatic Cancer" was presented by Straub et al. They documented the incidence of a delay in diagnosis of PDA due to an early misdiagnosis and assessed the clinical impact of this diagnostic delay. This study included 198 patients treated for PDA, whose records were reviewed for demographics, symptom description, date of symptom onset, date of true diagnosis, diagnoses attributed to the presenting symptoms during the 1 year prior to true diagnosis, stage at the time of true diagnosis, and operations, procedures, or tests performed prior to true diagnosis. The average age at diagnosis was 66 years. A total of 57 of the patients were misdiagnosed within the year prior to true diagnosis, and of these, 25 patients were subjected to an operation as a result of the misdiagnosis. The most common misdiagnoses were pancreatitis (17.5%), gallbladder disease (12.6%), and gastroesophageal or peptic ulcer disease (10.6%). Disease stage at diagnosis and overall survival were not judged by the authors to have been adversely affected by the delay. An initial misdiagnosis led to an average of 1.4 unnecessary diagnostic or surgical procedures costing on average $4,640 per patient. The most common of these misguided procedures was laparoscopic cholecystectomy. Patients with a delay in diagnosis frequently had symptoms not typically attributed to their misdiagnosis, most commonly jaundice (34%) and weight loss (78%).

"Barriers to Surgical Therapy for Pancreatic Cancer" was presented by Vanderveen et al. addressing the issue that not all patients with potentially resectable pancreatic adenocarcinoma undergo surgical therapy. Using the California Cancer Registry, they identified 3,204 patients with radiographic Stage I/II A tumors. They analyzed such factors as age, gender, urban vs rural residence, time period of treatment, race, and socioeconomic status (SES) as determinate factors impacting delivery of curative-intent surgical therapy. This group of patients was stratified by the performance of resection with curative intent in 27.8%, while 62.2% of these patients had no such procedure. Historic time periods seemed not to be an influence on this phenomenon. Significant barriers based on age were observed with surgical treatment performed in 44.3% of patients less than age 60 compared to only 13.7% of patients greater than age 75. Black race was associated with the lowest rate of surgical therapy (23% vs 28% overall) and patients from rural and small towns were more likely than urban residents to undergo surgical therapy (41% vs 27%). Patients in the highest SES quintile received surgical treatment in 33% of cases, while surgical treatment was only observed in 25% of cases from the lowest SES quintile. Although 58% of patients not subjected to surgical treatment with curative intent were treated with chemotherapy or radiation therapy, the survival benefit of this treatment was minimal compared to no treatment (7 vs 5 months, respectively). The authors concluded that these findings indicated a specific bias against surgical therapy rather than against therapeutic treatment in general. They postulated that targeted education of patients and community providers might improve the ratio of patients to whom surgical care is delivered.

The next paper, presented in the short format, concerned the question of whether the accuracy of CT can be enhanced by the addition of diagnostic laparoscopy and peritoneal lavage (DLPLC) for cytology. "Positive Peritoneal Lavage Cytology is a Predictor of Worse Survival in Locally-Advanced Pancreatic Cancer" was authored by Clark et al. who studied 196 consecutive patients following determination of not being a surgical candidate. They reported that the DLPLC protocol resulted in upstaging of 55 patients (28%) to Stage IV disease. The most common determinant of this advanced staging was positive cytology in the lavage fluid followed by diagnosis of hepatic metastases and peritoneal tumor deposits. These 55 patients with positive DLPLC results had a significantly shorter mean overall duration of survival compared to the remainder of the study group (11 vs 18 months; $p=0.011$). Positive peritoneal cytology as an individual variable was a predictor of shorter survival duration independent of serum CA 19–9, tumor size, multiple mesenteric vessel involvement, location of tumor and evidence of peritoneal or liver metastases by diagnostic laparoscopy ($p=0.005$). This improved accuracy of staging by DLPLC should be considered in the planning of patient treatment and also considered in the execution and interpretation of chemoradiotherapy trials.

The final paper of the meeting by Schneider et al. was entitled "Racial Differences in Survival for Pancreatic Adenocarcinoma: a Case-Controlled Population-Based Analysis using Propensity-Score Matching." The authors addressed the issue regarding the registry-based conclusion that African–Americans (AA) have an increased incidence, higher surgical mortality, and lower survival rate for pancreatic adenocarcinoma (PA) relative to the white (W) population in the USA. They performed a retrospective and matched study to mitigate the effects of baseline heterogeneity in the study population and to examine the true effect of race on survival in PA. Using the data from the Surveillance, Epidemiology, and End Results (SEER) registry to identify an initial patient pool of 35,946 patients, they were able to utilize their propensity score matching technique to perform a case-controlled analysis to better delineate the effect of race on survival. A one-to-one matching scheme produced a final cohort of 7,140 patients (3,635 AA and 3,505 W). After matching, survival functions were determined for the AA and W groups and

compared. There was a significantly better survival duration in W as opposed to AA patients (median 4 months for AA vs 5 months for W., $p<0.001$). However, there were significant differences between AA and W patients in terms of demographics, year of diagnosis, tumor size and grade, and receipt of radiation and surgical therapy. These findings make direct comparison between two groups prone to bias, possibly resulting in distorted statistics as a result of confounding. When the matched cohort was examined in depth, taking these disparities into account, the survival advantage of white patients persisted. This study suggests that this difference in survival may be the result of such confounding factors as combined conditions, socioeconomic factors, and access to care not currently measured by the SEER registry.

This paper concluded the 43rd annual meeting of the Pancreas Club. Northwestern University Feinberg School of Medicine was the site of the initial meeting of the Pancreas Club in 1966 under the leadership of Marion C. Anderson, MD.

J Gastrointest Surg (2009) 13:2212–2218
DOI 10.1007/s11605-009-0972-x

ORIGINAL ARTICLE

The Secretory Phospholipase A2 Gene is Required for Gastroesophageal Reflux-Related Changes in Murine Esophagus

Ashok Babu · David Mauchley · Xianzhong Meng · Anirban M. Banerjee · Fabia Gamboni-Robertson · David A. Fullerton · Michael J. Weyant

Received: 5 May 2009 / Accepted: 15 July 2009 / Published online: 12 August 2009

Abstract
Background The initial response of esophageal mucosa to gastroduodenal reflux is inflammation and hyperplasia. Secretory phospholipase A_2 ($sPLA_2$) is a known mediator of gut inflammation, and its levels are increased in Barrett's esophagus. We hypothesized that the $sPLA_2$ gene is required to produce esophageal mucosal hyperplasia in response to gastroduodenal reflux.
Methods C57BL/6 (n=5) $sPLA_2^{-/-}$ mice and C57BL/$6^{Cg\text{-}Tg(PLA2G2A)703N16}$ mice (n=4) $sPLA_2^{-/+}$ underwent a side-to-side surgical anastomosis between the duodenum and gastroesophageal junction (DGEA). Control animals [$sPLA_2^{-/-}$ (n=5), $sPLA_2^{-/+}$ (n=4)] underwent laparotomy with incision and repair of the esophagus. Tissue was harvested after 4 weeks, and H&E staining was performed to quantify esophageal mucosal thickness. Ki67 and $sPLA_2$ immunostaining were performed to quantitate differences in cell division and $sPLA_2$ expression.
Results Mice expressing human $sPLA_2$ had a 2.5-fold increase in thickness of the esophageal mucosa as compared to controls (p=0.01). A 6.5-fold increase in proliferation (p=0.02) and a twofold increase in $sPLA_2$ expression (p=0.04) were demonstrated in animals exposed to gastroduodenal reflux.
Conclusions The presence of $sPLA_2$ is necessary for early mucosal hyperplasia produced by exposure of the esophagus to gastroduodenal contents. $sPLA_2$ expression is upregulated by gastroduodenal reflux, strengthening its role as a critical mediator of early mucosal hyperplasia.

Keywords Gastroesophageal reflux (GERD) · Esophageal mucosal inflammation

Introduction

Gastroesophageal reflux disease (GERD) is the most common disorder of the esophagus affecting 7% of the USpopulation.[1] Gastroesophageal reflux disease can lead to reflux esophagitis as well as the metaplasia of Barrett's esophagus.[2] The characteristic lesion produced by GERD is one of hyperplasia and mucosal thickening. The central factor in the development of these problems related to GERD is inflammation of the esophageal mucosa.[3,4] Understanding the cellular mechanisms behind the observed hyperplasia is integral to understanding the subsequent pathology produced in the esophageal mucosa such as esophagitis and transformation to malignancy.[4] To date, only limited investigation into the cellular mechanisms underlying esophageal inflammation has been undertaken as most studies have focused only on clinical aspects of the disease.

Histological evidence of exposure of esophageal mucosa to reflux includes basal cell hyperplasia, acanthosis, or thickening of the squamous epithelium, and eosinophilic infiltration of the mucosa.[5] The study of the events that lead to this pre-neoplastic lesion can provide valuable insight into chemoprevention of esophageal adenocarcinoma. Re-

This paper was presented as a poster at the 2008 Society of Thoracic Surgeons Annual Meeting January 2008 in Fort Lauderdale, Florida.

Funding: University of Colorado Academic Enrichment Funds

A. Babu · D. Mauchley · X. Meng · A. M. Banerjee · F. Gamboni-Robertson · D. A. Fullerton · M. J. Weyant (✉)
Division of Cardiothoracic Surgery, Department of Surgery, University of Colorado Denver School of Medicine Aurora, 12631 East 17th Avenue, C310, Aurora, CO 80045, USA
e-mail: Michael.Weyant@ucdenver.edu

cently, the group of phospholipase A2 enzymes has been implicated as a mediator of intestinal inflammation and identified as playing a possible role in tumor development. This group of enzymes is responsible for liberating arachidonic acid from phospholipids for eicosanoid production.[6] A subtype of this group, group IIa secretory phospholipase A2 ($sPLA_2$), is thought to play a role in the pathogenesis of inflammatory bowel disease,[7] mucosal apoptosis,[8] as well as in antigen-presenting cell-mediated intestinal tumorigenesis.[9] Levels of $sPLA_2$ have also been shown to be elevated in samples of human Barrett's esophagus as well as adenocarcinomas, indicating a potential role of $sPLA_2$ in the development of both of these pathologic lesions.[10]

We have observed in a murine model of gastroduodenal reflux that species of mice reported to be deficient in $sPLA_2$ do not manifest the usual histologic changes of hyperplasia and mucosal thickening in response to reflux.[11] In the present study, we demonstrate that the introduction of group IIa $sPLA_2$ into the naturally deficient C57BL/6 mouse restores its ability to generate mucosal hyperplasia in response to gastroduodenal reflux.

Materials and Methods

Generation of Gastroduodenal Reflux in Murine Model

Eight to 10-week-old C57BL/6 (n=5) $sPLA_2^{-/-}$ (Jackson Labs, Bar Harbor, ME, USA) and C57BL/$6^{Cg\text{-}Tg(PLA2G2A)703N16}$ (C57BL/6 microinjected with human $sPLA_2$ gene) $sPLAV_2^{-/+}$ (n=4; Taconic Farms, Germantown, NY, USA) mice aged 8–10 weeks weighing 18–22 g were fed regular chow (Harlan Teklad #2018 Madison, WI, USA) and water ad libidum. Animals were allowed to acclimatize for 10 days prior to surgery. Animals were fasted but allowed access to water for 24 h prior to experimental procedure. Mice were anaesthetized by the intraperitoneal injection of ketamine (80 mg/kg, Fort Dodge Animal Health, Fort Dodge, IA, USA) and xylazine (12 mg/kg, VEDCO, St. Joseph, MO, USA). Body temperature was monitored rectally and maintained at 36.5°C using a heating lamp. Under sterile conditions and with the aid of an operating microscope (Leica MZ95, Wetzlar, Germany), a side-to-side anastomosis was performed between the first portion of the duodenum and the gastroesophageal junction using 10–0 nylon sutures [duodenogastroesophageal anastomosis (DGEA)].[12] Animals were then recovered under a heating lamp. Control animals underwent similar anesthesia and laparotomy with incision and closure of the esophagus superior to the gastroesophageal junction without anastomosis (n=5 C57BL/6; n=4 C57BL/$6^{Cg\text{-}Tg(PLA2G2A)703N16)}$). Animals then were fed ad libitum and weighed weekly to monitor weight gain. The Animal Care and Use Committee at the University of Colorado at Denver Health Sciences Center approved the protocol to perform the necessary survival surgery and tissue harvesting for this project [protocol #77205206(05)1E].

Tissue Harvesting

The mice were euthanized 28 days after surgical induction of gastroduodenal reflux using inhaled carbon dioxide. The entire esophagus and stomach was then removed and flushed with OCT medium (O.C.T. Tissue-Tek, Torrance, CA, USA). Care was taken to identify and use only tissue above the anastomosis for study. Three segments of tissue originating just above the anastomosis were cut into 5-mm lengths, embedded in OCT medium, and frozen in a way that would allow axial sectioning of the esophageal lumen. Serial 5-μm sections were then mounted onto glass slides for histological analysis. This study presents data obtained only from the blocks that were closest to the anastomosis, thus comparing the same segment from all animals.

Morphological Analysis of Esophageal Tissue

Hematoxylin and eosin staining was performed to evaluate mucosal morphology. Four digital images taken around the circumference of each specimen were acquired and three measurements of mucosal thickness were made at equal intervals within each digital image by a blinded observer. This technique was used to accurately estimate average response in light of some variation in mucosal thickness around the circumference of the esophagus. The use of thickness measurement has been suggested and described previously both for mucosal hyperplasia as well as basal cell hyperplasia.[13,14] Data were compared by ANOVA with post hoc Tukey's test for a significance level of $p<0.05$.

Immunofluorescent Staining

Cryosections (5 μm thick) of esophageal tissue were prepared with a cryostat (IEC Minotome plus, Needham Heights, MA, USA) and collected on poly-L-lysine-coated slides. Sections were treated with a mixture of 70% acetone and 30% methanol for 5 min, then fixed with 4% paraformaldehyde for 10 min. Sections were washed with phosphate-buffered saline (PBS), blocked with 10% normal serum for 30 min, and incubated overnight with either polyclonal goat anti-human group II $sPLA_2$ [Santa Cruz Biotechnology, Santa Cruz, CA, USA, cross-reaction with mouse group II $sPLA_2$, 5 μg/ml in PBS containing 1% bovine serum albumin (BSA)] or polyclonal rabbit anti-human Ki67 (Novus Biologicals, Littleton, CO, USA, cross-reaction with mouse Ki67, 5 μg/ml in PBS containing

1% BSA) antibodies. After washing with PBS, sections were incubated with Cy3-conjugated matched IgG (Jackson Immunoresearch, West Grove, PA, USA, 1:150 dilution with PBS containing 1% BSA). To assess specificity, adjacent sections were incubated with non-immune matched IgG (5 μg/ml in PBS containing 1% BSA) and otherwise processed identically. Primary incubation was performed at 4°C, and all other incubations were performed at room temperature. bis-Benzimide was used to stain nuclei (DAPI, imaged on the blue channel) and WGA to stain cell membranes (labeled with Alexa 488 and imaged on the green channel). $sPLA_2$ and Ki67 were imaged using the red (Cy3) channel. Microscopic observation and photography were performed with a Leica DMRXA confocal microscope (Leica Mikroskopie und Systeme GmbH, Wetzlar, Germany).

Image Quantitation

$sPLA_2$ and Ki67 images were quantitated with SlideBook version 4.0 software (I. I. I, Denver, CO, USA). Four random images were taken from each esophageal section at ×40 magnification. All images were taken while blinded to the Cy3 channel. Images were masked to exclude 95% of nonspecific fluorescence as determined from images of negative controls. SlideBook was then used to determine the area (μm^2) of positive staining. Mean area/field was calculated for each section. Data were compared by ANOVA with post hoc Tukey's test for a significance level of $p<0.05$.

Results

Outcome of Surgical Procedure and Health of Mice

In this study, there was no surgical mortality. Weight at completion of study was not different between DGEA and control group, consistent with the previous study (24.6±0.4 vs. 25.5±0.8 g, $p=0.13$). There was no mortality to 28 days. The animals appeared grossly normal at the termination of the experiment. Upon visual inspection of the esophageal tissue after harvest, there grossly did not appear to be any differences among the study groups. Tumor tissue was not grossly identified in any of the specimens. The anastomotic areas in all DGEA animals were identified to be patent as demonstrated by passing a probe through the anastomosis in each animal.

Mucosal Thickness Increased only in the Presence of Both Reflux and $sPLA_2$

Mucosal thickness was measured as an indicator of hyperplasia. C57BL/6 $sPLA_2^{-/-}$ mice had no significant change in mucosal thickness in response to DGEA at 4 weeks. However, C57BL/6 mice microinjected with human Group IIa $sPLA_2$ ($sPLA_2^{+/-}$) undergoing DGEA developed a 2.5-fold increase in thickness of the esophageal mucosa as compared to ($sPLA_2^{+/-}$) sham-operated animals ($p=0.01$). There was no significant difference between strains with respect to mucosal thickness in the control sham-operated groups (Fig. 1).

Introduction of $sPLA_2$ Leads to Cell Proliferation in Response to Reflux

There was no change in cell proliferation in wild-type C57BL/6 $sPLA_2^{-/-}$ animals undergoing DGEA as compared to sham controls at 4 weeks. However, in keeping with the change in epithelial thickness, C57BL/6 ($sPLA_2^{+/-}$) animals had a 6.5-fold increase in Ki67 staining ($p=0.02$), demonstrating a greater number of proliferating cells in response to reflux only in the presence of $sPLA_2$ (Fig. 2).

$sPLA_2$ Levels in the Esophagus are Increased in Response to Gastroduodenal Reflux

In this study, we found that there was no significant staining for $sPLA_2$ in the esophagus of C57BL/6 $sPLA_2^{-/-}$ mice both in the control and DGEA groups. In the C57BL/6 $sPLA_2^{+/-}$ mice, there was a basal level of enzyme expression in the sham-operated animals at 4 weeks. Animals undergoing reflux surgery had a twofold ($p=0.04$) increase in levels of the enzyme after 4 weeks (Fig. 3).

Discussion

Mucosal hyperplasia is known to be one of the earliest responses of the human esophagus to gastroesophageal reflux.[5,15] This study demonstrates a requirement for group IIa secretory phospholipase A_2 for the development of mucosal thickening and increased cell proliferation in a murine model of gastroduodenal reflux. These changes are only apparent in a strain of animal which has been reconstituted with human $sPLA_2$. Importantly, production of this inflammatory enzyme is increased in response to gastroduodenal reflux in the transgenic animals, suggesting a mechanistic link between reflux, $sPLA_2$, and subsequent mucosal proliferation.

This model, utilizing a duodenogastroesophageal junction anastomosis to expose the esophagus to gastric and biliary secretions, had been originally developed in rats and was described to produce esophageal adenocarcinoma and changes similar to Barrett's esophagus in rats over a 40-week period.[12] We have recently adapted this model in mice due to the wider choice of genetically manipulated models. We previously demonstrated that BALB/c mice,

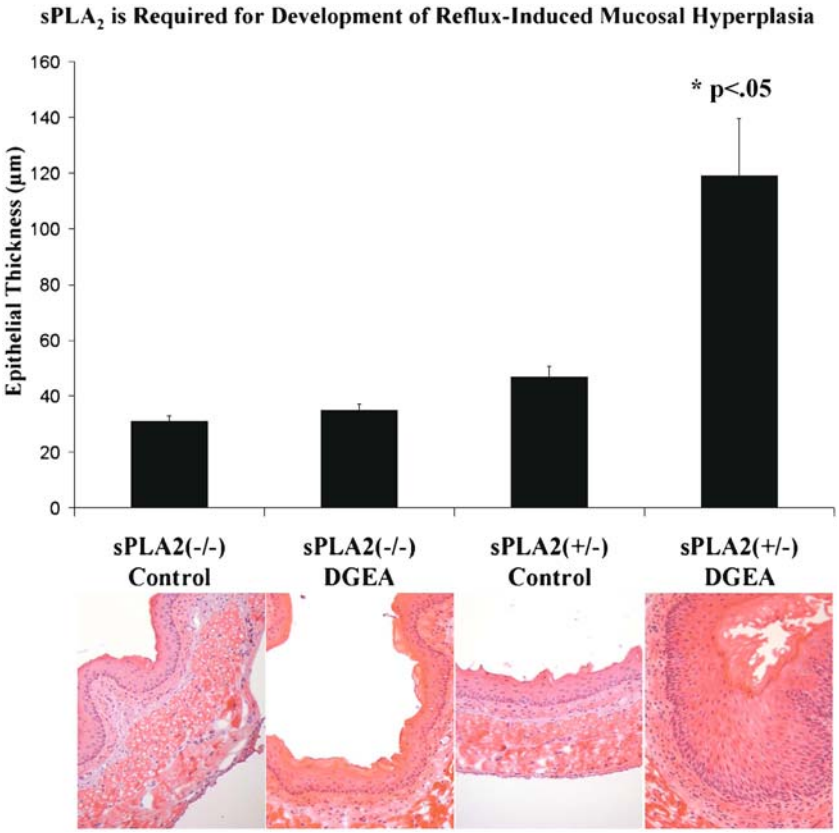


Figure 1 Only $sPLA_2$ expressing animals develop mucosal hyperplasia in response to reflux. Esophageal epithelial thickness was unchanged in C57BL/6 wild-type animals exposed to reflux as compared to sham controls at 4 weeks. In contrast, C57BL/6 animals expressing $sPLA_2$ had a significant increase in epithelial thickness in response to reflux.

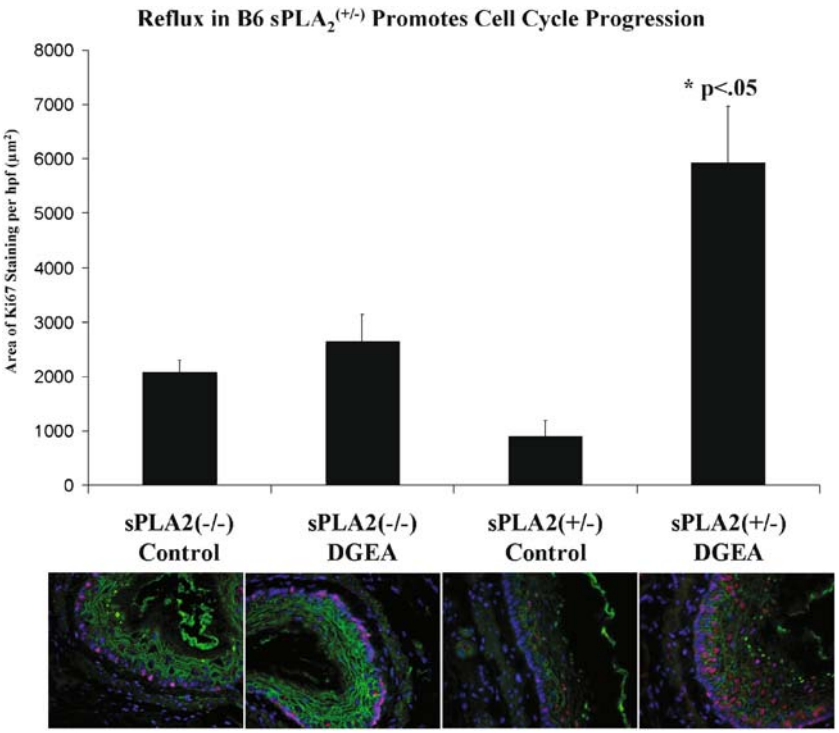


Figure 2 Number of dividing cells is increased in reflux animals with $sPLA_2$ expression as evidenced by increased Ki67 staining area. There was no significant difference in Ki67 staining area among wild-type animals and transgenic control animals.

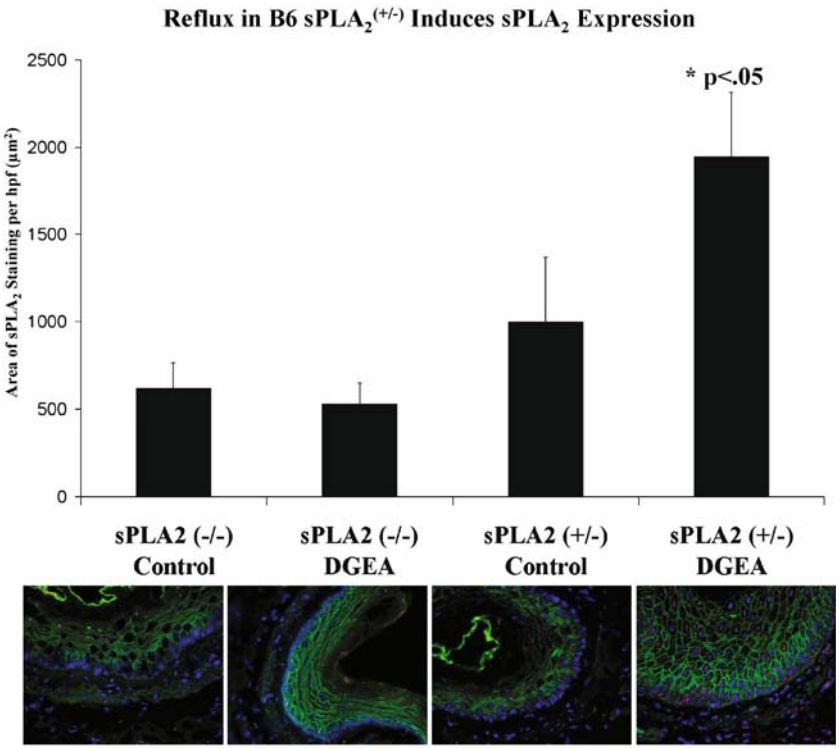


Figure 3 Immunofluorescent staining for $sPLA_2$ demonstrates no significant staining in C57BL/6 wild-type animals as expected. There is a low basal level of expression in $sPLA_2^{(+/-)}$ control animals which is significantly induced by gastroduodenal reflux.

which naturally express $sPLA_2$, had a robust hyperplastic response of the esophageal epithelium in response to gastroduodenal reflux.[11] This led us to hypothesize about a causative role for $sPLA_2$ in this model.

Phospholipase A_2 refers to a group of enzymes which catalyze the rate-limiting step in the metabolism of phospholipids to produce arachidonic acid. Group IIa secretory PLA_2 is a 14-kDa member of this family that has been implicated in a variety of inflammatory diseases including pancreatitis, septic shock, and inflammatory bowel disease.[16–18] Studies of human esophageal tissue have revealed elevated levels of $sPLA_2$ in both Barrett's mucosa as well as esophageal adenocarcinoma, indicating a possible role of $sPLA_2$ in growth and metaplastic transformation of these cells.[10] It is unclear whether the role of $sPLA_2$ in these observed changes is related to arachidonic acid metabolites[19,20] or whether there is another as yet undescribed mechanism. The potent effects of $sPLA_2$ on inflammatory disease are well established; however, its mechanistic link to carcinogenesis remains unknown.

Epidermal growth factor (EGF) and its receptor epidermal growth factor receptor (EGFR) play a fundamental role in the regulation of cell proliferation, differentiation, and survival (anti-apoptosis) and are constitutively expressed in esophageal epithelium.[21] EGFR activation induces nuclear expression of proto-oncogenes such as Fos, Jun, and Myc. EGF receptor and c-myc are overexpressed in Barrett's specialized columnar epithelium and esophageal cancer.[22,23] Interestingly, there is a link between arachidonic acid metabolites and EGF signaling. The release of arachidonic acid and subsequent metabolism is an early requirement for EGF-induced mitogenesis.[24–26] Additionally, exogenous prostaglandin F_2 in the presence of EGF is required for the significant induction of c-myc RNA levels, suggesting a synergy between exogenous arachidonic acid metabolites and EGF in the expression of proto-oncogenes.[27] These are relevant findings considering that EGF/EGFR signaling is an important pathway regulating cell proliferation in the esophageal mucosa as well as its described role in esophageal malignancy.[28,29] In a non-EGF-dependent pathway, $sPLA_2$ expressed by macrophages has been demonstrated to mediate phosphorylation of Akt which leads to downstream growth regulatory effect in these cells.[30] We have planned studies using these surrogate markers of EGF signaling pathways to establish the link between $sPLA_2$ and EGF, which may increase our understanding of $sPLA_2$ as a growth-regulating factor in the esophageal mucosa.

The transgenic mouse used in this study was first generated by Grass et al.[31] in 1996 via microinjection of the human Group IIa $sPLA_2$ gene along with promoter sites to a C57BL/6 embryo. These animals were viable and were found to express high levels of the enzyme in multiple tissues including serum, liver, skin, and intestine. They had a unique phenotype which consisted of hyperkeratosis, epidermal hyperplasia, and adnexal hyperplasia. In contrast to skin disorders such as psoriasis which are characterized by epidermal hyperplasia with inflammation, these animals

did not have inflammatory change in the skin. The authors hypothesized that the reconstituted enzyme likely had a direct effect on cell proliferation and/or apoptosis in the epidermis. The current study capitalized on the natural disruption of $sPLA_2$ in the wild-type C57BL/6 animal and this transgenic model to definitively explore the requirement of $sPLA_2$ for reflux-induced mucosal hyperplasia.

In support of a causative role of $sPLA_2$ in reflux-induced mucosal hyperplasia, we have demonstrated significant induction of $sPLA_2$ expression in esophageal mucosa exposed to reflux for 4 weeks. Though $sPLA_2$ induction in the setting of an inflammatory insult is not surprising, this is the first report of such in an animal reflux model. It is also consistent with previous reports of $sPLA_2$ overexpression in the setting of metaplastic change[11] and implies a $sPLA_2$-dependent effect on esophageal mucosal proliferation in the setting of reflux.

Our observations suggest that $sPLA_2$ is an important regulator of esophageal mucosal growth and the hyperplasia produced by GERD. The relevance of histologic changes seen in this model with respect to Barrett's esophagus as well as esophageal carcinoma remains unknown. However, in similar rodent models, the progression from epithelial hyperplasia to Barrett's metaplasia has been demonstrated, suggesting that these are indeed clinically significant changes.[32]

Given the potential role of sPLA2 in esophageal malignancy as demonstrated by Lagorce-Pages et al.,[10] we will focus our future efforts on studying the role of sPLA2 in the growth and proliferation of human esophageal cancer cells as well. These studies will focus mainly on the use of established human esophageal carcinoma cell lines. Drug inhibitor studies performed in sPLA2-competent mice will also provide further evidence to the importance of this mediator in reflux-related epithelial changes.

Conclusion

In summary, we have shown that the presence of sPLA2 is required for reflux to induce histologic change in otherwise genetically identical animals, highlighting sPLA2 as a potential agent to be studied in the treatment of GERD-related mucosal changes as well as chemoprevention of esophageal cancer.

References

1. Pace F, Santalucia F, Bianchi Porro G. Natural history of gastro-oesophageal reflux disease without oesophagitis. Gut 1991;32:845–848.
2. Zhang HY, Spechler SJ, Souza RF. Esophageal adenocarcinoma arising in Barrett esophagus. Cancer Lett 2009;275:170–177.
3. Lee JS, Oh TY, Ahn BO, Cho H, Kim WB, Kim YB, Surh YJ, Kim HJ, Hahm KB. Involvement of oxidative stress in experimentally induced reflux esophagitis and Barrett's esophagus: clue for the chemoprevention of esophageal carcinoma by antioxidants. Mutat Res 2001;480–481:189–200.
4. O'Riordan JM, Abdel-latif MM, Ravi N, McNamara D, Byrne PJ, McDonald GS, Keeling PW, Kelleher D, Reynolds JV. Proinflammatory cytokine and nuclear factor kappa-B expression along the inflammation–metaplasia–dysplasia–adenocarcinoma sequence in the esophagus. Am J Gastroenterol 2005;100:1257–1264.
5. Takubo K, Honma N, Aryal G et al. Is there a set of histologic changes that are invariably reflux associated? Arch Pathol Lab Med 2005;129:159–163.
6. Diaz BL, Arm JP. Phospholipase A(2). Prostaglandins Leukot Essent Fat Acids 2003;69:87–97.
7. Haapamaki MM, Gronroos JM, Nurmi H, Irjala K, Alanen KA, Nevalainen TJ. Phospholipase A2 in serum and colonic mucosa in ulcerative colitis. Scand J Clin Lab Invest 1999;59:279–287.
8. Wang TC, Goldenring JR, Dangler C et al. Mice lacking secretory phospholipase A2 show altered apoptosis and differentiation with *Helicobacter felis* infection. Gastroenterology 1998;114:675–689.
9. Markova M, Koratkar RA, Silverman KA et al. Diversity in secreted PLA2-IIA activity among inbred mouse strains that are resistant or susceptible to Apc Min/+ tumorigenesis. Oncogene 2005;24:6450–6458.
10. Lagorce-Pages C, Paraf F, Wendum D, Martin A, Flejou JF. Expression of inflammatory secretory phospholipase A2 and cytosolic phospholipase A2 in premalignant and malignant Barrett's oesophagus. Virchows Arch 2004;444:426–435.
11. Babu AN, Meng X, Banerjee A et al. Secretory phospholipase A2 is required to produce histologic changes associated with gastroduodenal reflux in a murine model. J Thorac Cardiovasc Surg 2008;135:1220–1227.
12. Chen X, Yang G, Ding WY, Bondoc F, Curtis SK, Yang CS. An esophagogastroduodenal anastomosis model for esophageal adenocarcinogenesis in rats and enhancement by iron overload. Carcinogenesis 1999;20:1801–1808.
13. Ismail-Beigi F, Horton P, Pope CE. Histological consequences of gastroesophageal reflux in man. Gastroenterology 1970;58:163–174.
14. Allende DS, Yerian LM. Diagnosing gastroesophageal reflux disease: the pathologist's perspective. Adv Anat Pathol 2009;16(3):161–165.
15. Dent J. Microscopic esophageal mucosal injury in nonerosive reflux disease. Clin Gastroenterol Hepatol 2007;5:4–16.
16. Touqui L, Alaoui-El-Azher M. Mammalian secreted phospholipases A2 and their pathophysiological significance in inflammatory diseases. Curr Mol Med 2001;1:739–754.
17. Nevalainen TJ. Serum phospholipases A2 in inflammatory diseases. Clin Chem 1983;39:2453–2459.
18. Vadas P, Purzanski W. Role of secretory phospholipase A2 in the pathobiology of disease. Lab Invest 1986;55:391–404.
19. Smith JB, Willis AL. Aspirin selectively inhibits prostaglandin production in human platelets. Nat New Biol 1971;231:235–237.
20. Samuelson B, Dahlen SE, Lindgren JA, Rouzer CA, Serhan CN. Leukotrienes and lipoxins: structures, biosynthesis and biological effects. Science 1987;237:1171–1175.
21. Ji H, Sharpless NE, Wong KK. EGFR targeted therapy: view from biological standpoint. Cell Cycle 2006;5(18):2072–2076.
22. Lu SH, Hsieh LL, Luo FC, Weinstein IB. Amplification of the EGF receptor and c-myc genes in human esophageal cancers. Int J Cancer 1988;42:502–505.

23. al-Kasspooles M, Moore JH, Orringer MB, Beer DG. Amplification and over-expression of the EGFR and erbB-2 genes in human esophageal adenocarcinomas. Int J Cancer 1993;54:213–219.
24. Mulherkar R, Rao R, Rao L, Patki V, Chauhan VS, Deo MG. Enhancing factor protein from mouse small intestines belongs to the phospholipase A2 family. FEBS Lett 1993;317:263–266.
25. Sellmayer A, Uedelhoven WM, Weber PC, Bonventre JV. Endogenous non-cyclooxygenase metabolites of arachidonic acid modulate growth and mRNA levels of immediate-early response genes in rat mesangial cells. J Biol Chem 1991;266(6):3800–3807.
26. Nolan RD, Danilowicz RM, Eling TE. Role of arachidonic acid metabolism in the mitogenic response of BALB/c 3T3 fibroblasts to epidermal growth factor. Mol Pharmacol 1988;33(6):650–656.
27. Handler JA, Danilowicz RM, Eling TE. Mitogenic signaling by epidermal growth factor (EGF), but not platelet-derived growth factor, requires arachidonic acid metabolism in BALB/c 3T3 cells. Modulation of EGF-dependent c-myc expression by prostaglandins. J Biol Chem 1990;265(7):3669–3673.
28. Katayama M, Shoji M, Satomi S. Differential growth properties of normal and malignant esophageal epithelial cells: a possible cross talk between transforming growth factor-beta1 and epidermal growth factor signaling. Tohoku J Exp Med 2005;206(1):61–71.
29. Wilkinson NW, Black JD, Roukhadze E, Driscoll D, Smiley S, Hoshi H, Geradts J, Javle M, Brattain M. Epidermal growth factor receptor expression correlates with histologic grade in resected esophageal adenocarcinoma. J Gastrointest Surg 2004;8:448–453.
30. Park DW, Kim JR, Kim SY, Sonn JK, Bang OS, Kang SS, Kim JH, Baek SH. Akt as a mediator of secretory phospholipase A2 receptor-involved inducible nitric oxide synthase expression. J Immunol 2003;170:2093–2099.
31. Grass DS, Felkner RH, Chiang MY et al. Expression of human group II PLA2 in transgenic mice results in epidermal hyperplasia in the absence of inflammatory infiltrate. J Clin Invest 1996;97(10):2233–2241.
32. Ireland AP, Peters JH, Smyrk TC et al. Gastric juice protects against the development of esophageal adenocarcinoma in the rat. Ann Surg 1996;223:358–362.

J Gastrointest Surg (2009) 13:2219–2225
DOI 10.1007/s11605-009-0975-7

ORIGINAL ARTICLE

Functional Esophagogastric Junction Obstruction with Intact Peristalsis: A Heterogeneous Syndrome Sometimes Akin to Achalasia

John R. Scherer · Monika A. Kwiatek · Nathanial J. Soper · John E. Pandolfino · Peter James Kahrilas

Received: 15 June 2009 / Accepted: 15 July 2009 / Published online: 12 August 2009

Abstract
Background Some patients with suspected achalasia are found on manometry to have preserved peristalsis, thereby excluding that diagnosis. This study evaluated a series of such patients with functional esophagogastric junction (EGJ) obstruction.
Methods Among 1,000 consecutive high-resolution manometry studies, 16 patients had functional EGJ obstruction characterized by impaired EGJ relaxation and intact peristalsis. Eight patients with post-fundoplication dysphagia and similarly impaired EGJ relaxation were studied as a comparator group with mechanical obstruction. Intrabolus pressure (IBP) was measured 1 cm proximal to the EGJ. Sixty-eight normal controls were used to define normal IBP. Patients' clinical features were evaluated.
Results Functional EGJ obstruction patients presented with dysphagia (96%) and/or chest pain (42%). IBP was significantly elevated in idiopathic and post-fundoplication dysphagia patients versus controls. Among the idiopathic EGJ obstruction group treated with pneumatic dilation, BoTox™, or Heller myotomy, only the three treated with Heller myotomy responded well. Among the post-fundoplication dysphagia patients, three of four responded well to redo operations.
Conclusion Functional EGJ obstruction is characterized by pressure topography metrics demonstrating EGJ outflow obstruction of magnitude comparable to that seen with post-fundoplication dysphagia. Affected patients experience dysphagia and/or chest pain. In some cases, functional EGJ obstruction may represent an incomplete achalasia syndrome.

Keywords Esophagus · Achalasia · Dysphagia · Manometry

Introduction

The physiological defects in achalasia are attributable to loss of function by myenteric plexus ganglion cells, particularly inhibitory neurons.[1] However, because achalasia is rarely diagnosed on the basis of histopathology, this neural defect is usually inferred from its functional consequences rather than directly demonstrated. Hence, achalasia is diagnosed by demonstrating impaired esophagogastric junction (EGJ) relaxation and absent peristalsis without an obstructing lesion to otherwise explain these anomalies.[2] However, it is also clear that some dysphagic patients with suspected achalasia exhibit heterogeneity with respect to how completely the achalasia syndrome is expressed; while many have a flaccid esophagus, others have spastic contractions of the esophagus, many have preserved esophageal longitudinal muscle contraction, and some may have preserved peristalsis with manometric evidence of outflow obstruction.[3,4] The latter group, with functional EGJ obstruction, is particularly interesting, as this group would be detectable only by manometry; there would be no anticipated endoscopic or fluoroscopic

J. R. Scherer · M. A. Kwiatek · J. E. Pandolfino · P. J. Kahrilas (✉)
Department of Medicine, Division of Gastroenterology, Feinberg School of Medicine, Northwestern University, 676 N. St. Clair Street, Suite 1400, Chicago, IL 60611, USA
e-mail: p-kahrilas@northwestern.edu

N. J. Soper
Department of Surgery, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

abnormalities. However, esophageal manometry is a test that has been historically plagued by limitations with respect to accuracy and reproducibility calling the very existence of this syndrome into question.[5–7]

Recent years have witnessed an evolution in esophageal manometry to a methodology that is now more accurately termed high-resolution esophageal pressure topography. With this technology, intraluminal pressure is plotted as a continuum both in time and spatially along the length of the esophagus facilitating an objective, quantitative analysis beyond that which was possible with conventional manometry. Furthermore, esophageal pressure topography plots can be "interrogated" using customized algorithms to calculate objective numerical indices of EGJ relaxation, peristaltic function, or intrabolus pressure (IBP), all with excellent reproducibility.[8–10] As such, high-resolution esophageal pressure topography would seem an appropriate methodology with which to evaluate functional EGJ obstruction. Is this a novel clinical entity, perhaps an incomplete expression of an achalasia syndrome? Or is this simply a manifestation of the imperfect specificity of the tools available to quantify EGJ relaxation? The aim of this study was to address these questions by identifying patients with isolated functional EGJ obstruction and exploring both the physiological consequences of that finding in terms of esophageal IBP and the associated clinical syndromes with which these individuals present.

Methods

Patient Population and Clinical Assessment

A series of 1,000 consecutive high-resolution esophageal pressure topography studies performed between February 2004 and January 2007 at Northwestern Memorial Hospital was reviewed to identify patients with functional EGJ obstruction defined by the combination of intact peristalsis and impaired EGJ relaxation, defined as a mean EGJ integrated relaxation pressure (IRP) of 15 mmHg or greater.[11] Manometric studies and clinical records of patients with functional EGJ obstruction were then analyzed in detail to further characterize the syndrome. Endoscopic records were retrieved to identify and exclude patients with mechanical EGJ obstruction. Patients who had previously undergone anti-reflux surgery and were undergoing evaluation for dysphagia were analyzed as a comparator group to the idiopathic functional obstruction patients with respect to consequences on peristaltic function and esophageal IBP. In addition to the study group, 68 asymptomatic volunteer subjects without hiatus hernia were studied with the identical manometry protocol to serve as the control arm for the esophageal pressure topography analysis of esophageal IBP. The study protocol was approved by the Northwestern University Institutional Review Board.

An investigator blinded to manometric analysis reviewed the medical records of each patient with functional EGJ obstruction to evaluate the predominant symptom at time of the manometry study, subsequent medical or surgical treatment rendered, and clinical response to that treatment. A successful treatment was defined as one with satisfactory symptom response such that no further intervention was recommended for 12 months as documented at a follow-up clinic visit. An unsuccessful treatment response was defined as one followed by the need for an additional intervention within 12 months or poor symptomatic response documented during the follow-up visit.

Manometry Protocol

Patients underwent a standardized manometry protocol after a brief interview and exam to assess symptoms. A solid-state manometry assembly with 36 pressure sensors spaced at 1-cm intervals (OD 4.2 mm) was used (Manoscan™, Sierra Scientific Instruments Inc., Los Angeles, CA). The recording characteristics of this device have been previously described.[12] The transducers were calibrated at 0 and 100 mmHg using externally applied pressure prior to the study. The manometric assembly was placed transnasally and positioned to record from the hypopharynx to the stomach with approximately five intragastric sensors. Studies were performed in a supine position after at least a 6-h fast. The protocol included a 3-min baseline period and ten 5-ml water swallows.

Esophageal Pressure Topography Analysis

All pressure topography analysis was done using ManoView™ software with data tracings viewed in the color pressure topography mode. End-expiratory EGJ pressure was measured during the 3-min baseline recording using the eSleeve™ tool spanning the entire EGJ. In instances that there was a double-peaked EGJ pressure profile during inspiration, the proximal peak was taken to be the lower esophageal sphincter (LES) and the distal the crural diaphragm (CD). Hiatus hernia was defined using the criterion of ≥1.5 cm separation between the LES and CD during the baseline recording. In instances of hiatus hernia, end-expiratory LES and CD measurements were made by restricting the eSleeve™ domain to each of these elements respectively.

EGJ relaxation was analyzed using the ManoView™ IRP tool.[11] The default settings on the IRP tool establish a 6 cm×10 s domain after the swallow and calculates the lowest mean eSleeve™ pressure for four contiguous or

non-contiguous seconds of relaxation within that window. However, in the setting of hiatus hernia, the IRP could conceivably be indicative of either LES relaxation or CD relaxation. Thus, the default IRP setting spanning both the LES and the CD components was reported as IRP_{EGJ}, and the IRP boundaries were adjusted to a 2-cm domain capturing each EGJ element independently. Separate measurements were then made of IRP_{LES} and IRP_{CD}. All IRP measurements through the EGJ were referenced to concurrent intragastric pressure.

After characterizing EGJ relaxation, a detailed analysis was done of the associated distal esophageal IBP, reflecting the pressure within the fluid compartmentalized between the EGJ and distal esophageal contraction. IBP was measured using a new ManoView™ tool denoted in the software as IBP2. IBP2, hereafter designated max-IBP, is the greatest IBP obtained for a contiguous or non-contiguous 3-s period within the same temporal boundaries used to calculate the IRP. Typically, the 3 s of greatest IBP occurred close to the end of the relaxation window as the peristaltic contraction arrived at the distal esophagus. All IBP measurements were referenced to atmospheric pressure. Hence, the value of max-IBP could exceed the value of IRP_{EGJ}, as they were measured at different times within the relaxation window and the latter was referenced to intragastric pressure. The derivation of these measures is illustrated in Fig. 1.

Manometry studies were then further analyzed to characterize distal peristaltic weakness or dysfunction. This was done using: (1) the isobaric contour tool set at 30 mmHg to ascertain whether the peristaltic wavefront was intact, (2) the contractile front velocity (CFV) to ascertain normal propagation velocity, and (3) the distal contractile amplitude to identify hypertensive contractions. Each swallow was characterized as: (1) normal (intact isobaric contour, CFV <10 cm/s, mean contractile amplitude <180 mmHg), (2) hypotensive (>3 cm break in the 30 mmHg isobaric contour between the distal segment and the EGJ), (3) absent peristalsis (complete failure of contraction), (4) hypertensive (CFV <10 cm/s and mean contractile amplitude >180 mmHg), (5) spastic (rapidly propagated contraction with CFV ≥10 cm/s), (6) elevated IBP (>30 mmHg IBP_{max}), or (7) panesophageal pressurization (simultaneous esophageal pressurization to greater than 30 mmHg extending from the upper esophageal sphincter to the EGJ).[2]

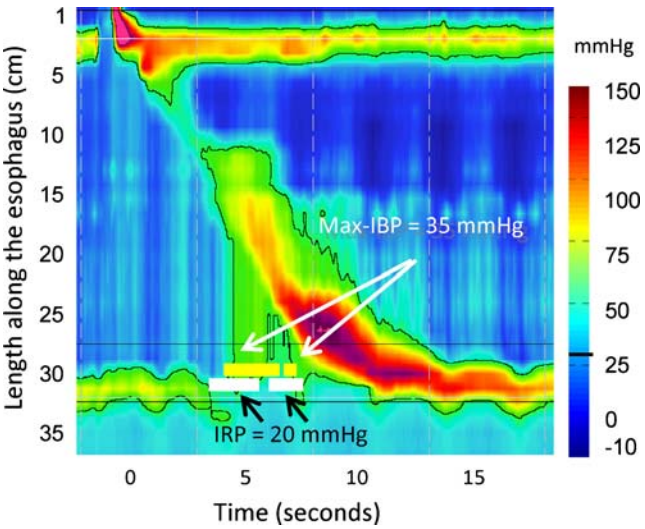


Figure 1 Representative example of a patient with functional EGJ obstruction. Max-IBP (*yellow*) is the greatest IBP obtained for a contiguous or non-contiguous 3-s period within the same 10-s temporal boundary used to calculate the IRP (*white*). This patient later responded favorably to Heller myotomy. The IRP is calculated with ManoView™. Pressure is referenced to atmospheric with the 30 mmHg isobaric contour highlighted in *black*.

Statistical Analysis

The manometric parameters and clinical variables obtained from medical records were summarized using mean, median, 95th percentile, and standard deviation. IRP and IBP measures were also summarized as the overall mean among the ten test swallows or the worst three values among the ten test swallows to accentuate the observed variability. Unpaired two-sample two-tail Student's *t* test was used to compare the mean values of manometric parameters and clinical variables among the asymptomatic control, idiopathic functional obstruction, and post-fundoplication groups.

Results

Study Population

Of the 1,000 patients evaluated, 78 had evidence of impaired EGJ relaxation on the basis of elevated IRP but did not meet diagnostic criteria for achalasia, a typical example of which is illustrated in Fig. 2. From this group, 38 patients exhibited a high frequency of peristaltic defects, but insufficient to meet criteria for achalasia, and were excluded. Additionally, 16 patients were excluded because of mechanical EGJ obstruction: five with paraesophageal hernia, four with esophageal cancer, three with eosinophilic esophagitis, two with strictures, one with a gastroplasty, and one with obstructing gastroesophageal varices. This left 16 patients with idiopathic functional obstruction as exemplified in Fig. 1 and eight patients with post-fundoplication dysphagia. Age and sex were similar between these groups. Healthy controls, however, were younger than the patient groups (Table 1). For comparison, 129 of the 1,000 patients evaluated in the consecutive series had achalasia; 30 had a prior diagnosis, and 99 were newly diagnosed. The pressure

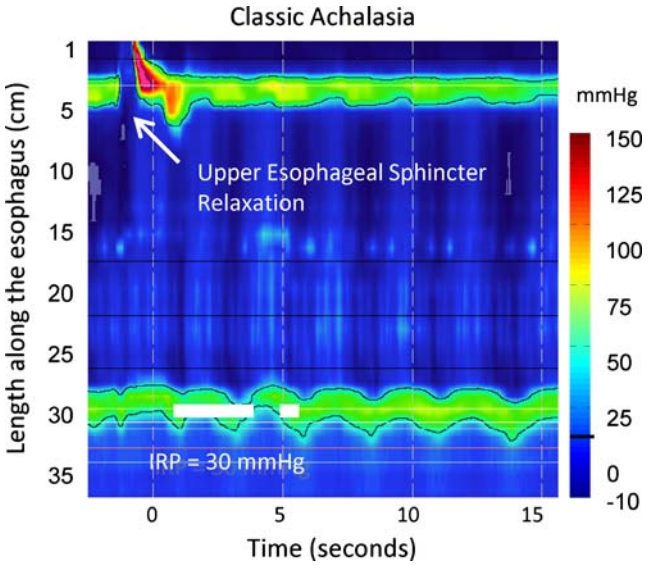


Figure 2 High resolution esophageal pressure topography study consistent with classic achalasia exhibiting aperistalsis and impaired EGJ relaxation. Compare this study to that in Fig. 1 consistent with functional EGJ obstruction exhibiting intact peristalsis and impaired EGJ relaxation. The IRP is calculated with ManoView™ in both examples. In this example, pressure is referenced to intragastric pressure and the 15 mmHg isobaric contour is highlighted in *black*.

topography characteristics of the achalasia patients were reported on earlier.[3]

Dysphagia was the dominant symptom among the functional EGJ obstruction patients (Table 1). All patients presented with a dominant complaint of either dysphagia or chest pain. The post-fundoplication group was notable for complaining of chest pain significantly more than the idiopathic group. Seven patients were found to have hiatus hernia: four post-fundoplication and three idiopathic.

Table 1 Demographic Characteristics and Symptom Profile Among Subject Groups

	Subject group		
	Asymptomatic controls (n=68)	Post-fundoplication dysphagia (n=8)	Idiopathic functional EGJ obstruction (n=16)
Age	27±5	57±15*	57±13*
Gender, % male	53	38	31
Hiatus hernia (%)	0	4 (50%)	3 (19%)
Dysphagia (%)	0	8 (100%)	15 (94%)
Chest Pain (%)	0	6 (75%)**	4 (25%)
Heartburn± regurgitation (%)	0	6 (75%)	9 (56%)
Globus (%)	0	0	3 (19%)

*p<0.05, vs. asymptomatic controls; **p<0.05, vs. idiopathic functional obstruction

Manometric Variables

The idiopathic functional obstruction patients exhibited similar manometric characteristics compared to the post-fundoplication dysphagia patients, a model of mechanical obstruction (Table 2). Both groups exhibited impaired (but similar) EGJ relaxation pressures. Furthermore, distal esophageal max-IBP was significantly greater than in the control subjects in both subject groups, especially in post-fundoplication dysphagia patients. In addition to max-IBP, the other discriminating variable between the patient groups was EGJ pressure, which was greater in the idiopathic EGJ obstruction patients. The index that most accentuated the IBP abnormality in the patient groups was the max-IBP (worst 3; Table 2 and Fig. 3).

Specific to patients with hiatus hernia, the IRP analysis was done both to encompass the entire EGJ as well as restricted to the LES and CD components (Table 3). Although the IRP_{EGJ} was numerically greater in the post-fundoplication dysphagia group, this difference was not significant. More notable was that one of the three idiopathic EGJ obstruction patients with a hernia had EGJ relaxation pressures entirely dependent on the CD rather than the LES, whereas in others, the IRP_{LES} was greater (Fig. 4). This suggests that, in some hiatus hernia patients, the CD and not the LES is responsible for functional EGJ obstruction.

The composite characteristics of all individual swallows for functional obstruction subjects are provided in Table 4. The majority of swallows demonstrated functional esophageal obstruction as defined by an elevated max-IBP. Swallows displaying hypertensive peristalsis were seen more frequently in patients with idiopathic functional obstruction. Rarely, pressure topography findings associated with achalasia such as pan-esophageal pressurization or spasm were evident on isolated swallows. On the whole, only 4.6% of swallows demonstrated absent peristalsis.

Table 2 EGJ and IBP Measures Among Subject Groups

Manometric measure	Subject group		
	Normal subjects (n=68)	Post-fundoplication dysphagia (n=8)	Idiopathic functional EGJ obstruction (n=16)
EGJ pressure (mmHg)	16±8	25±17*	40±17*,**
Mean IRP (mmHg)	9±3	21±7*	22±5*
Max-IBP (all) (mmHg)	11±4	40±12*	32±6*,**
Max-IBP (3 worst) (mmHg)	13±3	47±15*	40±14*

*p<0.05, vs. asymptomatic control; **p<0.05, vs. post-fundoplication

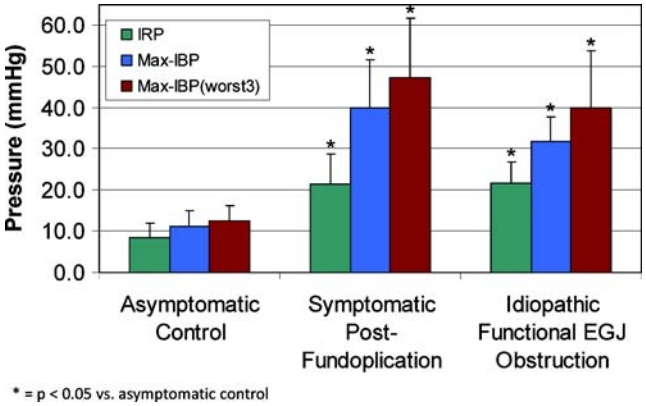


Figure 3 Comparison of IRP, max-IBP, and max-IBP (worst 3) among subject groups. All of these manometric measures are significantly elevated in functional EGJ obstruction compared with controls. Among them, max-IBP (worst 3) best discriminated functional EGJ obstruction from controls.

Clinical Outcomes

The clinical response of idiopathic functional obstruction patients to conventional achalasia therapies (BoTox™, pneumatic dilation, and Heller myotomy) was assessed. Regarding the idiopathic group, the hiatus hernia patient with CD functional obstruction was eliminated from analysis leaving 15 patients subject to an average of 1.1 interventions per patient over a mean follow-up period of 16 months; three patients were lost to follow-up. Overall, nine patients were treated with one or more of these therapies (three pneumatic dilation, three Heller myotomy, two BoTox™, and one standard dilation) and generally exhibited a poor response to therapy with an overall success rate of only 33% for the final intervention. There was no instance in which non-surgical therapy was effective, whereas Heller myotomy was successful in all three individuals so treated (one of whom is illustrated in Fig. 1). Among the eight post-fundoplication dysphagia patients, four underwent redo operations to which three responded favorably.

Table 3 Relaxation Pressures of EGJ Components in EGJ Obstruction Patients with Hiatus Hernia

Manometric measure	Subject group	
	Post-fundoplication dysphagia (n=4)	Idiopathic functional EGJ obstruction (n=3)
IRP_{EGJ} (mmHg)	24.8±9.2	17.5±2.7
IRP_{LES} (mmHg)	24.3±9.4	16.9±2.3
IRP_{CD} (mmHg)	18.4±13.0	8.5±6.5

Discussion

The aim of this study was to characterize the clinical characteristics of patients with functional EGJ obstruction and preserved peristalsis. The major findings were that these patients experience dysphagia as a dominant symptom and that the physiology of idiopathic functional EGJ obstruction mirrors that of a known model of mechanical EGJ obstruction, post-fundoplication dysphagia. In both cases, swallowing is associated with significantly elevated distal esophageal IBP, arguing that these patients truly have EGJ outflow obstruction as opposed to a measurement artifact. Furthermore, a subset of patients with idiopathic functional EGJ obstruction with preserved peristalsis respond to treatment for achalasia, suggesting that, in some cases, this condition likely represents the incomplete expression of an achalasia syndrome. The extent of overlap between the diagnoses of functional EGJ obstruction and achalasia depends on how strictly one defines absent peristalsis. In the current study, we excluded 38 patients from the functional EGJ obstruction group because they exhibited such a high proportion of peristaltic defects that some might consider them achalasics; we did not but were not willing to rule out that possibility either. Another rationale for excluding these indeterminate patients was that the degree of their peristaltic dysfunction was so severe as to preclude the measurement of IBP.

Post-fundoplication dysphagia serves as the iatrogenic model of idiopathic functional esophageal obstruction: EGJ relaxation is impaired, flow through the EGJ is reduced, and distal esophageal IBP is increased.[13] In a series of 34 post-fundoplication patients, IBP was found to be significantly increased, remaining elevated for at least 2 years after surgery.[14] The development of secondary achalasia as a late consequence has also been observed following anti-reflux surgery.[15] Furthermore, post-fundoplication dysphagia has been shown to resolve in parallel with the reduction of IBP following conversion to partial fundoplication.[16] In the current series, we applied a systematic analysis of IBP using an algorithm devised for pressure topography plots to demonstrate that the degree of IBP developed in idiopathic functional EGJ obstruction was similar to that observed in post-fundoplication dysphagia. Among several indices of IBP tested, we found that, comparing the maximal IBP in the post-deglutitive window for the three most abnormal swallows (max-IBP) was the best discriminator between normal controls and functional obstruction patients due to the large variation in IBP observed in a ten-swallow series.

Of the 16 patients with idiopathic functional obstruction, three were noted to have hiatus hernias. In one instance, it was the CD rather than the LES that appeared to be the focus of deglutitive resistance to bolus transit, suggesting the hernia itself to be the cause of dysphagia in this

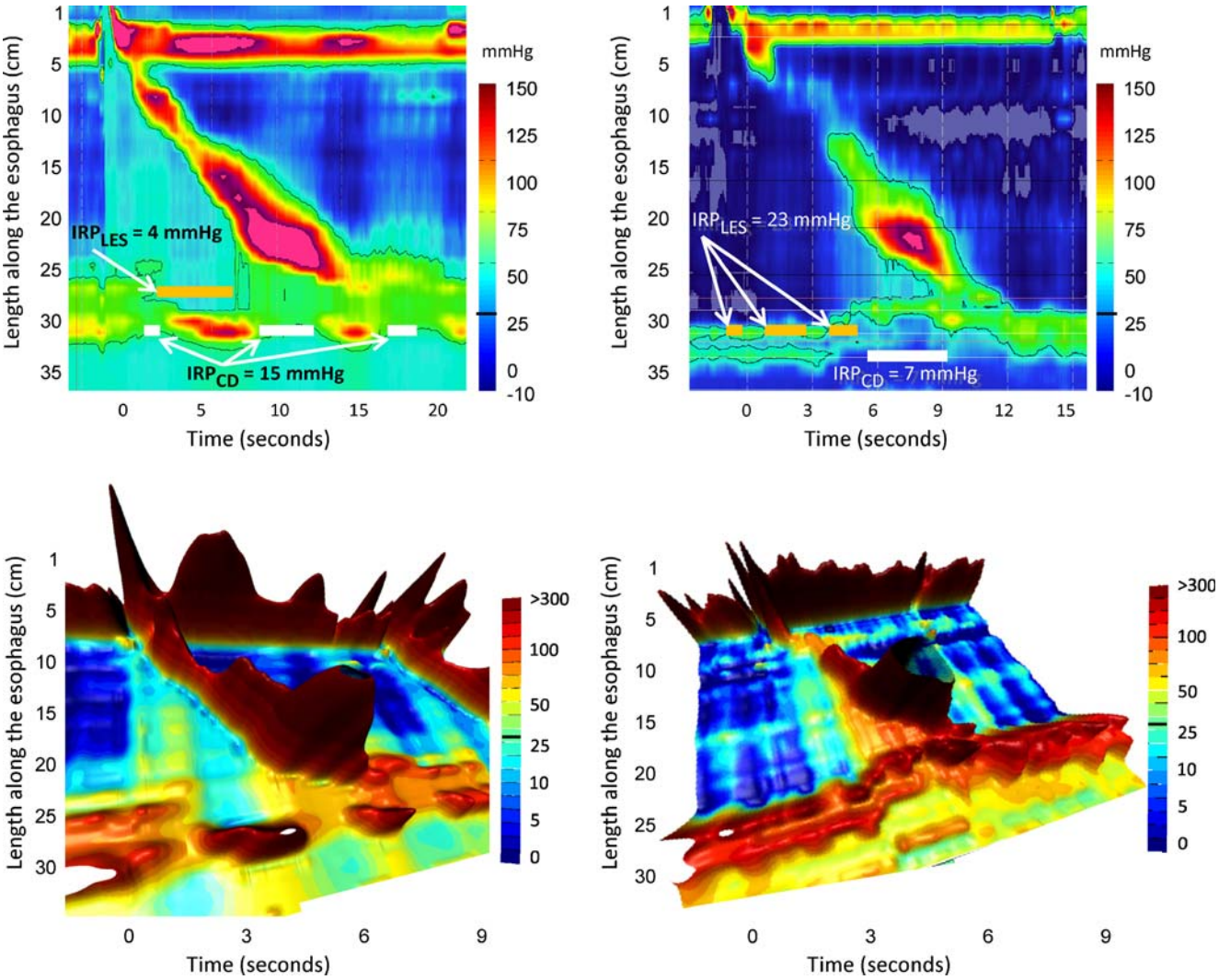


Figure 4 High-resolution esophageal pressure topography (*top*) and landscape (*bottom*) plots of a hiatus hernia patient with functional EGJ obstruction attributable to the CD (*left*) and another hiatus hernia patient with EGJ functional obstruction attributable to the LES (*right*). In each case, the corresponding IRP_{CD} and IRP_{LES} values are shown.

Table 4 Characterization of Individual Swallows Among Functional Obstruction Subtypes

Esophageal contraction	Subject Group	
	Post-Fundoplication Dysphagia	Idiopathic Functional EGJ Obstruction
Normal (%)	15 (19%)	33 (21%)
Hypotensive peristalsis (%)	1 (1%)	9 (6%)
Absent peristalsis (%)	1 (1%)	10 (6%)
Hypertensive peristalsis (%)	0	13 (8%)
Spasm (%)	0	5 (3%)
Panesophageal pressurization (%)	0	4 (3%)
Max-IBP > 30 mmHg (%)	63 (79%)	86 (54%)

individual. In the remaining 15 patients, we had no explanation for their dysphagia other than functional EGJ obstruction. Nonetheless, we expect this to be a heterogeneous group with some individuals having a variant expression of achalasia and others likely having an undetected mechanical etiology of EGJ outflow obstruction. Certainly, the treatment efficacy that we experienced is consistent with that hypothesis. In fact, the only patients who experienced a satisfactory response to treatment were the three treated with laparoscopic Heller myotomy. While these data perhaps serve to demonstrate a proof of concept, they also emphasize the need to further characterize these patients to find better predictors of treatment response and physiological markers of treatment effect. Were failed therapies a consequence of misdiagnosis or inadequate treatment? Was treatment response paralleled by decreased

IBP? Were there histopathological markers of achalasia in treatment responders? Clearly, we need to address these questions in future studies.

IBP is attributable to the balance between peristaltic forces acting to move the bolus through the esophagus and downstream resistance to that movement. As evident from data in Table 2 and Fig. 3, normal values of esophageal IBP are low, on the order of 10 mmHg, confirming that the esophagus and EGJ are normally relatively compliant. However, with functional EGJ obstruction, IBP values will often exceed 30 mmHg. This degree of IBP can be likened to balloon distention, a stimulus known to elicit symptoms of chest pain, pressure, and heartburn.[17,18] The genesis of these symptoms is presumably by wall strain activating tension-sensitive afferent nerves in the esophageal submucosa and muscularis propria.[19,20] Physiologically, the range of pressure thresholds stimulating vagal and spinal afferents varies from 5 to 50 mmHg,[21,22] values consistent with those observed in functional EGJ obstruction patients, arguing that elevated IBP may be the primary stimulus for the perception of dysphagia. Future research into the relationship between sensory thresholds, IBP, allodynia, and hyperalgesia will likely shed further light on this.

In summary, idiopathic functional EGJ obstruction with preserved peristalsis is associated with quantifiable outflow obstruction from the esophagus comparable in severity to post-fundoplication dysphagia. This functional defect was well demonstrated by elevated maximal IBP in the worst three of ten test swallows (max-IBP). Lastly, some patients with idiopathic functional EGJ obstruction may represent an early or variant expression of achalasia. To what degree this might progress, over what length of time, and with what frequency will need to be addressed by long-term follow-up studies.

Acknowledgment This work was supported by R01 DC00646 (PJK & JEP) from the Public Health Service.

References

1. Boeckxstaens GE. Achalasia: virus-induced euthanasia of neurons? Am J Gastroenterol 2008;103:1610–1612.
2. Kahrilas PJ, Ghosh SK, Pandolfino JE. Esophageal motility disorders in terms of pressure topography: the Chicago classification. J Clin Gastroenterol 2008;42:627–635.
3. Pandolfino JE, Kwiatek MA, Nealis T, Bulsiewicz W, Post J, Kahrilas PJ. Achalasia: it's not all one disease—subclassification by high-resolution manometry. Gastroenterology 2008;135:1383–1391.
4. Hirano I, Tatum RP, Shi G, Sang Q, Joehl R, Kahrilas PJ. Manometric heterogeneity in patients with idiopathic achalasia. Gastroenterology 2001;120:789–798.
5. Kahrilas PJ, Clouse RE, Hogan WJ. American Gastroenterological Association technical review on the clinical use of esophageal manometry. Gastroenterology 1994;107:1865–84.
6. Vaezi MF, Richter JE. Diagnosis and management of achalasia. Am J Gastroenterol 1999;94:3406–3412.
7. Pandolfino JE, Kahrilas PJ. AGA technical review on the clinical use of esophageal manometry. Gastroenterology 2005;128:209–224.
8. Pandolfino JE, Ghosh SK, Zhang Q, Jarosz A, Shah N, Kahrilas PJ. Quantifying EGJ morphology and relaxation with high-resolution manometry: a study of 75 asymptomatic volunteers. Am J Physiol Gastrointest Liver Physiol 2006;290:G1033–1040.
9. Ghosh SK, Pandolfino JE, Zhang Q, Jarosz A, Shah N, Kahrilas PJ. Quantifying esophageal peristalsis with high-resolution manometry: a study of 75 asymptomatic volunteers. Am J Physiol Gastrointest Liver Physiol 2006;290:G988–G997.
10. Ghosh SK, Kahrilas PJ, Lodhia N, Pandolfino JE. Utilizing intraluminal pressure differences to predict esophageal bolus flow dynamics. Am J Physiol Gastrointest Liver Physiol 2007;293:G1023–G1028.
11. Ghosh SK, Pandolfino JE, Rice J, Clarke JO, Kwiatek M, Kahrilas PJ. Impaired deglutitive EGJ relaxation in clinical esophageal manometry: a quantitative analysis of 400 patients and 75 controls. Am J Physiol Gastrointest Liver 2007;293:G878–G885.
12. Pandolfino JE, El-Serag HB, Zhang Q, Shah N, Ghosh SK, Kahrilas PJ. Obesity: a challenge to esophagogastric junction integrity. Gastroenterology 2006;130:639649.
13. Ghosh SK, Kahrilas PJ, Zaki T, Pandolfino JE, Joehl RJ, Brasseur JG. The mechanical basis of impaired esophageal emptying postfundoplication. Am J Physiol Gastrointest Liver Physiol 2005;289:G21–G35.
14. Scheffer RC, Samsom M, Frakking TG, Smout JP, Gooszen HG. Long-term effect of fundoplication on motility of the oesophagus and oesophagogastric junction. Br J Surg 2004;91:1466–1472.
15. Stylopoulos N, Bunker CJ, Rattner DW. Development of achalasia secondary to laparoscopic Nissen fundoplication. J Gastrointest Surg 2002;6:368–378.
16. Bais JE, Wijnhoven BP, Masclee AA, Smout AJ, Gooszen HG. Analysis and surgical treatment of persistent dysphagia after Nissen fundoplication. Br J Surg 2001;88:569–576.
17. Drewes AM, Schipper K-P, Dimcevski G, Petersen P, Andersen O, Gregersen H, Arendt-Nielsen L. Multimodal assessment of pain in the esophagus: a new experimental model. Am J Physiol 2002;283:G95–G103.
18. Drewes AM, Schipper K-P, Dimcevski G, Petersen P, Andersen O, Gregersen H, Arendt-Nielsen L. Multi-modal induction and assessment of allodynia and hyperalgesia in the human esophagus. Eur J Pain 2003;7:539–549.
19. Yu S, Undem BJ, Kollarik M. Vagal afferent nerves with nociceptive properties in guinea-pig oesophagus. J Physiol 2005;563:831–842.
20. Sengupta JN, Petersen J, Medda BK, Shaker R. Mechanical and chemical properties of distension-sensitive vagal afferent fibers innervating the esophagus of rat. Gastroenterology 2002;122:155.
21. Sengupta JN, Kauvar D, Goyal RK. Characteristics of vagal esophageal tension-sensitive afferent fibers in the opossum. J Neurophysiol 1989;61:1001–1010.
22. Sengupta JN, Saha JK, Goyal RK. Stimulus–response function studies of the esophageal mechanosensitive nociceptors in sympathetic afferents of opossum. J Neurophysiol 1990;64:796–812.

J Gastrointest Surg (2009) 13:2226–2232
DOI 10.1007/s11605-009-0994-4

ORIGINAL ARTICLE

Roux-en-Y Reconstruction for Failed Fundoplication

Konstantinos I. Makris · Tommy Lee · Sumeet K. Mittal

Received: 26 May 2009 / Accepted: 10 August 2009 / Published online: 2 September 2009

Abstract
Background Redo fundoplication has acceptable outcomes in patients with failed previous fundoplications. However, a subset of patients require Roux-en-Y (RNY) reconstruction for symptom relief.
Aim The aim of this study was to demonstrate safety and efficacy of RNY reconstruction for failed fundoplications.
Method Retrospective review of data on patients who underwent short-limb RNY gastrojejunostomy (GJ) or esophagojejunostomy (EJ) between the years 2005 and 2007 was performed.
Results Twenty-two patients underwent RNY reconstructions. Fourteen (64%) patients had one, six (27%) patients had two, and 2 (9%) patients had three previous anti-reflux procedures. RNY GJ was performed in 18 patients and EJ in four patients. Gastrectomy was performed in 13 of these patients. Seven patients (32%) had ten major or minor complications within the 30-day postoperative period, without any mortality observed. At a mean follow-up of 23 months, completed in 21 of these patients (95%), the average heartburn score was 0.38 (range, 0–2). The average regurgitation score was 0.23 (range, 0 to2) and the average dysphagia score was 0.7 (range, 0–2). The mean postoperative BMI was 25.4 compared to a preoperative BMI of 31.
Conclusion RNY reconstruction with GJ or EJ for failed anti-reflux procedures is a safe, valid surgical option in difficult situations, where a redo fundoplication is either non-feasible or expected to fail. However, it is associated with higher morbidity.

Keywords Gastroesophageal reflux disease · Roux-en-Y · Gastrojejunostomy · Esophagojejunostomy · Fundoplication

Introduction

The lower esophageal sphincter complex acts as a physiologic barrier, preventing continuous reflux from the high-pressure stomach into the low-pressure esophagus. Gastroesophageal reflux disease (GERD), which affects nearly 20% of the population in the USA, is a result of this barrier dysfunction. Surgical fundoplication re-creates a barrier between the stomach and the esophagus, restoring near-normal physiology. With the advent of minimally invasive surgery, laparoscopic anti-reflux procedures have gained widespread acceptance. Excellent long-term results have been reported with greater than 90% patient satisfaction on a 5- to 10-year follow-up.[1–4]

Postoperatively, recurrence of previous symptoms or emergence of new undesirable symptoms should be considered surgical failure and has been reported in 2–30% of patients.[3,5–10] A subset of these patients require reoperative intervention, which may include redo fundoplication, esophagogastric resection, and/or diversion of the gastric reservoir.

Gastrectomy with Roux-en-Y (RNY) reconstruction has been used as an antireflux procedure before.[11,12] The RNY gastric bypass (with the distal stomach left in situ) has also been shown to be an effective surgical treatment for GERD in obese patients[13–17] as well as in patients with scleroderma.[18]

The role of RNY for primary and reoperative treatment of GERD continues to evolve. We present our initial experience with RNY gastrojejunostomy (GJ) and esophagojejunostomy (EJ) for previously failed fundoplications.

K. I. Makris · T. Lee · S. K. Mittal (✉)
Department of Surgery, Creighton University Medical Center,
601 North 30th Street, Suite 3700,
Omaha, NE 68131, USA
e-mail: skm03198@creighton.edu

Materials and Methods

Data Collection

All patients undergoing primary and reoperative antireflux surgery at the Creighton University Medical Center (CUMC) were entered into a prospectively maintained database. After approval from the Institutional Review Board, the database was queried to retrieve patients who underwent RNY GJ or EJ as reoperative intervention after previous antireflux surgery.

All of the patients had undergone an extensive preoperative workup, consisting of upper endoscopy, barium swallow, manometry, 24-h pH monitoring, and gastric emptying study.

Data regarding presenting symptoms, previous procedures, preoperative work-up, operative findings, postoperative course, and complications were collected. Attempt was made to contact all patients at least 1 year after surgery. A standard questionnaire (Table 1) used at our center pertaining to foregut symptoms, use of antireflux medications, and patient satisfaction was administered. The data was entered into an Excel database (Microsoft Excel ®) and analyzed.

Surgical Technique

Our operative approach consisted of two steps. The first step was to dismantle the previous fundoplication and repair the recurrent hiatal hernia, if present. The second step was to perform an EJ or GJ, depending on the primary pathology. In patients with undilatable esophageal stricture or significant intraoperative damage to the gastroesophageal junction (GEJ), an EJ was performed. Otherwise, a small gastric pouch (70–100 cc) was created using linear staplers. In some patients, a larger gastric pouch was left in place with recreation of a fundoplication above the GJ. Early in our series, we performed open procedures and resected the distal stomach. However, with growing experience, we performed more laparoscopic procedures and preferred to leave the distal stomach in situ. Gastrointestinal tract continuity was reestablished in all patients with a short (60-cm long) RNY alimentary limb to prevent bile reflux. The biliary limb was 20 cm long. Schematic representation of the postoperative anatomy is shown in Fig. 1.

Results

Demographics

Thirty-five patients underwent RNY GJ or EJ for failed antireflux surgery from January 2005 to October 2007 by the senior author (SKM) at the CUMC. Twenty-two patients (14 female and eight male) with at least 1 year follow-up are included in this study. Their mean age is 55 years (range, 34–78 years) and preoperative mean body mass index (BMI) was 31 (range 20–49). A total of 32 antireflux procedures had previously been performed on these 22 patients with a mean of 1.45 per patient (range, 1–3; Table 2).

Preoperative Assessment

The primary presenting symptom for reoperative surgery was heartburn in seven patients (32%), dysphagia in seven (32%), and chest pain in four (18%). Three (14%) presented with epigastric complaints and one (5%) with combined chest pain and dyspnea from an acutely herniated intrathoracic stomach. The preoperative findings are shown in Table 3.

In the majority of cases, the preoperative anatomical deformity was confirmed by the intraoperative findings. However, in one case, a tight GEJ due to scarring was identified during the operation, whereas a prolapsing gastric polypoid lesion was preoperatively thought to be the cause of symptoms (dysphagia).

Procedures and Postoperative Care

Fourteen of the 22 operations were done via laparotomy, four laparoscopically, two were converted to open, and two procedures were completed with a combined abdominal and thoracic approach. Four of the patients had EJ

Table 1 Creighton University Foregut Symptom Severity Scoring System

Score	Heartburn	Dysphagia	Regurgitation	Chest pain	Nausea/vomiting
0	None	None	None	None	None
1	Minimal—episodic, no treatment is required	Once a week or less	Mild—after straining or large meal	Minimal—episodic	Minimal—episodic
2	Moderate—controlled with medication	More than once a week, requiring dietary adjustment	Moderate—positional	Moderate—reason for visit	Moderate—reason for visit
3	Severe—interferes with daily activity or not controlled with medication	Severe, preventing ingestion of solid food	Severe—constant regurgitation with or without aspiration	Severe—interferes with daily activity	Severe—interferes with daily activity

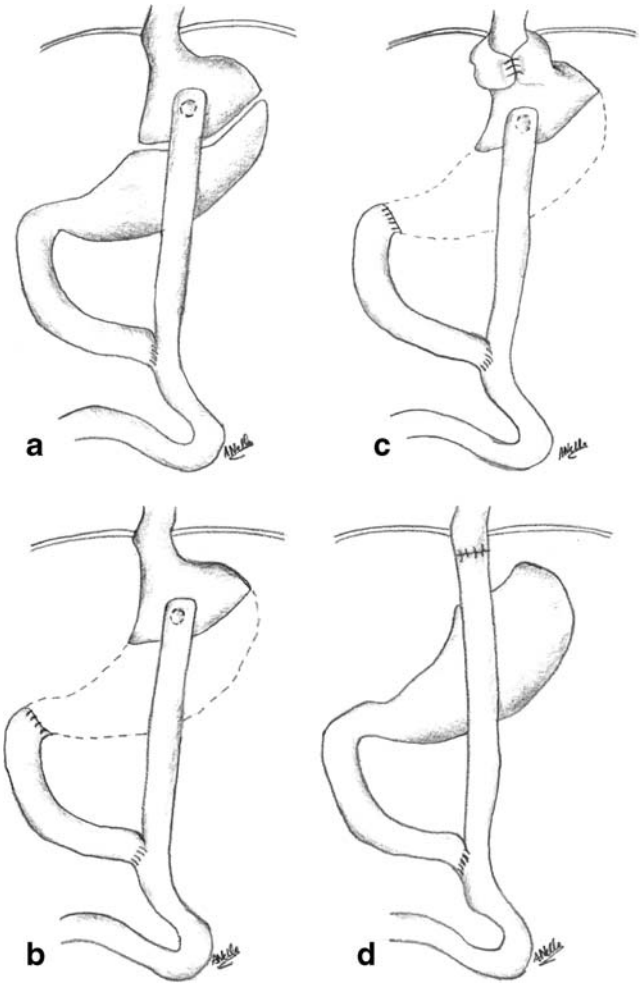


Figure 1 Postoperative RNY anatomy. **a** GJ (n=5); **b** GJ with gastrectomy (n=8); **c** GJ with gastrectomy and fundoplication (n=5); **d** EJ (n=4). *RNY* Roux-en-Y, *GJ* gastrojejunostomy, *EJ* esophago-jejunostomy.

reconstruction, while 18 had GJ, of which five had a larger gastric pouch with a recreated fundoplication. In 13 patients, the distal stomach was resected, and in nine, it was left in situ. The types of the procedures performed are summarized in Table 4, and the postoperative anatomy is demonstrated in Fig. 1.

Table 2 Demographic Data

Total number of patients	22
Male/female	8:14
Age (years)	55 (range, 34–78)
BMI	31 (range, 20–49)
Mean number of previous operations	1.45 (range, 1–3)
Number of patients with 1 previous operation	14 (64%)
Number of patients with 2 previous operations	6 (27%)
Number of patients with 3 previous operations	2 (9%)

Table 3 Preoperative Findings (Coexistent Findings Are Accounted For Separately)

Preoperative findings	Number
Sliding hiatal hernia	6
Paraesophageal hiatal hernia	6
Intrathoracic fundoplication	2
Slipped Nissen	7
Tight/twisted Nissen	3
Disrupted fundoplication	3
Delayed gastric emptying	9
Distorted stomach	1
Esophageal stricture	2
Gastric polyp prolapse into esophagus	1
Esophageal diverticulum/ intraluminal stitch	1
Perforated gastric ulcer (Cameron)	1

The diet was advanced in a stepwise fashion from clear liquids to full liquids and then to six small meals daily. The patients were not placed on bariatric diet, but they were counseled by a dietician and instructed on dumping syndrome symptoms with high-sugar food consumption. Most patients had a temporary gastrostomy or jejunostomy tube placed at the time of surgery, especially if the procedure was done via laparotomy. Tube feeds were administered if prolonged nothing by mouth status was required. Discharge criteria included diet tolerance, adequate bowel function, and satisfactory pain control.

Perioperative Morbidity and Mortality

There was no in-hospital or 30-day mortality. Ten complications occurred in seven (32%) patients (Table 5) within the 30-day postoperative period. The mean hospital stay was 10 days (range, 4–46). The majority of the patients remained in the hospital for less than 10 days. Only five patients were hospitalized for more than 10 days because of complications.

One-Year Outcomes

The follow-up, performed via telephone interviews, was completed in 21 out of the 22 patients (95%) and consisted of at least a 12-month postoperative period. The mean follow-up was 23 months (range, 12–44).

The average heartburn score was 0.38 (range, 0–2). The average dysphagia score was 0.7 (range, 0–2), the average regurgitation score was 0.23, all chest pain scores were 0, and the average nausea score was 0.42 (Table 6). Two patients complained of diarrhea and three of abdominal pain.

Three (14%) patients remained on proton pump inhibitors for reflux, of which one graded his subsequent reflux

Table 4 Type of Roux-en-Y (RNY) Procedures Performed

	Number
Surgical approach	
Open	14
Laparoscopic	4
Laparoscopic—converted to open	2
Combined thoracotomy and laparotomy	2
Total	22
Type of RNY reconstruction	
EJ	4
GJ to small gastric pouch	13
GJ with fundoplication above	5
Total	22
Distal stomach	
Resected	13
Left in situ	9
Total	22

symptoms as 0 and two as 2. Three (14%) different patients required continuation of metoclopramide for intermittent nausea.

The mean satisfaction level reported was eight on a scale from 1 to 10. Eleven patients (52%) rated their satisfaction level as 9–10, seven patients (33%) as 7–8, and three patients as 6 or less. Twenty patients (95%) would recommend their procedure to a friend if needed.

The mean postoperative BMI of the 21 patients followed-up was 25.4. As shown in Fig. 2, most of the weight loss was observed in patients with a BMI of greater than 30. The patients with a BMI of 30 or less essentially maintained their weight. No patient was postoperatively found to have a BMI of less than 20.

Discussion

Reoperations for previously failed antireflux procedures have increasingly become common with an estimated doubling of their occurrence over the last decade.[4] They are technically more challenging due to obscured anatomy and scarring, resulting in a higher incidence of hollow viscus perforations and vagal injury. Other factors, such as short esophagus[3] and delayed gastric emptying, further compound the complexity of the procedure. These anatomical and physiological factors account for a higher morbidity and a lower success rate of reoperative fundoplicatons compared to primary surgery.[19,20] A morbidity of 4–40% and a mortality rate of 0–4.9% have been reported.[3,19–21]

Traditional antireflux surgery aims to restore the incompetent barrier between the gastric reservoir and the esophagus. An alternative surgical approach is the removal or redirection of the gastric reservoir. This option appears especially attractive in situations where a redo fundoplication would be expected to have a high failure rate. RNY diversion has been used as a valid antireflux surgical option for many years.[11,12]

Csendes et al. have reported excellent outcomes with RNY reconstruction as a primary anti-reflux procedure both after antrectomy and vagotomy[22] and after duodenal switch and vagotomy.[23] Signs of regression of Barrett's metaplasia were demonstrated in these patients. Given their radical nature, widespread application of these procedures as primary surgical treatment for GERD has not gained acceptance.[24]

Many studies[13–17] have demonstrated the effectiveness of weight-loss-directed RNY gastric bypass in the treatment of GERD in obese patients. This is a particularly difficult group of patients to treat, in which poorer outcomes have been reported with fundoplications.[25,26] Additionally, in the obese patients with previously failed antireflux procedures, conversion to a RNY gastric bypass has been shown to be feasible with significant subsequent reduction of reflux symptoms.[27,28]

Williams et al.[29] reported better outcomes for patients undergoing RNY GJ as compared to those undergoing redo fundoplications, even though preoperatively, they had more esophageal changes and greater number of previous procedures. They showed improved symptom control and decreased need for further operative interventions, though they experienced significantly higher complication rate. In

Table 5 Postoperative 30-Day Morbidity

Postoperative complications	Number
Abdominal compartment syndrome, multi-organ system failure	1
Acute transhiatal stomach/small bowel herniation	1
Anastomotic bleeding	2
Anastomotic stricture	1
Fascial dehiscence, evisceration/wound infection	1
Large pleural effusion requiring thoracocentesis	1
Small bowel obstruction	3
Total	10

Table 6 One-Year Symptom Follow-up

Severity score	Symptoms, number of patients				
	Heartburn	Dysphagia	Regurgitation	Chest pain	Nausea
0	16	9	17	21	13
1	2	9	3	0	7
2	3	3	1	0	1
3	0	0	0	0	0

our series, we show similar symptom resolution and high patient satisfaction with RNY reconstructions.

A recent study demonstrated the safety and efficacy of near-EJ with RNY reconstruction for recurrent GERD, although significant morbidity was reported.[30] Most of the procedures were completed laparoscopically. The characteristic feature of this procedure was an extremely small pouch of 5–10 ml capacity, with the intention to maximally reduce the amount of acid-producing stomach remaining connected to the esophagus. A gastrostomy tube was placed in the distal stomach.

The indications for RNY as a treatment option for failed antireflux surgery have not been clearly defined. Situations where a redo fundoplication would be expected to have a high failure rate should bring RNY into consideration. These situations include obesity (where not only fundoplication has higher failure rate, but weight loss is also desirable), short esophagus (since Collis gastroplasty with fundoplication has poorer results than a straight forward fundoplication), delayed gastric emptying, history of multiple failed fundoplications, injured or scarred fundus, and very poor esophageal motility (where a fundoplication may result in disabling dysphagia).

A short-limb RNY GJ to a small gastric pouch is an attractive alternative to a redo fundoplication. Occasionally, patients with an undilatable distal esophageal stricture (either primary peptic or secondary to previous operation) or patients who sustain significant damage to the GEJ during the dismantling of the previous fundoplication, will require resection of the distal esophagus and proximal stomach with RNY EJ.

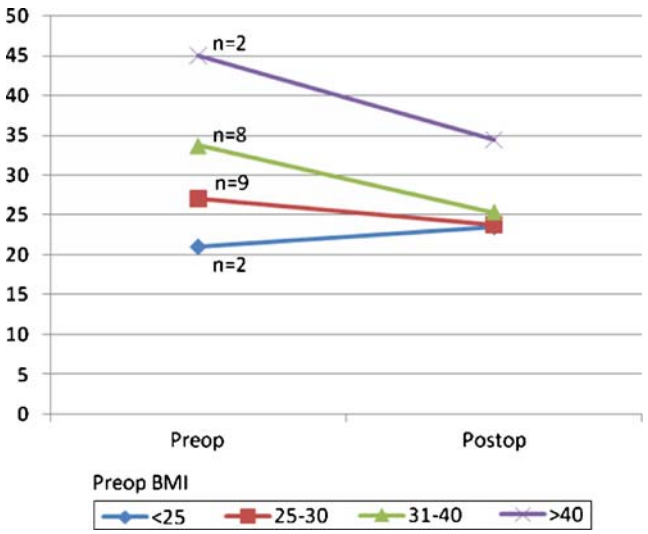


Figure 2 Postoperative BMI changes.

The answer to the question of whether the distal gastric remnant should be left in situ or resected is not clear. Obvious concerns about leaving the distal stomach include retained antrum syndrome and possible bleeding from gastroduodenal ulcerations. However, the major advantage of leaving the distal stomach in place is its availability for a possible gastric pull-up if the patient needs an esophageal resection in the future. This is particularly important in patients with Barrett's esophagus or poor esophageal motility. In our study, we found no difference in patient symptom resolution and satisfaction, either with or without distal gastric resection.

There are three important technical differences between RNY reconstruction for failed fundoplications and the bariatric procedure. First, we leave a larger gastric pouch (70–100 cc) to allow improved meal size. Although we do not have objective data to compare patient satisfaction between different pouch sizes, our patients report high satisfaction without recurrent GERD symptoms. There is always a concern with bleeding from the GJ anastomosis, and more recently, we have started fashioning our pouch in a vertical fashion with little or no fundus included. Second, we create a large GJ to allow rapid transit of food out of the gastric pouch, preventing regurgitation into the esophagus. Third, we measure the biliary limb to be about 20 cm long, with a 60-cm-long alimentary limb, in order to limit the malabsorption associated with the usual bariatric procedure. As a result of these modifications, the majority of the patients maintain a healthy BMI, with the more obese ones losing a significant amount of weight (although not to the extent of a bariatric procedure). We anticipate that with short-limb reconstructions, patients will have decreased nutritional problems. We are in the process of obtaining nutritional parameters for our patients to objectively assess this.

Morbidity is not negligible with RNY procedures as has previously been reported by Williams and Awais.[29,30] However, in our view, this can be considered a safe surgical approach in the context of reoperative surgery on patients

who have undergone multiple previous operations. Significant adhesions are encountered and the gastric blood supply can be compromised by the previous operations. Sound surgical technique and experience with these reoperative interventions can mitigate the complication rate. High patient satisfaction and symptom resolution is attained with the RNY procedures in this difficult-to-treat group of patients with incapacitating symptoms.

The conclusions that can be drawn are limited by the retrospective nature of our study and the relatively small number of patients included in this initial reporting of our experience. The heterogeneity of the procedures performed may be considered confounding; however, the common underlying physiologic antireflux effect of the RNY reconstruction is of great importance. Longer follow-up, beyond the minimum duration of 1 year reported in our study, will also be needed to validate the initial results of patient satisfaction.

Conclusion

RNY reconstruction with GJ or EJ for failed antireflux procedures is a safe, valid surgical option in difficult situations, where a redo fundoplication is either non-feasible or expected to fail.

Acknowledgements We thank Aikaterini A. Nella, MD for the medical illustration and Janese Gerhardt, RN for the follow-up data collection.

References

1. Horgan S, Pohl D, Bogetti D, Eubanks T, Pellegrini C. Failed antireflux surgery; what have we learned from reoperations? Arch Surg 1999;134:809–817.
2. Bais JE, Horbach JM, Masclee AA, Smout AJ, Terpstra JL, Gooszen HG. Surgical treatment for recurrent gastro-oesophageal reflux disease after failed antireflux surgery. Br J Surg 2000; 87: 243–249.
3. Iqbal A, Awad Z, Simkins J, Shah R, Haider M, Salinas V, Turaga K, Karu A, Mittal SK, Filipi CJ. Repair of 104 failed anti-reflux operations. Ann Surg 2006;244:42–51.
4. Ohnmacht GA, Deschamps C, Cassivi SD, Nichols FC 3rd, Allen MS, Schleck CD, Pairolero PC. Failed antireflux surgery: results after reoperation. Ann Thorac Surg 2006;81:2050–2054.
5. DeMeester TR, Bonavina L, Albertucci M. Nissen fundoplication for gastroesophageal reflux disease: evaluation of primary repair in 100 consecutive patients. Ann Surg 1986;204:9–20.
6. Shirazi SS, Schulze K, Soper RT. Long-term follow-up for treatment of complicated chronic reflux esophagitis. Arch Surg 1987;122:548–552.
7. Stirling MC, Orringer MB. Surgical treatment after the failed antireflux operation. J Thorac Cardiovasc Surg 1986;92:667–672.
8. Hunter JG, Trus TL, Branum GD, Waring JP, Wood WC. A physiologic approach to laparoscopic fundoplication for gastroesophageal reflux disease. Ann Surg 1996;223:673–685.
9. Jamieson GG, Watson DI, Britten-Jones R, Mitchell PC, Anvari M. Laparoscopic Nissen fundoplication. Ann Surg 1994; 220:137–145.
10. Peters JH, Heimbucher J, Kauer WK, Incarbone R, Bremner CG, DeMeester TR. Clinical and physiologic comparison of laparoscopic and open Nissen fundoplication. J Am Coll Surg 1995; 180:385–393.
11. Washer GF, Gear MWL, Dowling BL, Gillison EW, Royston CM, Spencer J. Randomized prospective trial of Roux-en-Y duodenal diversion versus fundoplication for severe reflux oesophagitis. Br J Surg 1984;71:181–184.
12. Salo JA, Lempinen M, Kivilaakso E. Partial gastrectomy with Roux-en-Y reconstruction in the treatment of persistent or recurrent oesophagitis after Nissen fundoplication. Br J Surg 1985;72:623–625.
13. Smith SC, Edwards CB, Goodman GN. Symptomatic and clinical improvement in morbidly obese patients with gastroesophageal disease following Roux-en-Y gastric bypass. Obes Surg 1997; 7(6):479–484.
14. Frezza EE, Ikramuddin S, Gourash W, Rakitt T, Kingston A, Luketich J, Schauer P. Symptomatic improvement in gastroesophageal reflux disease (GERD) following laparoscopic Roux-en-Y gastric bypass. Surg Endosc 2002;16:1027–1031.
15. Perry Y, Courcoulas AP, Fernando HC, Buenaventura PO, McCaughan JS, Luketich JD. Laparoscopic Roux-en-Y gastric bypass for recalcitrant gastroesophageal reflux disease in morbidly obese patients. JSLS 2004;8(1):19–23.
16. Patterson EJ, Davis DG, Khajanchee Y, Swanström LL. Comparison of objective outcomes following laparoscopic Nissen fundoplication versus laparoscopic gastric bypass in the morbidly obese with heartburn. Surg Endosc 2003;17(10):1561–1565.
17. Nelson LG, Gonzalez R, Haines K, Gallagher SF, Murr MM. Amelioration of gastroesophageal reflux symptoms following Roux-en-Y gastric bypass for clinically significant obesity. Am Surg 2005;71(11):950–953.
18. Kent MS, Luketich JD, Irshad K, Awais O, Alvelo-Rivera M, Churilla P, Fernando HC, Landreneau RJ. Comparison of surgical approaches to recalcitrant gastroesophageal reflux disease in the patient with scleroderma. Ann Thorac Surg 2007;84:1710–1716.
19. DePaula AL, Hashiba K, Baffuto M, Machado CA. Laparoscopic reoperations after failed and complicated antireflux operations. Surg Endosc 1995;9:681–686.
20. Siewert JR, Isolauri J, Feussner H. Reoperation following failed fundoplication. World J Surg 1989;13:791–796.
21. Hiebert CA, O'Mara CS. The Belsey operation for hiatal hernia: a twenty year experience. Am J Surg 1979;137:532–535.
22. Csendes A, Bragheto I, Burdiles P, Smok G, Henriquez A, Parada F. Regression of intestinal metaplasia to cardiac or fundic mucosa in patients with Barrett's esophagus submitted to vagotomy, partial gastrectomy and duodenal diversion. A prospective study of 78 patients with more than 5 years of follow up. Surgery 2006; 139(1):46–53.
23. Csendes A, Braghetto I, Burdiles P, Díaz JC, Maluenda F, Korn O. A new physiologic approach for the surgical treatment of patients with Barrett's esophagus: technical considerations and results in 65 patients. Ann Surg 1997;226(2):123–133.
24. Lillemoe K. A new approach for the surgical treatment of Barrett's esophagus. Ann Surg 1997;226(2):121–122.
25. Morgenthal CB, Lin E, Shane MD, Hunter JG, Smith CD. Who will fail laparoscopic Nissen fundoplication? Preoperative prediction of long-term outcomes. Surg Endosc 2007;21:1978–1984.
26. Perez AR, Moncure AC, Rattner DW. Obesity adversely affects the outcome of antireflux operations. Surg Endosc 2001;15: 986–989.
27. Raftopoulos I, Awais O, Courcoulas AP, Luketich JD. Laparoscopic gastric bypass after antireflux surgery for the treatment of

gastroesophageal reflux in morbidly obese patients: initial experience. Obes Surg 2004;14(10):1373–1380.
28. Houghton SG, Nelson LG, Swain JM, Nesset EM, Kendrick ML, Thompson GB, Murr MM, Nichols FC, Sarr MG, et al. Is Roux-en-Y gastric bypass safe after previous antireflux surgery? Technical feasibility and postoperative symptom assessment. Surg Obes Relat Dis 2005;1(5):475–480.
29. Williams VA, Watson TJ, Gellersen O, Feuerlein S, Molena D, Sillin LF, Jones C, Peters JH. Gastrectomy as a remedial operation for failed fundoplication. J Gastrointest Surg 2007;11:29–35.
30. Awais O, Luketich JD, Tam J, Irshad K, Schuchert MJ, Landreneau RJ, Pennathur A. Roux-en-Y near esophagojejunostomy for intractable gastroesophageal reflux after antireflux surgery. Ann Thorac Surg 2008;85:1954–1961.

J Gastrointest Surg (2009) 13:2233–2238
DOI 10.1007/s11605-009-0980-x

ORIGINAL ARTICLE

Gastric Cardia Carcinoma is Associated with the Promoter -77T>C Gene Polymorphism of X-Ray Cross-Complementing Group 1 *(XRCC1)*

Giovanni Corso · Daniele Marrelli · Corrado Pedrazzani · José Carlos Machado · Stefano Mancini · Raquel Seruca · Franco Roviello

Received: 15 June 2009 / Accepted: 21 July 2009 / Published online: 7 August 2009

Abstract
Purpose X-ray repair cross complementing group 1 (*XRCC1*) is one of the major DNA repair proteins involved in the bas-excision repair pathway. Several single-nucleotide polymorphisms in the *XRCC1* gene are identified and related with increased cancer risk development. In particular, the -77T>C polymorphism located on the promoter region relates with lung cancer risk development. The aim of this study is to analyze the -77T>C allelic frequencies in a population composed of 456 primary gastric cancer patients (GC) and 507 blood donor controls.
Methods GC patients were observed at the University of Siena, Italy; clinicopathological data and family history were available for the cancer group. The control group is composed of blood donors. Constitutional genomic DNA was PCR amplified, and *XRCC1* -77T>C was detected using restriction enzyme BsrB I and analyzed in a 3% agarose gel.
Results The -77C>C homozygous genotype was significantly associated with increased risk of gastric cardia carcinoma (p=0.023) with an odds ratio of 1.65 (95% confidence interval 1.14 to 2.4). In the family history stratification, we report a significant association (p=0.043) between the -77T>C polymorphism and GC cases with familial lung cancer aggregation.
Conclusions Our results suggest that the *XRCC1* -77T>C polymorphism is a relevant host susceptibility factor for gastric cardia cancer development and specific subsets of familial clustering of GC.

Keywords Gastric cancer · Single nucleotide genetic polymorphism · Risk factor

Introduction

Gastric cancer (GC) remains the second leading cause of cancer-related death and the fourth most common epithelial neoplasia worldwide.[1,2] Recently, a gradual decrease in incidence and mortality rate in intestinal GC has been observed;[3] conversely, the diffuse histotype is showing a constant trend of increasing incidence in other geographic area.

Several genetic, epigenetic, and environmental factors interact causing a cumulative effect in the early steps of gastric carcinogenesis; among these, human genetic polymorphisms

G. Corso · D. Marrelli · C. Pedrazzani · F. Roviello
Department of Human Pathology and Oncology,
Section of General Surgery and Surgical Oncology,
Translational Research Laboratory, University of Siena,
Siena, Italy

G. Corso · J. C. Machado · R. Seruca
Institute of Molecular Pathology and Immunology of the
University of Porto (IPATIMUP),
Porto, Portugal

G. Corso · D. Marrelli · C. Pedrazzani · F. Roviello
Istituto Toscano Tumori,
Florence, Italy

J. C. Machado · R. Seruca
Faculdade de Medicina da Universidade do Porto,
Porto, Portugal

S. Mancini
Department of Surgery, University of Siena,
Siena, Italy

G. Corso (✉)
Policlinico le Scotte,
Viale Bracci,
53100 Siena, Italy
e-mail: corso5@unsi.it

in some inflammation-related genes are related with an increased risk of *Helicobacter pylori* related GC.[4–8] Continuous exposure to etiological risk factors, like *H. pylori*, causes an alteration of the DNA repair system leading to an increase mutation rate in the epithelial cells of the host.[9]

Functional polymorphisms in DNA repair genes have been demonstrated to alter the DNA repair activity and have been associated with different types of neoplasia, namely lung cancer.[10] One of such genes is the X-Ray Cross-Complementing Group 1 (*XRCC1*; OMIM *194360) that is one of the major DNA repair proteins involved in the base-excision repair pathway.[11,12]

In *XRCC1*, the functional polymorphism -77T>C (rs3213245), located in the promoter region, decreases the DNA repair efficiency leading to increased cancer susceptibility.[12] Recently, Hao and colleagues demonstrated that the -77T>C polymorphism in the *XRCC1* gene 5′ untranslated region contributes to its diminished function since it shows high affinity to Sp1 leading to *XRCC1* reduced transcriptional activity. Further, C allele of *XRCC1* gene has been associated with increased risk of lung cancer.[13]

In the present study, we aimed at determining the association between T>C polymorphism of the *XRCC1* gene and risk of GC development using a series of 507 controls and 456 patients with primary GC from two Italian geographic areas (with high and low incidence of GC). Moreover, we studied the clinicopathologic features of patients and tumors, including the family history of these GC patients, namely, history related to members affected with lung cancer within the family.

Methods

Study Population

A total of 963 subjects were enrolled in this study; 456 cases were GC patients who underwent surgical treatment for resectable GC between 1989 and 2008 at the Department of Human Pathology and Oncology, Hospital of the University of Siena, Italy. The control group included 507 unselected healthy blood donors, recruited after obtaining informed consent in the period 2001–2003 at the same Hospital Center; all blood donors were case-unrelated.

We studied 176 women in the cases and 129 women in controls. The recruitment of the patients and controls was concentrated in two geographic areas: Central Italy (748 cases, 77.7%) and Southern Italy (215 cases, 22.3%). Central Italy represents a high-risk area and Southern Italy a low-risk area for GC.

In the GC group, 303 cases (66.4%) were of intestinal histotype and 153 (33.6%) of diffuse type; tumor location was subdivided into cardia (70 cases, 15.3%) and noncardia (386 cases, 84.7%) carcinoma. In the cancer group, we evaluated the correlation between GC, the genotype polymorphism of *XRCC1* gene, and the smoking habits. Smoking history was available in 381 GC patients; overall, we stratified all individuals as smoker or no smoker and correlated the cigarette tobacco consumption with the -77T>C genotype. In the control population, no report of smoking habits was available.

Family History for Lung Cancer

This study was approved by the Local Ethics Committee, and informed consent was obtained from all recruited subjects. Oncological anamnesis and family history were investigated, adopting the detailed method described previously.[14,15] Family history was available for 443 GC probands; familial data were not obtained from 13 individuals. A detailed family history of GC was carefully collected including the presence of patients with lung cancer in first-degree relatives within the family. Forty-three (9.4%) GC probands showed a family history for lung cancer at first-degree relatives in the patient's family.

DNA Extraction, Promoter Amplification, and Genotyping

For GC patients constitutional DNA was extracted from 50 mg of normal gastric tissue after histopathological examination, in accordance with the Puregene DNA Purification Kit Protocol (Gentra Systems, Minneapolis, USA); for healthy blood donors, constitutional DNA was extracted from whole blood using the same protocol. The *XRCC1* -77T>C was detected by using the polymerase chain reaction (PCR) restriction fragment length polymorphism assay. PCR conditions and adopted primers were described previously.[12] A 219-bp PCR product was digested with the restriction enzyme BsrB I (New England BioLabs, Beverly, MA, USA) and separated on a 3% agarose gel. The -77T allele has two restriction sites and produces three fragments of 116, 57, and 46 bp, and the -77C allele has only one restriction site, resulting in two fragments of 173 and 46 bp (Fig. 1). The accuracy of the assay was checked by direct sequencing of samples from -77T, -77T>C, and -77C polymorphism variant carriers.

Hardy–Weinberg Equilibrium and Statistical Analysis

The Hardy–Weinberg equilibrium in the control group was calculated with the formula:

$$p^2 - 2pq + q^2 = 1$$

where p is the frequency of dominant allele and q the frequency of the recessive allele. Deviation between

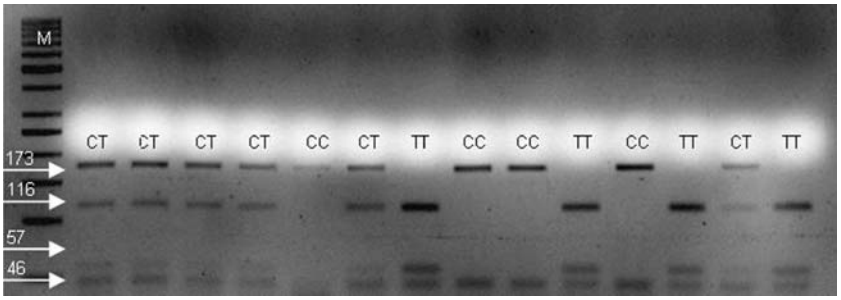


Figure 1 Genotype analysis at -77 promoter polymorphic site of *XRCC1* by digestion of PCR product with BsrB I restriction endonuclease. Band patterns of heterozygote with CT, homozygote with CC and TT.

expected and observed values was analyzed by means of Pearson's chi-square test. Comparison between genotype frequencies in the two groups under study was evaluated by means of Pearson's chi-square test. The genotypic specific risks were estimated as odds ratios with associated 95% confidence intervals (CI) by using correlation analysis and compared with Fisher's exact test. This analysis was repeated by stratifying for age (≤50/>50), gender (male/female), and area of residence (high-risk versus low-risk areas). Furthermore, the genotypic specific risks were also estimated separately for cardia/noncardia tumor location, intestinal/diffuse histotype, tumor advancement (early GC versus advanced GC), and family history for lung cancer. For statistical analysis, SPSS statistical package (version 15.0) was used.

Results

Table 1 summarizes the genotype frequencies for the *XRCC1* -77T>C polymorphism among the 456 controls and among the 507 patients with primary GC. Considering both populations, the polymorphisms did not deviate significantly from those expected under Hardy–Weinberg equilibrium. In controls, the frequency of T allele was 0.61, and the frequency of the C allele was 0.39 (χ^2 0.3; p=0.96). In the cancer group, the allelic frequency was 0.58 for the T allele and 0.42 for the C allele (χ^2 0.07; p=0.96). The frequencies of the TT, TC, and CC genotypes were 34%, 48%, and 18% in the cancer group versus 37%, 47%, and 16% in normal healthy individuals, respectively. The distribution was not statistically different between the two groups (p=0.577). Odds ratios (95% confidence interval) associated with TC, CC, and C carrier were 1.05 (0.93–1.19), 1.13 (0.88–1.45), and 1.05 (0.96–1.15), respectively; no significant cancer risk appeared to be associated with the distinct genotypes. Further, in Table 1, we stratified the genotype frequencies for the *XRCC1* - 77T>C polymorphism and the genotype-specific risk according to age of onset (before and after 50 years), gender, and geographic risk areas (high-risk and low-risk areas). No significant difference in genotype frequencies and corresponding odds ratios was found.

The analyses between the genotype frequencies for the *XRCC1* -77T>C polymorphism and pathological character-

Table 1 *XRCC1* Genotype Frequencies in Cancer and Control Groups with the Correlated Genotypic Specific Risks (Odds Ratios and 95% Confidence Limits)

	Number of cases	Cancer group (%) n=456			Control group (%) n=507			p value	Odds ratio (95% CI)		
		TT	CT	CC	TT	CT	CC		CT	CC	C carrier
Age											
≤50	405	39	47	14	39	47	14	1.000	1.00 (0.71–1.40)	0.99 (0.45–2.17)	1.01 (0.76–1.33)
>50	558	34	48	18	33	45	22	0.612	1.02 (0.85–1.23)	0.88 (0.63–1.23)	1.01 (0.77–1.33)
Gender											
Male	658	35	47	18	37	47	16	0.779	1.01 (0.97–1.17)	1.12 (0.82–1.51)	0.96 (0.78–1.18)
Female	305	33	50	17	40	44	16	0.487	1.14 (0.91–1.43)	1.17 (0.74–1.86)	0.83 (0.62–1.12)
Risk areas											
High-risk	748	35	47	18	39	44	17	0.465	1.09 (0.95–1.26)	1.13 (0.84–1.50)	0.89 (0.74–1.07)
Low-risk	215	32	50	18	28	57	15	0.522	0.91 (0.73–1.13)	1.07 (0.63–1.84)	1.13 (0.75–1.72)
Total	963	34	48	18	37	47	16	0.577	1.05 (0.93–1.19)	1.13 (0.88–1.45)	1.05 (0.96–1.15)

Table 2 Stratification According to Lauren Histotype, Tumor Site and Stage, Family History, and Smoking Status

	No. of cases	Cancer group (%) n=456			*p* value[a]	Odds ratio (95% CI)		
		TT	CT	CC		CT	CC	C carrier
Lauren								
Intestinal	303	34	47	19	0.473	1.05 (0.92–1.21)	1.19 (0.90–1.56)	1.06 (0.95–1.17)
Diffuse	153	35	49	16	0.863	1.05 (0.88–1.24)	1.02 (0.70–1.48)	1.03 (0.90–1.18)
Tumor site								
Cardia	70	26	48	26	0.059	1.18 (0.95–1.46)	1.65 (1.14–2.4)**	1.18 (1.02–1.38)
Noncardia	386	36	48	16	0.897	1.03 (0.91–1.17)	1.03 (0.79–1.36)	1.02 (0.93–1.13)
Tumor advancement								
Early	61	43	46	11	0.554	0.93 (0.71–1.22)	0.70 (0.35–1.38)	0.92 (0.73–1.15)
Advanced	395	33	48	19	0.334	1.07 (0.95–1.21)	1.20 (0.93–1.55)	1.07 (0.97–1.18)
Family history for LC								
Positive	43	21	51	28	0.043	1.28 (1.01–1.63)	1.89 (1.25–2.85)***	1.26 (1.07–1.49)*
Negative	400	36	48	16	0.893	1.03 (0.91–1.17)	1.05 (0.80–1.37)	1.02 (0.93–1.13)
Smoking status								
No	185	34	52	14	0.679	1.14 (0.77–1.67)	0.83 (0.53–1.43)	1.08 (0.76–1.53)
Yes	196	34	43	23	0.0038	1.11 (0.75–1.62)	1.78 (1.12–2.8)	1.28 (0.90–1.82)

LC lung cancer

*p=0.032; **p=0.023; ***p=0.015, Fisher's exact test

[a] Comparison with 507 cases of the control group

istics of the tumors is presented in Table 2. No significant associations were found between the distinct genotypes and Lauren's classification of the tumors and wall invasion (early versus advanced). In contrast, when GC patients were divided according to tumor site (cardia and noncardia cancer), a significant difference in *XRCC1* -77T>C genotype frequencies was observed. In individuals with cardia carcinoma, the risk was higher for *XRCC1* -77C homozygote [odds ratio (OR)=1.65, 95% CI 1.14 to 2.4; p=0.015 (Fisher's exact test)] (Table 2). Interestingly, *XRCC1* heterozygous individuals did not show an increased risk of cardia cancer (OR=1.18 CI 1.02–1.38).

Additionally, we investigated the family history of cancer taking in account, specifically, the presence of family members affected with lung carcinomas, since *XRCC1* -77T>C polymorphism has been previously associated with lung cancer. We verified a significant association between GC cases with *XRCC1* -77C homozygote genotype and -77C carriers (p=0.043) and familial aggregation of lung cancer.

Since tobacco exposure is a well-known carcinogen involved in lung cancer development, we analyzed, whenever described in the clinical reports, the smoking habits of the patients enrolled in the study. Considering the smoking habits (smoker versus nonsmoker), we found a significant association between GC smokers and the genotype -77C>C (p=0.038; Table 2).

Discussion

XRCC1 protein is required for maintenance of DNA repair activity during single-strand break events caused by damaging agents. Human cell lines carrying *XRCC1*-deficient function are hypersensitive to DNA-damaging agents.[16] The -77C>C promoter polymorphism of *XRCC1* induces a functional deficiency in the gene, and its presence has been associated to human cancer, namely, with non-small cell lung cancer.[13] The association between the presence of the -77C>C promoter polymorphism of *XRCC1* and increased risk of lung cancer was verified by case control studies.[12,17,18]

Recently, we verified that some of the families with clustering of GC also show members affected with lung cancer,[15] leading us to hypothesize that, in this particular subset of GC, a susceptible genetic factor and/or a particular environmental factor are likely to play a pivotal role. In accordance to this hypothesis and as the first step of our analyses, we studied the putative relationship between *XRCC1* -77T>C polymorphisms and familial aggregation of GC, in particular familial cases of GCs also harboring lung cancer in direct relatives. Regarding family history of GC patients, we analyzed 43 GC cases with positive family history for lung cancer and demonstrated a significant correlation with *XRCC1* -77C allele and the presence of lung cancer in first-degree relatives. This data confirms that

familial aggregation of gastric and lung cancer is associated to susceptible genetic risk factors that do not occur in familial forms of stomach cancer associated to germ line defects of tumor suppressor genes, namely, E-cadherin and p53, as previously suggested by Pedrazzani and colleagues.[15,19,20] In addition, we analyzed the association between the -77C>C promoter polymorphism of *XRCC1* and the clinicopathologic characteristics of the patients and tumors. Since in GC clear differences exist concerning the epidemiological data, etiological factors, and clinical differences, between cardia and noncardia tumors[21] and between intestinal and diffuse histotypes,[22] a stratified analysis was performed.

We found an association between the *XRCC1* -77C>C and increased risk for developing cardia carcinoma. According to our findings, GC cases with cardia location and homozygous genotype for the *XRCC1* -77C allele show an increased risk for GC. As reported previously, cardia adenocarcinoma is considered a distinct clinical entity with different prognostic factors. In accordance to this, it has been proposed that cardia cancer needs a different classification considering the different characteristics of cardia cancer since the current tumor–node–metastases staging system has been considered inadequate.[23,24] Moreover, the association between *XRCC1* -77C allele and cardia carcinoma is novel, and it is one of few genetic alterations described in this subtype of GC since till now no specific molecular phenotypes are related with this carcinoma. In contrast, no associations were found between *XRCC1* -77C allele and other clinicopathologic features of the patients and tumors.

Further, it has been suggested that exposure to various environmental factors represent essential components of GC tumorigenesis. Factors such as tobacco consumption,[25] dietary habits,[26] and *H. pylori* infection[27] have been demonstrated to be involved in the multifactorial process of gastric carcinogenesis. Our results show that GC patients carrying the genetic susceptibility for some DNA repair genes, as the promoter *XRCC1* -77T>C polymorphism, concomitantly are exposed to tobacco consumption. Our results allow us to speculate that gastric cardiac carcinoma is associated to deficient activity of the *XRCC1* gene due to -77T>C polymorphism and a concomitant history of smoking habits.

Our study reports some limitations that should be explained. Firstly, because our study was a hospital-based study, with cases recruited from hospitals and controls recruited from the community population as blood donors, the study subjects may not be representative of the general population. However, we believe that our results are unlikely to be attributable to selection bias because we used a relatively large number of incident cases and matched the controls to the cases on age, sex, and residential area. Second, because both populations, cancer and control groups, were recruited from different incidence area, Southern and Central Italy (respectively, low and high incidence areas), the -77T>C polymorphism may not explain a common risk factor. Nevertheless, our results did not identify significant correlation between stratified populations and -77T>C polymorphism, and both groups were in Hardy–Weinberg equilibrium. Third, smoking status and family history were evaluated only in cancer groups without correlation in respect to control group; we will provide to assess a complete smoking status also in control group in a further study to quantify the risk of cardia GC development in -77C allele carriers. This is the first study reported in literature; furthermore, other case control studies from different population in multicenter groups should confirm our results to improve the increased risk of cardia GC in subjects carrying this single nucleotide polymorphism.

Conclusion

In conclusion, we identified a novel biomarker involved in DNA repair for assessing cardiac GC risk that occurs in patients with a positive history of tobacco consumption. In familial clustering of GC, the presence of lung cancer in relatives may indicate that these patients can be carriers of *XRCC1* - 77T>C polymorphism risk allele.

Acknowledgments This work was supported by Istituto Toscano Tumori ("Gene expression profile and therapeutic implication in gastric cancer. From the clinical overview to the translational research"; Grant ITT-2007) and by Fundação para a Ciência e a Tecnologia ("Exploring the role of E-Cadherin-HER interaction in the search of molecular biomarkers for the clinical management of gastric cancer patients"; grant ref PIC/IC/82923/2007 and PhD grant ref SFRH/BD/40090/2007).

Competing interests The author(s) declare that they have no competing interests.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74–108.
2. Bray F, Sankila R, Ferlay J, Parkin DM. Estimates of cancer incidence and mortality in Europe in 1995. Eur J Cancer 2002;38:99–166.
3. La Vecchia C, Lucchini F, Negri E, Boyle P, Maisonneuve P, Levi F. Trends of cancer mortality in Europe, 1955–1989: I, Digestive sites. Eur J Cancer 1992;28:132–235.
4. Canedo P, Corso G, Pereira F, Lunet N, Suriano G, Figueiredo C, Pedrazzani C, Moreira H, Barros H, Carneiro F, Seruca R, Roviello F, Machado JC. The interferon gamma receptor 1 (IFNGR1) -56C/T gene polymorphism is associated with increased risk of early gastric carcinoma. Gut 2008;57:1504–1508.

5. Canedo P, Figueiredo C, Machado JC. After *Helicobacter pylori*, genetic susceptibility to gastric carcinoma revisited. Helicobacter 2007;12(Suppl 2):45–49.
6. Marrelli D, Pedrazzani C, Berardi A, Corso G, Neri A, Garosi L, Vindigni C, Santucci A, Figura N, Roviello F. Negative *Helicobacter pylori* status is associated with poor prognosis in patients with gastric cancer. Cancer 2009;115:2071–2080.
7. Machado JC, Figueiredo C, Canedo P, Pharoah P, Carvalho R, Nabais S, Castro Alves C, Campos ML, Van Doorn LJ, Caldas C, Seruca R, Carneiro F, Sobrinho-Simões M. A proinflammatory genetic profile increases the risk for chronic atrophic gastritis and gastric carcinoma. Gastroenterology 2003;125:364–371.
8. Figueiredo C, Machado JC, Pharoah P, Seruca R, Sousa S, Carvalho R, Capelinha AF, Quint W, Caldas C, van Doorn LJ, Carneiro F, Sobrinho-Simões M. *Helicobacter pylori* and interleukin 1 genotyping: an opportunity to identify high-risk individuals for gastric carcinoma. J Natl Cancer Inst 2002;94:1680–1687.
9. Machado AM, Figueiredo C, Touati E, Máximo V, Sousa S, Michel V, Carneiro F, Nielsen FC, Seruca R, Rasmussen LJ. *Helicobacter pylori* infection induces genetic instability of nuclear and mitochondrial DNA in gastric cells. Clin Cancer Res 2009;15:2995–3002.
10. Wei Q, Cheng L, Hong WK, Spitz MR. Reduced DNA repair capacity in lung cancer patients. Cancer Res 1996;56:4103–4107.
11. Li WQ, Zhang L, Ma JL, Zhang Y, Li JY, Pan KF, You WC. Association between genetic polymorphisms of DNA base excision repair genes and evolution of precancerous gastric lesions in a Chinese population. Carcinogenesis 2009;30:500–505.
12. Hu Z, Ma H, Lu D, Zhou J, Chen Y, Xu L, Zhu J, Huo X, Qian J, Wei Q, Shen H. A promoter polymorphism (-77T>C) of DNA repair gene XRCC1 is associated with risk of lung cancer in relation to tobacco smoking. Pharmacogenet Genomics 2005;15:457–463.
13. Hao B, Miao X, Li Y, Zhang X, Sun T, Liang G, Zhao Y, Zhou Y, Wang H, Chen X, Zhang L, Tan W, Wei Q, Lin D, He F. A novel T-77C polymorphism in DNA repair gene XRCC1 contributes to diminished promoter activity and increased risk of non-small cell lung cancer. Oncogene 2006;25:3613–36120.
14. Roviello F, Corso G, Pedrazzani C, Marrelli D, De Falco G, Suriano G, Vindigni C, Berardi A, Garosi L, De Stefano A, Leoncini L, Seruca R, Pinto E. High incidence of familial gastric cancer in Tuscany, a region in Italy. Oncology 2007;72:243–247.
15. Pedrazzani C, Corso G, Velho S, Leite M, Pascale V, Bettarini F, Marrelli D, Seruca R, Roviello F. Evidence of tumor microsatellite instability in gastric cancer with familial aggregation. Fam Cancer 2009;8:215–220.
16. Brem R, Hall J. XRCC1 is required for DNA single-strand break repair in human cells. Nucleic Acids Res 2005;33:2512–2520.
17. Brem R, Cox DG, Chapot B, Moullan N, Romestaing P, Gérard JP, Pisani P, Hall J. The XRCC1 -77T->C variant: haplotypes, breast cancer risk, response to radiotherapy and the cellular response to DNA damage. Carcinogenesis 2006;27:2469–2474.
18. Hsieh WC, Cheng YW, Lin CJ, Chou MC, Chen CY, Lee H. Prognostic significance of X ray cross-complementing group 1 T-77C polymorphism in resected non-small cell lung cancer. Jpn J Clin Oncol 2009;39:81–85.
19. Roviello F, Corso G, Pedrazzani C, Marrelli D, De Falco G, Berardi A, Garosi L, Suriano G, Vindigni C, De Stefano A, Leoncini L, Seruca R, Pinto E. Hereditary diffuse gastric cancer and E-cadherin: description of the first germline mutation in an Italian family. Eur J Surg Oncol 2007;33:448–451.
20. Corso G, Pedrazzani C, Marrelli D, Pinto E, Roviello F. Familial gastric cancer and Li Fraumeni syndrome. Eur J Cancer Care 2009; in press.
21. Lindblad M, Rodríguez LA, Lagergren J. Body mass, tobacco and alcohol and risk of esophageal, gastric cardia, and gastric non-cardia adenocarcinoma among men and women in a nested case-control study. Cancer Causes Control 2005;16:285–294.
22. Laurén PA, Nevalainen TJ. Epidemiology of intestinal and diffuse types of gastric carcinoma. A time-trend study in Finland with comparison between studies from high- and low-risk areas. Cancer 1993;71:2926–2933.
23. Lagarde SM, ten Kate FJ, Reitsma JB, Busch OR, van Lanschot JJ. Prognostic factors in adenocarcinoma of the esophagus or gastroesophageal junction. J Clin Oncol 2006;24:4347–4355.
24. Pedrazzani C, de Manzoni G, Marrelli D, Roviello F. It is time for a proper staging system for adenocarcinoma of the gastroesophageal junction. J Clin Oncol 2007;25:907–908.
25. La Torre G, Chiaradia G, Gianfagna F, De Lauretis A, Boccia S, Mannocci A, Ricciardi W. Smoking status and gastric cancer risk: an updated meta-analysis of case-control studies published in the past ten years. Tumori 2009;95:13–22.
26. Palli D, Russo A, Ottini L, Masala G, Saieva C, Amorosi A, Cama A, D'Amico C, Falchetti M, Palmirotta R, Decarli A, Mariani Costantini R, Fraumeni JF Jr. Red meat, family history, and increased risk of gastric cancer with microsatellite instability. Cancer Res 2001;61:5415–5419.
27. Brenner H, Bode G, Boeing H. *Helicobacter pylori* infection among offspring of patients with stomach cancer. Gastroenterology 2000;118:31–35.

J Gastrointest Surg (2009) 13:2239–2244
DOI 10.1007/s11605-009-0971-y

ORIGINAL ARTICLE

Subtotal Gastrectomy as Treatment for Distal Multifocal *Early Gastric Cancer*

Paolo Morgagni · Caterina Marfisi · Andrea Gardini · Daniele Marrelli · Luca Saragoni · Franco Roviello · Giovanni Vittimberga · Domenico Garcea · For the Italian Research Group for Gastric Cancer (I.R.G.G.C.)

Received: 21 April 2009 / Accepted: 15 July 2009 / Published online: 12 August 2009

Abstract
Introduction Multifocal early gastric cancer (MEGC) is frequently observed and represents a serious risk when minimally invasive treatments are performed.
Patients and Methods We present the experience of two Italian centers situated in a relatively high incidence area for gastric cancer. Out of a total of 791 surgical resections for EGC carried out in two Italian centers from 1976 to 2006, we identified 98 patients with multifocal EGC (12.3%). Two hundred and sixteen lesions were observed. Generally sited near the principal tumors, secondary lesions were, however, sometimes detected distally from the upper primary lesion. No secondary lesions were detected in the upper third when the principal lesion was sited at the lower third.
Results Survival of MEGC patients was not significantly lower than that of patients with monofocal EGC. No cases of gastric remnant relapse were observed at a mean follow-up of 9 years (range 1–28) after subtotal gastrectomy.
Discussion When EGCs are detected, the possibility of MEGC must always be investigated by endoscopy and chromoendoscopy. When a MEGC is found in the lower third of the stomach and chromoendoscopy of the upper third has been performed, subtotal gastrectomy can be considered as sufficient treatment.

Keywords Early gastric cancer · Multifocal early gastric cancer · Subtotal gastrectomy · Surgical treatment

P. Morgagni (✉) · C. Marfisi · A. Gardini · G. Vittimberga · D. Garcea
Department of General Surgery, Pierantoni-Morgagni Hospital,
Via Forlanini 34,
47100 Forlì, Italy
e-mail: p.morgagni@ausl.fo.it

D. Marrelli · F. Roviello
Surgical Oncology Unit, University of Siena,
Policlinico Le Scotte, Via le Bracci,
53100 Siena, Italy

L. Saragoni
Pathology Unit, Morgagni-Pierantoni Hospital,
Via Forlanini 34,
47100 Forlì, Italy

Introduction

Multifocality is a rare condition in advanced gastric cancer, but not unusual in early gastric cancer (EGC) lesions, with an incidence of about 10%. In 1957, Moertel presented the following criteria for the diagnosis of multifocal early gastric cancer (MEGC): each lesion is histopathologically malignant, and each one is separated from the others by a normal gastric wall; lesions are not the result of local extension of or metastasis from another gastric tumor.[1] Moertel also affirmed that if the depth of invasion is the same in two or more lesions, the one extending over the greatest area should be regarded as the main lesion, with the others considered as accessories. Although more accurate endoscopy techniques, such as chromoendoscopy and magnified imaging, are frequently used to identify MEGC, this condition is often only diagnosed by a pathologist and, therefore, not before surgical treatment. For this reason, some surgeons submit EGC patients to total

gastrectomy, thus, avoiding the risk of missing gastric remnant lesions. This approach is generally considered too aggressive, especially if we take into account comorbidities and quality of life in patients submitted to total gastrectomy.

The aim of this retrospective study was to report the experience of two Italian surgical units situated in two hospitals in north-central Italy. In particular, clinical outcome after subtotal gastrectomy for multifocal EGC was evaluated and compared to that of patients with unifocal EGC.

Patients and Methods

From 1976 to 2006, 791 patients underwent resection for early gastric cancer in two Italian surgical units (Department of General Surgery, Morgagni-Pierantoni Hospital, Forlì and the Surgical Oncology Unit of Siena University). Ninety-eight of these patients (12.3%) had multifocal lesions according to Moertel's criteria. All patients were classified according to tumor size, Japanese macroscopic type,[2] Lauren's histological type,[3] and TNM classification.[4] Patients with synchronous advanced gastric cancer or other tumors were excluded. Age, sex, histologic and macroscopic type, size, and site were compared to identify risk factors for multifocal EGC.

Subtotal gastrectomy was performed for tumors located in the lower two thirds of the stomach, with removal of the greater and lesser omentum and gastrojejunal Billroth II reconstruction. Total gastrectomy was carried out for tumors located in the upper gastric third, with Roux-en-Y reconstruction. D1 lymph node dissection was generally performed in elderly or critical patients, while en bloc D2 lymphadenectomy, in accordance with Japanese Gastric Cancer Association recommendations, was preferred for all other patients.[2] Although hand-sewn anastomosis was usually performed, we used staplers for esophagojejunal anastomosis and sometimes for duodenal remnants.

Death from postoperative complications was considered an event if it occurred during hospitalization. No patients were submitted to adjuvant or neoadjuvant therapy. Follow-up ultrasonography and serum-marker evaluation were carried out every 6 months for the first 5 years. Endoscopic checkups were carried out annually after surgery for a period of 5 years given the incidence of gastric remnant carcinoma and the importance of evaluating for esophagitis or reflux, both treated pharmacologically. Once 5 years had passed, endoscopy was performed after a further 2 years and every 3 years thereafter.

Survival times were measured from the date of surgery until death. Univariate analysis was performed by tracing Kaplan–Meier survival curves,[5] and comparison of survival curves was based on the logrank test. Multivariate analysis was carried out according to the logistic regression model for categorical variables. All p values were based on two-sided testing (threshold value $p=0.05$) and statistical analysis was carried out using SPSS test (software package 13.0 version Chicago Inc.).

Results

Ninety-eight MEGC patients were operated on between 1976 and 2006, representing 12.3% of the 791 patients consecutively submitted to surgery for EGC in the two hospital departments. Patient characteristics are summarized in Table 1. The variable most at risk for multifocality in our patients was mucosal EGC<1 cm sited at the lower third, but only tumor site (OR 2.007 [95%CI: 1.15–3.49], $p=0.014$) and T infiltration (OR 1.747 [95%CI: 1.05–2.88] $p=0.029$) were considered as independent risk factors at multivariate analysis, the former being the most significant (Table 2). Conversely, we did not find any correlation between multifocality and sex, age >70 years, macroscopic type, histologic type, differentiation, or lymphatic diffusion. With regard to tumor size, we also considered 2 or 3 cm as cutoff values, but these did not prove to be statistically significant. Macroscopic type did not represent a risk factor even when polipoid (I, IIa) and ulcerated lesions (IIc, III) were considered together. We generally found two EGCs and only rarely three or more multifocal tumors; principal and secondary lesions were sited at the lower third of the stomach. In particular, of the 216 lesions detected, 82 patients had two lesions, 12 patients had three, and four had four. In four patients the principal lesion was sited at the upper third, in 21 at the middle third and in 73 at the lower third; two secondary lesions were detected at the upper third, 31 at the middle third, and 86 at the lower third (Fig. 1). Chromoendoscopy during endoscopy improved detection of MEGC, but as it has only become standard practice for EGC in the last few years, no definitive conclusions on differences before and after its application can be drawn.

Twenty-nine patients presented diffuse gastric cancer and 69 intestinal histologic type. With respect to the known association between familial gastric cancer and multifocality, more frequent in younger adults with diffuse type, four patients from the former group were under 50 years of age, but none had a family history of the disease.

Eighty-nine patients with distal multifocal EGC were submitted to subtotal gastrectomy with Billroth II reconstruction, while nine patients with upper third lesions underwent total gastrectomy with Roux-en-Y reconstruction. No patient with distal multifocal early gastric cancer was submitted to total gastrectomy if >2 cm of normal mucosa was observed from the resection line. As the study

Table 1 Clinicopathological factors of patients with and without multifocal early gastric cancer

	Unifocal (%) *N*=693		Multifocal (%) *N*=98		*P* value
Sex					ns
Male	396	(57.1)	62	(63.3)	
Female	297	(42.9)	36	(36.7)	
Age (years)					ns
<70	401	(57.9)	48	(49)	
>70	292	(42.1)	50	(51)	
Macroscopic type					ns
1	94	(13.5)	12	(12.3)	
2a	55	(7.9)	6	(6.1)	
2b	34	(4.9)	3	(3.1)	
2c	328	(47.3)	50	(51)	
3	168	(24.3)	26	(26.5)	
Unknown	14	(2.1)	1	(1)	
Site					0.001
Fundus/corpus	275	(39.7)	25	(25.5)	
Antrum	418	(60.3)	73	(74.5)	
Size					0.049
≤ 1 cm	126	(18.2)	21	(21.4)	
>1 cm	512	(73.9)	54	(55.1)	
Unknown	55	(7.9)	23	(23.5)	
T1					0.002
a	346	(49.9)	62	(63.3)	
b	347	(50.1)	36	(36.7)	
Histological type					ns
Intestinal	530	(76.5)	69	(70.4)	
Diffuse/mixed	158	(22.8)	29	(29.6)	
Unknown	5	(0.7)			
Histological grade					ns
1	221	(31.9)	38	(38.8)	
2	190	(27.4)	24	(24.5)	
3	272	(39.3)	34	(34.7)	
Unknown	10	(1.4)	2	(2)	
Lymphatic diffusion					ns
N0	598	(86.3)	88	(89.8)	
N+	95	(13.7)	10	(10.29	

ns not significant

was conducted over a relatively long period, and as D2 lymphadenectomy was still infrequent during the 1980s, only 24 D2 dissections were performed, with a mean number of 24.9 lymph nodes dissected. Taking into account all the patients, a mean of 17.7 lymph nodes were dissected, 18.1 in MEGCs (range 4–54) and 17.2 in single EGCs (range 3–62). The relatively low number of lymph nodes obtained stems from the fact that during the first few years of the study, sampling of fresh lymph node tissue was not performed by the surgeon station by station but rather "en bloc," with only one piece of formalin-embedded tissue sent to the pathologist. MEGC patients had a lower, nonsignificant number of lymph node metastases than those with EGC, and 10 patients were classified as N1 (11.3% vs.16.2%, respectively; p=0.42).

Table 2 Logistic regression analysis for variables associated with multifocality

Explanatory variable	Odds ratio	95% CI	*P* value
Site	2.007	1.15–3.49	0.014
T1a/b	1.747	1.05–2.88	0.029
Size			ns

ns not significant

Five- and 10-year survival of MEGC patients was 92.6% and 89.8%, respectively, not significantly different from those with unifocal EGC (93.3% and 89.6%, respectively; p=0.41; Fig. 2). Patients submitted to subtotal gastrectomy had 5- and 10-year survival rates of 91.9% and 88%, respectively, while

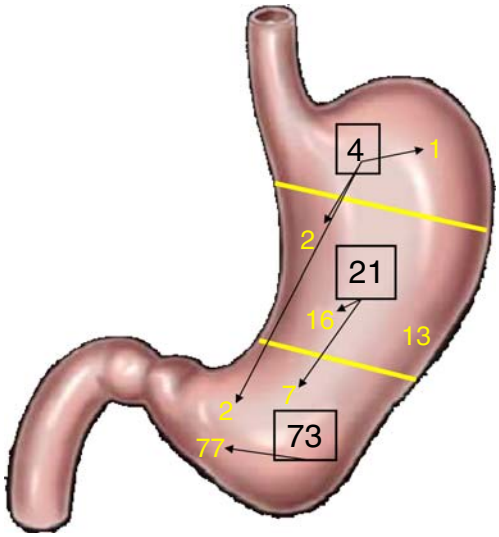


Figure 1 Site of secondary lesions related to primary EGC. The *boxes* show the number of primitive lesions, while the *arrows* indicate the sites and number of secondary lesions.

all patients who underwent total gastrectomy for upper lesions showed 100% 10-year survival. Although this difference is important, it must be remembered that only nine total gastrectomies were performed.

No gastric remnant recurrence was observed in MEGC patients after a median follow-up of 9 years (range 1–28), while 10 of the 574 patients with single EGC who underwent subtotal gastrectomies developed a new gastric cancer or had gastric remnant relapse (1.7%) during the same follow-up period. One of the 10 patients was diagnosed with a new, well-differentiated T2 gastric remnant adenocarcinoma (histologically similar to the first one radically resected) only 11 months after the first surgical treatment and was submitted to total gastrectomy. The other nine patients developed gastric remnant recurrence or new gastric cancer after a median follow-up of 7.4 years (range 3–21).

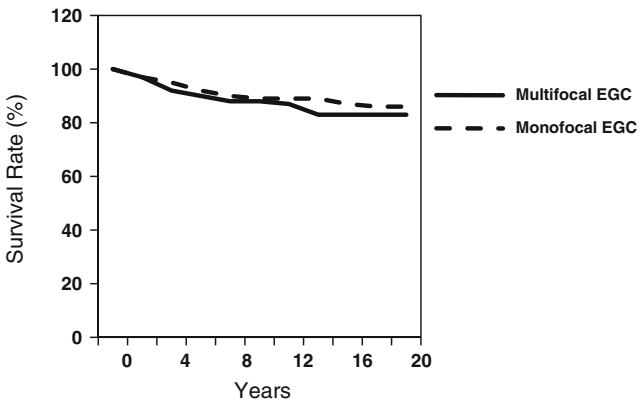


Figure 2 Long-term survival of patients with and without multifocal EGC.

Discussion

Multifocality is a condition described in 0.8–22% of EGC.[6] Often diagnosed by the pathologist after surgical treatment rather than preoperatively by the endoscopist (about 35% of missed lesions are reported in Eastern studies[7] and even more in Western series[8]), multifocality represents a risk for undertreatment. Generally observed in early lesions, multifocality is not very frequent in advanced gastric cancer. Kitamura, reporting a 7.4% incidence of MEGC but only 3.02% of multifocal advanced gastric cancer, tried to explain this difference by referring to the theory of collision cancer, which suggests that two different early synchronous lesions may fuse together after lateral and vertical growth, becoming a single advanced cancer.[9]

Similarly, in our experience, MEGC represents around 12% of EGCs and is rare in advanced stages. Some authors consider the large areas of intestinal metaplasia and dysplasia, frequently present in elderly patients, as a precursor of multifocality. Furthermore, an average age of 65 years is generally believed to be a risk factor for MEGC, 5–8 years higher than the age considered most at risk for monofocal lesions.[10,11]

The male sex, mucosal lesions, differentiated histologic type, elevated macroscopic type, tumor size <2 cm, and lower third site have been found to be the most important risk factors for MEGC. Literature data is, however, still somewhat contradictory. Takeshita found a higher incidence of depressed macroscopic type in his series of 61 MEGCs,[7] while Huguier observed a high number of nondifferentiated histologic type EGCs in his relatively small patient population.[12] Genetic factors such as germline mutations in the *E-caderin* gene have also been reported to be involved in a small number of signet ring cell diffuse histotype EGCs with multiple foci.[13,14] Twenty-nine of our patients presented diffuse carcinoma, but as no hereditary cancers were hypothesized, genetic studies were not conducted.

Our data identified mucosal EGC sited in the antrum as an independent risk factor for MEGC. Tumors <1 cm were considered a significant, albeit not independent, risk factor. Although MEGC was also rarely diagnosed preoperatively in our series (50%), the increasing use of chromoendoscopy and magnifying endoscopy gradually led to a higher number of endoscopic diagnoses during the study period.

With regard to secondary lesions, two are generally observed, although four or five are not uncommon and as many as 43 synchronous lesions have also been reported.[6,9,10,15,16] In our series, 12 patients presented three lesions and only four had four lesions. Secondary lesions are generally observed in the same gastric third as the first tumor or in a lower third and are only rarely located in the proximal third. Kodama noticed that when the major lesion was located in the upper gastric third, the others were sited in the

lower one, whereas when the first lesion was in the lower third, the secondary lesions were generally in the same third.[6] In our case series, we likewise observed that secondary lesions were usually located near the principal one and were generally observed in the lower gastric third. In particular, 79.8% of the lesions were sited in the same area, 18.2% in an area near the principal lesion, and only 2% of main upper lesions showed secondary antral lesions (Fig. 1).

Secondary lesions, when differentiated, generally present the same histologic characteristics. Takeshita reported that in his case series, 61% of well-differentiated main lesions had well-differentiated secondary lesions, and only 13% of undifferentiated lesions showed the same histologic characteristics as the accessory lesions.[7]

In the literature, treatment of multifocal early gastric cancer does not differ from that of monofocal lesions, and endoscopic mucosal resection or subtotal gastrectomy are recommended if indications for each tumor are satisfied.[7,16] We agree with this approach and currently perform, when possible, endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). When criteria for EMR or ESD are not satisfied and distal MEGC is detected, we generally carry out subtotal gastrectomy for the following reasons: secondary lesions are generally sited in the lower third near the main lesion; secondary EGC sited in the upper gastric third are rare; randomized and retrospective studies have shown that patients submitted to subtotal gastrectomy have lower morbidity and mortality, a better quality of life and similar survival with respect to those who undergo total gastrectomy, in both early and advanced antral disease.[17,18]

The high incidence of misdiagnosis in MEGC makes it important to perform chromoendoscopy, a simple and inexpensive technique that allows small, hidden lesions to be detected in all EGC patients. Such a strategy could help reduce the incidence of missed lesions and gastric remnant carcinoma, reported in 1.1–2% of EGC patients submitted to subtotal gastrectomy.[10,19] The incidence of gastric remnant cancer in MEGC is no higher than that of unifocal EGC. Kodera and coworkers, in a series of 2061 EGC, observed a 2% incidence of gastric remnant cancer after a follow-up of 16 years, and only one (0.8%) patient in this subgroup had been diagnosed with MEGC.[10]

Although we did not observe any relapses or metachronous gastric remnant cancers in patients operated on for MEGC, 10 (1.7%) of the 574 patients who underwent subtotal gastrectomies for monofocal EGC had a gastric remnant cancer incidence similar to that reported in the literature. One of these was a patient treated for a single EGC of the lower third who was diagnosed with a second lesion in the upper third only 11 months after subtotal gastrectomy. In our opinion, this was a case of a missed synchronous lesion. The other relapses were detected over a period ranging from 3.5 to 16 years after subtotal gastrectomy.

Five- and 10-year survival rates in patients with distal MEGC treated with subtotal gastrectomy do not differ greatly from those with single EGC,[10] and MEGC is not considered as a prognostic factor.[20,21] The results from the present study would seem to confirm this observation, with survival curves similar for the two groups. Our findings also indirectly point to the effectiveness of subtotal gastrectomy in distal MEGC. Although patients with upper lesions treated with total gastrectomy presented better 5- and 10-year survival, few patients were treated, and data are not significant. However, we must underline that this is a retrospective study, and a control group (distal MEGC treated with total gastrectomy) is lacking.

In conclusion, MEGC is a rare occurrence, generally involving the lower gastric third and usually not detected by preoperative endoscopy. It is more frequent in patients with small differentiated mucosal EGC. The prognosis of MEGC is good, and treatment does not differ from that of monofocal EGC. For this reason, subtotal gastrectomy could be considered adequate treatment for lower and middle third MEGC. However, secondary lesions in the upper gastric third may be present, making preoperative chromoendoscopy and postoperative endoscopic follow-up strongly indicated.

Conflict of interest The authors have no conflicts of interest.

References

1. Moertel CG, Bargen JA, Soule EH. Multiple gastric cancer: review of the literature and study of 42 cases. Gastroenterology 1957;32:1095–103.
2. Japanese Gastric Cancer Association. The new Japanese Classification of Gastric Carcinoma. 2nd Engl. ed. Gastric Cancer 1998;1:10–24.
3. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. Acta Pathol Microbiol Scand 1965;64:31–49.
4. Sobin LH, Wittekind CH. TNM classification. In International Union Against Cancer (UICC). TNM classification of malignant tumours, 5th ed. New York: Wiley-Liss, 1997, pp 59–62.
5. Kaplan EL, Meier P. Non parametric estimation from incomplete observation. J Am Stat Assoc 1958;53:457–481.
6. Kodama M, Tur GE, Shiozawa N, Koyama K. Clinicopathological features of multiple primary gastric carcinoma. J Surg Oncol 1996;62:57–61.
7. Takeshita K, Tani M, Honda T, Saeki I, Kando F, Saito N, Endo M. Treatment of primary multiple early gastric cancer: from the viewpoint of clinicopathologic features. World J Surg 1997;21:832–836.
8. Borie F, Plaisant N, Millat B, Hay JM, Fagniez PL, De Saxce B. French Associations for Surgical. Research Treatment and prognosis of early multiple gastric cancer. Eur J Surg Oncol 2003;29:511–514.
9. Kitamura K, Yamaguchi T, Okamoto K, Otsuji E, Taniguchi H, Hagiwara A, Sawai K, Takahashi T. Clinicopathologic features of

synchronous multifocal early gastric cancers. Anticancer Res 1997;17:643–646.
10. Kodera Y, Yamamura Y, Okamoto K, Otsuji E, Taniguchi H, Hagiwara A, Sawai K, Takahashi T. Incidence, diagnosis and significance of multiple gastric cancer. Br J Surg 1995;82:1540–1543.
11. Noguchi Y, Ohta H, Takagi K, Takahashi T, Ohashi I, Kuno K, Kajitani T, Kato Y. Synchronous multiple early gastric carcinoma: a study of 178 cases. World J Surg 1985;9:786–793.
12. Huguier M, Ferro L, Barrier A. Early gastric carcinoma: spread and mulcentricity. Gastric Cancer 2002;5:125–129.
13. Pedrazzani C, Corso G, Marrelli D Roviello F. E-caderin and hereditary diffuse gastric cancer. Surgery 2007;142:645–657.
14. Charlton A, Blair V, Shaw D, Parry S, Guilford P, Martin IG. Hereditary diffuse gastric cancer: predominance of multiple foci of signet ring cell carcinoma in distal stomach and transitional zone. Gut 2004;53:814–820.
15. Baba Y, Ishikawa S, Ikeda K, Honda S, Miyanari N, Iyama K, Baba H. A patient with 43 synchronous early gastric carcinomas with a krukenberg tumor and pericardial metastasis. Gastric Cancer 2007;10:135–139.
16. Otsuji E, Kuriu Y, Ichikawa D, Okamoto K, Hagiwara A, Yamagishi H. Clinicopathologic characteristics and prognosis of synchronous multifocal gastric carcinomas. Am J Surg 2005;189:116–119.
17. Bozzetti F, Marubini E, Bonfanti G, Miceli R, Piano C, Gennari L. Subtotal versus total gastrectomy for gastric cancer. Five-year survival rates in a multicenter randomized Italian trial. Ann Surg 1999;2:170–178.
18. De Manzoni G, Verlato G, Rovello F, di Leo A, Marrelli D, Morgagni P, Pasini F, Paragoni L, Tomezzoli A. Italian Research Group for Gastric Cancer. Subtotal versus total gastrectomy for T3 adenocarcinoma of the antrum. Gastric Cancer 2004;7:183–184.
19. Sano T, Sasako M, Kinoshita T, Maruyama K. Recurrence of early gastric cancer. Follow-up of 1475 patients and review of the Japanese literature. Cancer 1993;72:3174–3178.
20. Folli S, Morgagni P, Roviello F, De Manzoni G, Marrelli D, Saragoni L, Di Leo A, Gaudio M, Nanni O, Carli A, Cordiano C, Dell'Amore D, Vio A. Italian Research Group for Gastric Cancer (IRGGC). Risk factors for lymph node metastases and their prognostic significance in early gastric cancer for the Italian Research Group for Gastric Cancer. Jpn J Clin Oncol 2001;31:495–499.
21. Roviello F, Rossi S, Marrelli D, Pedrazzani C, Corso G, Vindigni C, Morgagni P, Saragoni L, de Manzoni G, Tomezzoli A. Number of lymph node metastases and its prognostic significance in EGC: a multicenter Italian study. J Surg Oncol 2006;15:275–280.

J Gastrointest Surg (2009) 13:2245–2251
DOI 10.1007/s11605-009-0983-7

ORIGINAL ARTICLE

Rectal Distensibility and Symptoms After Stapled and Milligan–Morgan Operation for Hemorrhoids

Maura Corsetti · Paola De Nardi · Salvatore Di Pietro · Sandro Passaretti · Pier Alberto Testoni · Carlo Staudacher

Received: 29 April 2009 / Accepted: 24 July 2009 / Published online: 12 August 2009

Abstract
Introduction In a previous uncontrolled study, a reduction of rectal distensibility and volume thresholds for sensations have been related to the occurrence of fecal urgency and/or increased stool frequency after stapled hemorrhoidopexy.
Aim of the study The aim of this study was to compare rectal symptoms and sensory-motor function after stapled hemorrhoidopexy and Milligan–Morgan hemorrhoidectomy.
Methods The clinical records of 12 (four women) and ten patients (four women) with third- and fourth-degree hemorrhoids, respectively, who underwent stapled hemorrhoidopexy or Milligan–Morgan's hemorrhoidectomy, were evaluated. One week before and 6 months after surgery, rectal motor and sensory response to distension was assessed by an electronic barostat, and bowel and rectal symptoms were recorded by means of a 7-day diary and Bristol Index scale and psychological symptoms with SCL-90 questionnaire.
Results Rectal distensibility and volume thresholds for sensations were significantly lower after surgery ($P<0.02$) in the stapled group. Increased stool frequency and/or fecal urgency arose in 41% of patients in the stapled group and associated with altered rectal distensibility. No difference within and between groups could be demonstrated in SCL-90 score.
Conclusions Rectal distensibility and volume thresholds for sensations decrease after stapled hemorrhoidopexy. Altered rectal distensibility was associated with rectal urgency and/or increased stool frequency.

Keywords Hemorrhoids · Barostat · Rectal motor function · Rectal sensory function · Postoperative symptoms

Introduction

In 1998, Longo introduced an alternative approach to the treatment of hemorrhoidal disease. Since then, randomized studies and systematic reviews have shown that the procedure is as safe as conventional hemorrhoidectomy and is associated with shorter operating time, convalescence, less pain, and postoperative disability.[1]

However, persistent postoperative symptoms, such as pain, fecal urgency, or increase stool frequency, have been described after this procedure.[2,3] According to some authors, anal pain could be avoided if rectal mucosa excision is performed at a distance of at least 2–4 cm above the dentate line.[4–6] On the contrary, the pathophysiological mechanisms underlying fecal urgency and increased stool frequency are still unclear.

In a previous study, we have demonstrated a reduction of rectal distensibility and volume thresholds for sensations in patients treated with stapled hemorrhoidopexy, and a possible correlation between rectal functional alterations and postoperative disorders was postulated.[7] However, that study was uncontrolled, and the patients' symptoms were not evaluated.

Aim of the present study was to compare the effect of stapled hemorrhoidopexy and of Milligan–Morgan hemor-

M. Corsetti (✉) · S. Di Pietro · S. Passaretti · P. A. Testoni
Division of Gastroenterology and Gastrointestinal Endoscopy,
San Raffaele Scientific Institute,
Vita-Salute San Raffaele University,
Via Olgettina 58,
20132 Milan, Italy
e-mail: corsetti.maura@hsr.it

P. De Nardi · C. Staudacher
Department of Surgery, San Raffaele Scientific Institute,
Vita-Salute San Raffaele University,
Via Olgettina 58,
20132 Milan, Italy

rhoidectomy on rectal motor and sensory function and postoperative symptoms of patients with third- and fourth-degree hemorrhoids.

Patients and Methods

Patients

The present is a retrospective study involving 22 consecutive patients with third- and fourth-degree hemorrhoids referred to the Surgical Department between June and November 2007. Twelve patients (four women, mean age 48±9 years) underwent stapled hemorrhoidopexy (SH) and ten patients (four women, mean age 45±11 years) Milligan–Morgan hemorrhoidectomy (MMH). Type of surgical procedure was determined by surgeon's and patient's choice. Preoperative assessment included a full medical history, accurate proctological evaluation, and proctosigmoidoscopy or colonoscopy. No patient had previous proctological, rectal, or pelvic surgery; concomitant anal, rectal, or inflammatory bowel disease; chronic organic disease; and chronic medical treatments (including laxatives, psychotropic drugs, and analgesics) during the previous 6 months. The study was performed in accordance with the Declaration of Helsinki. All of the patients gave their written informed consent to the surgical procedure, to the rectal evaluations with the electronic barostat (which are routinely performed in our Gastroenterology Unit with the symptoms questionnaire to study the patients before and after surgery), and to the use and the publication of their data for scientific reasons. The gastroenterologist who performed analysis of the tracing was blind to the kind of surgical operation performed as another gastroenterologist placed and made the barostat to the patients.

Questionnaires

As routinely performed in our Gastroenterology Unit, during the week preceding each rectal evaluation, all the patients were asked to fulfill a daily questionnaire reporting the frequency and consistency of their bowel movements, episodes of fecal urgency in association with each defecation, of abdominal pain, and of fecal incontinence. The consistency of their stool was registered according to the seven-point scale of the Bristol Index[8] in which: 1= separate, hard lumps—like nuts; 2=sausage-shaped and lumpy; 3=sausage-shaped, cracked surface; 4=sausage or "snaky," smooth, soft; 5=soft blobs, clear-cut edges; 6= fluffy pieces, ragged edges, "mushy"; 7=watery, no solids.

They also completed a psychological symptoms checklist (SCL-90) that assesses symptom severity in the following areas: anxiety, depression, hostility, interpersonal sensitivity, obsessive–compulsive behavior, paranoia, phobic behavior, psychosis, and somatization. The checklist consists of 90 items that subjects are asked to score 0–4 (0=absent, 1=mild, 2=moderate, 3=intense, 4=severe) on the basis of the severity of their symptoms.[9] The same questionnaires were completed during the 6-month follow-up visit.

Materials

Visceral Distension Device

The rectal distensions were controlled by an electronic device consisting of a pressure transducer linked by means of an electronic feedback mechanism to a computer-driven air injection–aspiration system (Synectics Visceral Stimulator, Medtronic Synectics Medical, Milan, Italy).[10] A thin-walled plastic bag (Mobile Chemical Company, Pittsford, New York, USA) was tied 0.5 and 8.5 cm from the distal end of a double-lumen polyvinyl tube (Salem Sump Tube, Sherwood Medical, Petit Rechain, Belgium; outer diameter 4.7 mm). One lumen of the tube was attached to the pressure sensor and the other to the air injection–aspiration system. The intrabag pressure and volume were recorded by a computer using version 1.11 of the Polygram for Windows® program.

Experimental Procedure

As described in detail elsewhere,[7] briefly, the rectum was cleaned with 130 ml of a 16% sodium biphosphate and 6% sodium phosphate solution (Clismalax, Sofar SpA, Milan, Italy) the evening before the study and the same morning at least 2 h before the test. After an overnight fast, the patient was placed in the left-lateral position on a padded bed. The deflated bag was placed in the rectum with the caudal end 6 cm from the anal verge. To unfold the bag and for conditioning purposes, a first volume-controlled distension (100 ml/min) was performed up to a volume of 300 ml (a smaller volume in the case of intolerance), and the bag was then deflated. Each patient then underwent two distensions: a pressure-controlled stepwise (4 mmHg/2 min) and a volume-controlled ramp at 100 ml/min. During all the distension periods, the patients were asked to report their sensations of first distension, desire to defecate, urgency, or discomfort (1=first sensation, 4= discomfort) by means of a subject-operated marker device electronically connected to both the distending device and the computer.

Surgery

For both surgical procedures, bowel preparation was performed the same day of operation with a 250-ml enema. Antibiotic prophylaxis with a single dose of metronidazole

(500 mg intravenously) was administered before the induction of anesthesia. Deep-vein thrombosis prophylaxis was performed with low molecular weight heparin (3,000 IU/day) for patients older than 40. The procedures were performed under regional anesthesia with the patients in lithotomic position. Stapled hemorrhoidopexy was performed with PPH 03™, Ethicon Endo-Surgery device, according to the recommended technique.[11] MMH was performed with diathermy.[12] Clear liquid diet was started 4 h after operation and solid diet the following morning. There were no postoperative complications, and the patients were discharged the day after surgery. Postoperatively, the patients were encouraged to drink plenty of fluids and take a high-fiber diet. No laxative was prescribed unless already taken preoperatively. Oral analgesic were prescribed according to patients' needs.

Patients were reviewed at 1week and 1, 3, and 6 months after surgery.

Data Analysis

Rectal distensibility was analyzed in terms of the slope of the linear pressure/volume (mmHg/ml) or volume/pressure (ml/mmHg) relationships, respectively, during pressure-controlled or during volume-controlled rectal distensions. During stepwise pressure-controlled distension, the intraballoon pressure was calculated by averaging the values during each 2-min step of distension. During ramp volume-controlled distension, intraballoon pressure was recorded at 10 ml intervals. To calculate the slopes of the pressure–volume and of the volume–pressure relationships, the values of pressure and volume tolerated by at least 75% of patients (third quartile) were considered. The third quartile was 20 mmHg during pressure-controlled stepwise distension and 160 ml during volume-controlled ramp distension. The slope of volume-pressure relationship during volume ramp distension in healthy control subjects in our laboratory is 0.06±0.02 ml/mmHg.[13]

The thresholds for sensations were defined, respectively, as the first level of pressure and volume evoking sensation of first distension, desire to defecate, urgency, and discomfort.

Within- and between-group differences in stool frequency, stool form, symptom frequency, SCL-90 scores, rectal distensibility, and thresholds for sensations before and after surgical operation were assessed by using Wilcoxon's and Mann–Whitney *U* tests. Chi-square was applied to comparison of frequency data. $P=0.05$ (two-sided) was considered statistically significant.

With 12 and ten subjects in each group and a power of 0.80, it was possible to assess a difference in the variability of the investigated phenomena by using Wilcoxon's and Mann–Whitney *U* tests for paired and unpaired data with a significance level of 0.05 (two-tailed). Data are reported as mean values ± standard deviations (SD).

Results

Symptoms

During the week preceding the surgical operation, the frequency of bowel movement was 8±4 per week (bm/w) in the SH group and 6±2 bm/w in the MMH, without statistical difference ($P=0.14$). The Bristol index was, respectively, 3.6±1 and 3.8±1 ($P=0.79$). No patients referred abdominal pain, fecal urgency, or incontinence.

After surgical operation, the frequency of bowel movement was 14±10 bm/w in the SH group and 7±4 bm/w in the MMH, without statistical difference ($P=0.12$). In four out of 12 patients (33%) in SH group, the frequency of bowel movements per week increased from 10±7 to 22±8 ($P=0.006$). Four patients (33%) of the SH group showed new onset of fecal urgency on a daily basis. Overall, five out of 12 (41%) patients in the SH group reported urgency or increased bowel movements. Only one patient in each group reported urgency without modification in number of bowel movements and vice versa. The Bristol index did not change significantly in both groups (3±1 in the SH and 4±1 in the MMH group, $P=0.10$). None of the patients reported fecal incontinence.

At postoperative check-up, no late complications were recorded. At 6 months follow-up, staple line was always placed above the dentate line, with height between 1.5 and 2.5 cm. from the dentate line. No correlation between site of anastomosis and symptoms were found. Four patients had staples retained at anastomosis line. However, no correlation was observed between presence of staples and severity of symptoms.

Psychological Symptoms

The SCL-90 total scores did not differ significantly between the two groups before surgery (32±23 vs 42±26, $P=0.45$) and after surgery (24±18 vs 46±36, $P=0.19$) and in each group before and after surgery. Likewise, the SCL-90 total scores did not differ significantly before and after surgery in each group (respectively, $P=0.42$ and $P=0.84$).

Rectal Distensibility

Before surgical operation, the two groups were comparable for rectal distensibility during pressure stepwise distension (10±4 mmHg/ml in SH vs 13±6 mmHg/ml in MMH group, $P=0.30$) and during volume ramp distension (0.06±

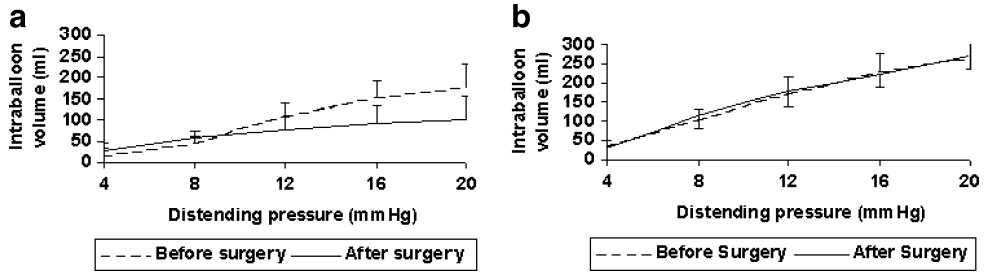


Figure 1 Pressure–volume relationship during pressure-controlled stepwise distension before and after stapled (**a**) and Milligan–Morgan hemorrhoidectomy (**b**).

0.03 ml/mmHg in SH vs 0.05±0.04 ml/mmHg in MMH group, P=0.62).

After surgery, rectal distensibility significantly decreased in all the patients of SH procedure during pressure stepwise distension (3.8±3 mmHg/ml, P=0.001) and during volume ramp distension (0.12±0.05, P=0.009), while it did not change in patients of MMH group (13±3 mmHg/ml during pressure stepwise distension, P=0.90 and 0.04±0.02 ml/mmHg during volume ramp distension, P=0.54, respectively).

After surgical operation, rectal distensibility was significantly different in the stapled group compared to Milligan–Morgan group during pressure stepwise (P=0.0002) and ramp volume distensions (P=0.01). Figures 1 and 2 show pressure–volume and volume–pressure relationships in both groups during each different rectal distension before and after surgical operation.

Before surgery, none of the patients in the two groups had a value of rectal distensibility above the mean±2 SD of the values of rectal distensibility in healthy subjects in our lab (>0.10 ml/mmHg). After surgery, all the patients with symptoms of increased stool frequency and/or urgency to defecate after stapled hemorrhoidopexy had a value of rectal distensibility above that value, whereas none of the patients in the MMH group and of the remaining patients in the SH group had rectal distensibility above that value.

Thresholds for Sensations During Rectal Distensions

Tables 1 and 2 show thresholds for sensations of first perception, desire to defecate, urgency, and discomfort in SH and MMH groups before and after surgery during pressure stepwise distension and during volume ramp distension, respectively. In MMH group, pressure and volume thresholds for sensations did not change significantly after surgical operation. On the contrary, in the SH group, volume thresholds for desire to defecate, urgency, and discomfort were lower after surgery during both distensions, and volume threshold for first perception was also significantly lower after surgery during volume ramp distension. Pressure thresholds for sensations were not significantly different before and after surgery in both groups.

Discussion

The aim of the present restrospective study was to compare functional outcome after stapled hemorrhoidopexy and Milligan–Morgan hemorrhoidectomy in order to clarify the possible pathophysiological mechanisms underlying the occurrence of increased stool frequency and/or fecal urgency after stapled operation. The results demonstrate that stapled operations reduce rectal distensibility and

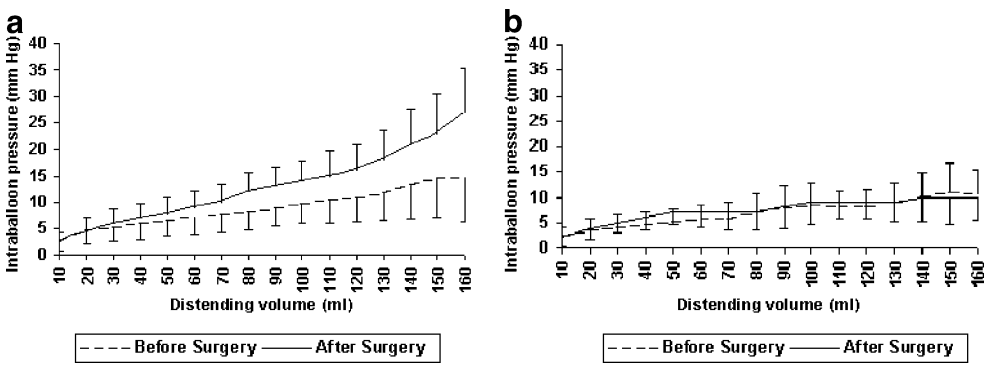


Figure 2 Volume–pressure relationship during volume-controlled ramp distension before and after stapled (**a**) and Milligan–Morgan hemorrhoidectomy (**b**).

Table 1 Pressure and Volume Thresholds for Sensations During Pressure Stepwise Distension Before and After Stapled and Milligan–Morgan Procedure

	Stapled procedure			Milligan–Morgan		
	Before surgery	After surgery	*P*	Before surgery	After surgery	*P*
Pressure thresholds						
FP	6±4	6±4	0.78	9±4	10±7	0.80
DD	12±7	9±3	0.15	16±11	16±16	0.94
UD	18±10	12±5	0.17	20±10	20±11	0.93
D	26±9	16±9	0.05	23±9	24±9	0.90
Volume thresholds						
FP	35±44	30±21	0.77	33±39	50±40	0.46
DD	107±71	47±17	0.009	131±40	137±114	0.66
UD	132±79	85±22	0.03	135±70	179±8	0.50
D	196±68	95±46	0.001	224±119	273±102	0.83

FP first perception, *DD* desire to defecate, *UD* urgency, *D* discomfort

thresholds for rectal sensations, while these are not modified by Milligan–Morgan hemorrhoidectomy. Moreover, the occurrence of urgency and/or increased bowel movements is reported only by the patients with a value of rectal distensibility above the upper limits of the normal values that in the present study is the 41% of the patients subjected to stapled procedure.

Previous studies, conducted by means of anorectal manometry, did not demonstrate alteration of rectal distensibility even if they reported reduced thresholds for sensations during rectal distension.[14] A reduced threshold for sensations, in absence of a concomitant evaluation of rectal motility, does not allow the discrimination between a primary alteration in the sensory afferent pathways or in the rectal motor response to distension. As recently pointed out, electronic barostat is the appropriate method to evaluate rectal sensitivity as it permits also the concomitant evaluation of rectal distensibility.[15] By means of the barostat, we reported in a previous paper a reduced distensibility after stapled hemorrhoidopexy.[7] The present study confirms the results of the previous one also demonstrating that this motor alteration is associated with the presence of symptoms of fecal urgency and/or increased bowel frequency.

Fecal urgency and/or increased stool frequency have been associated with a number of alterations, such as psychological factors influencing selective attention or a perceptual response bias for the sensation,[16] failure of colonic absorption inducing abnormal rectal distension by stool,[17] hypersensitive rectum,[18] and reduced rectal distensibility that limits the reservoir function of the rectum and increases the chance that stool induces the sensation.[19] In the present study, the inclusion of a psychological evaluation in all the patients before and after surgery demonstrated that there were no differences in psychological distress between and in the two groups. The stool consistency did not change after surgery as documented by the Bristol index. On the contrary, rectal distensibility and the thresholds for sensations became significantly reduced after stapled but not after Milligan–Morgan hemorrhoidectomy. Moreover, a value of rectal distensibility above the upper limit of normal values was recorded only in patients with symptoms of increased bowel movements and/or urgency.

Table 2 Volume and Pressure Thresholds for Sensations during Volume Ramp Distension Before and After Stapled and Milligan–Morgan Procedure

	Stapled Procedure			Milligan–Morgan		
	Before Surgery	After Surgery	P	Before Surgery	After Surgery	P
Volume thresholds						
FP	117±91	36±22	0.01	125±63	140±42	0.63
DD	155±87	62±21	0.009	167±60	180±14	0.48
UD	152±75	86±59	0.02	150±99	205±21	0.83
D	207±69	126±73	0.03	230±72	250±45	0.30
Pressure thresholds						
FP	11±7	6±4	0.08	13±6	14±5	0.84
DD	14±7	9±6	0.13	14±7	17±5	0.50
UD	19±13	12±5	0.18	18±6	19±7	0.84
D	25±16	21±10	0.48	20±8	20±6	0.52

FP first perception, *DD* desire to defecate, *UD* urgency, *D* discomfort

Theoretically, stapled hemorrhoidopexy should not alter rectal reservoir function, as it should consist only in excision of a ring of redundant mucosa of the rectum above the dentate line. However, previous papers have shown that some smooth muscle is invariably excised in stapled hemorrhoidopexy.[20–24] One of these papers clearly demonstrated that, in about 80% of the cases, the excised specimens contained not only mucosa and submucosa but more frequently than expected also smooth muscle of the internal anal sphincter (38% of the cases) and of the rectum (42% of the cases).[21] It is possible that the partial resection of muscular layer of rectal wall could alter the activation status of mechanoreceptors demonstrated to be present and to be involved in the motor and sensory response to distension of the rectum.[25]

Several papers investigated the occurrence of symptoms after stapled procedure with a follow-up of at least 6 months;[26–34] however, only few assessed the presence of urgency and of an increased stool frequency. The results of these studies are in line with those of the present study and reported a percentage of patients with urgency between 0% and 45%. Moreover, a recent consensus of expert surgeons on stapled hemorrhoidopexy reported the occurrence of urgency as a possible symptom after the procedure.[35]

The correlation between retained staples and postoperative symptoms is still not clear. In a recent review, Kubchandani et al.[36] published the results of a questionnaire distributed to the members of the American Society of Colon and Rectal Surgeons and reported 23.5% symptomatic and 37.1% asymptomatic unexpelled staples. On the other hand, excision of the staple line with staple removal has been advocated as effective for chronic pain, but no data on urgency and frequency have been reported so far.

Previous studies have suggested that stapled hemorrhoidopexy could induce alteration of anal continence as effect of anal dilatation during stapler introduction in the anus or of the resection of part of the anal sphincter muscle.[37] In the present study, the function of anal sphincter was not systematically studied, but none of the patients developed fecal incontinence after surgical operation. However, considering the demonstrated effect of stapled hemorrhoidopexy on rectal distensibility and the role that this alteration of rectal function could have on the occurrence of fecal incontinence,[15] a careful assessment of patients with factors predisposing to fecal incontinence should be encouraged in preoperative patients' selection

The present study has some weak points as it is retrospective and on a small number of patients. However, even with such a small population, we were able to demonstrate a statistically significant difference between the two groups of patients and, more important, to demonstrate a relationship between symptoms and altered motor and sensory rectal function. Even if these results have to be confirmed in larger and randomized controlled studies, they suggest that a careful selection of the patients should precede the stapled operation in order to avoid major problems for the patients.

References

1. Sutherland LM, Burchard AK, Matsuda K, Sweeney JL, Bokey EL, Childs PA, Roberts AK, Waxman BP, Maddern GJ. A systematic review of stapled hemorrhoidectomy. Arch Surg 2002;137:1395–1406.
2. Cheetam MJ, Mortensen NJM, Nystrom P-O, Kamm M, Phillips RKS. Persistent pain and faecal urgency after stapled hemorrhoidectomy. Lancet 2000;356:730–733.
3. Pescatori M, Gagliardi G. Postoperative complications after procedure for prolapsed hemorrhoids (PPH) and stapled transanal rectal resection (STARR) procedures. Tech Coloproctol 2008;12:7–19.
4. Longo A. Pain after stapled haemorrhoidectomy. Lancet 2000;356:2189.
5. Pescatori Mario. Pain after stapled haemorrhoidectomy. Lancet 2000;356:2188.
6. Correa-Rovelo JM, Tellez O, Obregon L, Duque-Lopez X, Miranda-Gomez A, Pichardo-Bahena R, Mendez M, Moran S. Prospective study of factors affecting postoperative pain and symptom persistence after stapled rectal mucosectomy for hemorroids: a need for preservation of squamous epithelium. Dis Colon Rectum 2003;46:955–962.
7. De Nardi P, Corsetti M, Passaretti S, Squillante S, Castellaneta AG, Staudacher C, Testoni PA. Evaluation of rectal sensory and motor function by means of the electronic barostat after stapled hemorrhoidopexy. Dis Colon Rectum 2008;51:1255–1260.
8. O'Donnell LJD, Virjee J, Heaton KW. Detection of pseudodiarrhoea by simple clinical assessment of intestinal transit rate. Br Med J 1990;300:439–440.
9. Derogatis LR, Melisaratos N. The brief symptom inventory: an introductory report. Physiol Med 1983;13:595–605.
10. Mularczyk A, Contessini-Avesani E, Cesana B, Bianchi PA, Basilisco G. Local regulation of postprandial motor responses in ileal pouches. Gut 1999;45:575–580.
11. Longo A. Treatment of hemorrhoidal disease by reduction of mucosa and hemorrhoidal prolapse with a circular stapling device: a new procedure. Proceedings of the 6th World Congress of Endoscopic Surgery, June 3, 1998. Monduzzi Editore, 1998.
12. Milligan ET, Morgan CN, Jones LE. Surgical anatomy of the anal canal and the operative treatment of haemorrhoids. Lancet 1937;2:1119–1124.
13. Corsetti M, Cesana B, Bhoori S, Basilisco G. Rectal hyperreactivity to distension in patients with irritable bowel syndrome: role of distension rate. Clin Gastroenterol Hepatol 2004;2:49–56.
14. Fantin AC, Hetzer FH, Christ AD, Fried M, Schwizer W. Influence of stapler hemorrhoidectomy on anorectal function and on patients' acceptance. Swiss Med Wkly 2002;132:38–42.
15. Bharucha AE. Outcome measures for fecal incontinence: anorectal structure and function. Gastroenterology 2004;126:S90–S98.
16. Whitehead WE, Palsson OS. Is rectal pain sensitivity a biological marker for irritable bowel syndrome: psychological influences on pain perception. Gastroenterology 1998;115:1263–1271.
17. Vassallo M, Camilleri M, Phillips SF, Brown ML, Chapman NJ, Thomforde GM. Transit through the proximal colon influences stool weight in the irritable bowel syndrome. Gastroenterology 1992;102:102–108.

18. Prior A, Maxton DG, Whorwell PJ. Anorectal manometry in irritable bowel syndrome: differences between diarrhoea and constipation predominant subjects. Gut 1990;31:458–462.
19. Distrutti E, Salvioli B, Azpiroz F, Malagelada JR. Rectal function and bowel habit in irritable bowel syndrome. Am J Gastroenterol 2004;99:131–137.
20. Kam MH, Mathur P, Peng XH, Seow-Choen F, Chew IWC, Kumarasinghe MP. Correlation of histology with anorectal function following stapled hemorrhoidectomy. Dis Colon Rectum 2005;48:1437–1441.
21. George BD, Shetty D, Lindsey I, Mortesen NJ Mc C, Warren BF. Histopathology of stapled hemorrhoidectomy specimens: a cautionary note. Colorectal Disease 2002;4:473–476.
22. Kairaluoma M, Nuorva K, Kellokumpu I. Day-case Stapled (circular) vs diathermy hemorrhoidectomy. A randomised, controlled trial evaluating surgical and functional outcome. Dis Colon Rectum 2003;46:93–99.
23. Ortiz H, Marzo J, Armendariz P, De Miguel M. Stapled hemorrhoidopexy vs diathermy excision for fourth-degree hemorrhoids: a randomized, clinical trial and review of the literature. Dis Colon Rectum 2005;48:809–815.
24. Ganio E, Altomare DF, Milito G, Gabrielli F, Canuti S. Long-term outcome of a multicentre randomized clinical trial of stapled hemorrhoidopexy versus Milligan–Morgan hemorrhoidectomy. Br Journal of Surg 2007;94:1033–1037.
25. Lynn PA, Olsson C, Zagorodnyuk V, Costa M, Brookes SJ. Rectal intraganglionic laminar endings are transduction sites of extrinsic mechanoreceptors in the guinea pig rectum. Gastroenterology 2003;125:786–794.
26. Au-Yong I, Rowsell M, Hemingway DM. Randomised controlled clinical trial of stapled haemorrhoidectomy vs conventional haemorrhoidectomy; a three and a half year follow-up. Colorectal Disease 2004;6:37–38.
27. Picchio M, Palimento D, Attanasio U, Renda A. Stapled vs open hemorrhoidectomy: long-term outcome of a randomised controlled trial. Int J Colorectal Dis 2006;21:668–669.
28. Boccasanta P, Venturi M, Stuto A, Bottini C, Caviglia A, Carriero A, Mascagni D, Mauri R, Sofo L, Landolfi V. Stapled transanal rectal resection for outlet obstruction: a prospective, multicenter trial. Dis Colon Rectum 2004;47:1285–1297.
29. Hetzer FH, Demartines N, Handschin A, Clavien P-A. Stapled vs excision hemorrhoidectomy. Arch Surg 2002;137:337–340.
30. Zacharakis E, Kanellos D, Pramateftakis MG, Kanellos I, Angelopoulos S, Mantzoros I, Betsis D. Long-term results after stapled haemorrhoidopexy for fourth-degree haemorrhoids : a prospective study with median follow-up of 6 years. Tech Coloproctol 2007;11:144–148.
32. Pessaux P, Tuech JJ, Laurent B, Regenet N, Lermite E, Simone M, Huten N, De Manzini N, Arnaud JP. Morbidity after stapled haemorrhoidectomy: long-term results about 140 patients and review of the literature. Ann Chir 2004;129:571–577.
32. Slawik S, Kenefick N, Greenslade GL, Dixon AR. A prospective evaluation of stapled haemorrhoidopexy/rectal mucosectomy in the management of 3rd and 4rth degree haemorrhoids. Colorectal Disease 2007;9:352–356.
33. Van de Stadt J, D'Hoore A, Duinslaeger M, Chasse E, Penninckx F. Long term results after excision haemorrhoidectomy versus stapled haemorrhoidopexy for prolapsing haemorrhoids; a Belgian prospective randomised trial. Acta Chir Belg 2005;105:44–52.
34. Lomanto D, Katara AN. Stapled haemorrhoidopexy for prolapsed haemorrhoids: short and long-term experience. Asian J Surg 2007;30:29–33.
35. Corman ML, Gravie JF, Hager T, Loudon MA, Mascagni D, Nystrom P-O, Seow-Choen F, Abcarian H, Marcello P, Weiss E, Longo A. Stapled haemorrhoidopexy: a consensus position paper by an international working party—indications, contra-indications and technique. Colorectal Disease 2003;5:30410.
36. Khubchandani I, Fealk MH, Reed JF. Is there a post-PPH syndrome? Tech Coloproctol 2009;13:141–144.
37. Ho YH, Seow-Choen F, Tsang C, Eu KW. Randomised trial assessing anal sphincter injuries after stapled hemorrhoidectomy. Br J Surg 2001;88:1449–55.

J Gastrointest Surg (2009) 13:2252–2259
DOI 10.1007/s11605-009-0986-4

ORIGINAL ARTICLE

Right Colonic Perforation in an Asian Population: Predictors of Morbidity and Mortality

Ker-Kan Tan · Junren Zhang · Jody Zhiyang Liu · Sharon Fengli Shen · Arul Earnest · Richard Sim

Received: 1 June 2009 / Accepted: 4 August 2009 / Published online: 26 August 2009

Abstract
Introduction Perforation of the colon is associated with significant morbidity and mortality. Pathologies arising from the right colon differ greatly between Asians and the Western population. The aims of our study were to evaluate the implications of perforated right colon in an Asian population and to identify factors that could predict the perioperative outcome.
Methods A retrospective review of all patients who underwent operative intervention for peritonitis from right colonic perforation from July 2003 to April 2008 was performed. Patients were identified from the hospital's diagnostic index and operating records. The severity of abdominal sepsis for all patients was graded using the Mannheim peritonitis index (MPI). All the complications were graded according to the classification proposed by Clavian and colleagues.
Results Fifty-one patients with a median age of 60 years (range, 22–93 years) formed the study group. Diverticulitis (47.1%) and malignancy (37.3%) accounted for the majority of the pathologies. Right hemicolectomy without diverting stoma (n=34, 66.7%) was performed most commonly. Of our patients, 74.5% had perioperative morbidity with 19 (37.3%) patients having grade III or worse complications. In our series, five (9.8%) patients died. On univariate analysis, American Society of Anesthesiologists (ASA) score ≥3, ≥2 premorbid conditions, raised MPI, raised creatinine, and stoma creation were related to more severe complications (grade III/IV). The following variables were correlated with in-hospital mortality: ASA score ≥3, raised MPI, hematocrit <33%, raised creatinine, malignant perforation, and stoma creation. On multivariate analysis, a higher ASA score ≥3 was predictive of significant morbidity, while both malignant perforation and stoma creation were associated with mortality.
Conclusion Diverticulitis is the commonest cause of right colonic perforation in Asians. Patients with higher ASA score and malignant perforation are at risk of higher morbidity and mortality. Resection with primary anastomosis is safe and patients who require stomas are more likely to do worse.

Keywords Perforation · Right colon · Outcome · Surgery

K.-K. Tan (✉) · J. Zhang · J. Z. Liu · S. F. Shen · R. Sim
Department of General Surgery, Tan Tock Seng Hospital,
11 Jalan Tan Tock Seng,
Singapore 308433, Singapore
e-mail: kerkan@gmail.com

A. Earnest
Clinical Research Unit, Tan Tock Seng Hospital,
Singapore, Singapore

Introduction

Perforation of the colon is a serious abdominal emergency. The commonest causes include malignancy and diverticulitis.[1,2] The operative mortality and morbidity in these patients remain significant despite advances in surgical techniques and perioperative care.[1,2]

Most of the published literature on the consequences of perforation of the colon has focused on the left colon due to the high incidence of diverticulitis and malignancy in the descending and sigmoid colon in the Western population.[3] However, numerous studies have shown that pathologies in

Table 1 The MPI

Risk factor score	Score
Age >50 years old	5
Female sex	5
Organ failure	7
Malignancy	4
Preoperative duration of peritonitis	4
Origin of sepsis not colonic	4
Diffuse generalized peritonitis	6
Exudate	
Clear	0
Cloudy, purulent	6
Fecal	12

Kidney failure=creatinine level>177 μmol/L or urea level> 167 mmol/L or oliguria<20 ml/h; pulmonary insufficiency=PO_2< 50 mmHg or PCO_2>50 mmHg; intestinal obstruction/paralysis>24 h or complete mechanical ileus, hypodynamic or hyperdynamic shock

the right colon differ significantly between Asians and the Western population.[4,5]

Colonic diverticulosis in Asians is more commonly confined in the right and in young adults.[5] This preponderance has been postulated to be genetically linked. This is in stark contrast to the Western population where diverticular disease is deemed an acquired disease affecting mostly the sigmoid and descending colon, with less common involvement of the cecum and ascending colon.[6]

Furthermore, the incidence of right-sided colon cancer was shown to be markedly lower in Asians compared to Whites and African Americans.[7] This phenomenon has also been attributed to genetic risk factors or other uncharacterized carcinogens.

In addition, while the appropriate surgical technique (Hartmann's procedure versus primary resection with/without diverting stoma) in handling left-sided colonic perforation is not firmly established despite extensive discussion,[3] the literature reviewing the need for a stoma in right-sided colonic perforation is lacking.

Thus, in view of the numerous unresolved issues surrounding perforation of the right colon, the primary aim of this study was to review the treatment and early outcome of patients who underwent emergency surgery for right colonic perforation. In addition, factors that might predict morbidity and mortality were also evaluated.

Methods

Study Population

Tan Tock Seng Hospital is a 1,300-bed hospital, the second largest in Singapore, and provides secondary and tertiary medical care for about 1.5 million people. A retrospective review of all patients who underwent operative intervention for peritonitis from right colonic perforation from July 2003 to April 2008 was performed. Patients were identified from the hospital's diagnostic index and operating records. Right-sided pathologies were regarded if it was located from the cecum till the transverse colon. Patients who suffered perforated colonic injuries from abdominal trauma were excluded.

The data collected included age, gender, American Society of Anesthesiologists (ASA) score, comorbid conditions, presenting signs and symptoms, and clinical parameters. Laboratory values, including full blood count and renal panel, were also recorded. In addition, duration from symptoms to surgery, duration from admission to surgery, operative findings and interventions, length of surgery, perioperative complications, mortality, and length of hospital stay were also documented.

The severity of abdominal sepsis for all patients was graded using the Mannheim peritonitis index (MPI; Table 1) with a score of >26 being defined as severe.[8] Classification of diverticulitis was assessed using Hinchey's classification,[9] and all colorectal cancers were staged according to the guidelines of the American Joint Committee of Cancer.[10] The grades of complications (GOC) were in concordance with the classification proposed by Clavian and colleagues (Table 2).[11–13]

Statistical analysis was performed using both univariate and multivariate analyses. The variables were analyzed to the various outcomes using Fisher's exact test, and their odds ratio and 95% confidence interval were also reported. For the multivariate analysis, the logistic regression model was applied. All analyses were performed using the SPSS 13.0 statistical package (Chicago, IL, USA) and all p values

Table 2 Classification of surgical complications

Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic, or radiological intervention
Grade IV	Life-threatening complication(s) requiring intensive care unit management (including organ dysfunction)
Grade V	Death of a patient

reported are two-sided, and p values of <0.05 were considered statistically significant.

Results

During the study period, 51 patients underwent surgery for perforation of the right colon. The median age of the study group was 60 years (range, 22–93 years). There were more females (n=28, 54.9%) in the study group and the majority of patients had an ASA score of 2 or 3 (n=39, 76.5%). Hypertension (n=22, 43.1%) was the commonest comorbid condition, with 23.5% having at least two comorbid conditions. There were four (7.8%) patients who were immunosuppressed from either chronic corticosteroid consumption (n=3) or human immunodeficiency virus (HIV) infection.

A total of 30 (58.8%) patients underwent preoperative computed tomographic (CT) scans before surgery, while the remaining 21 (41.2%) were operated after clinical assessment and may be assisted by the associated chest and/or abdominal X-rays. Table 3 illustrates the various characteristics of this study group.

Table 3 Characteristics of the 51 patients who underwent surgery for right colonic perforation

	n (%)
Median age, range (years)	60 (22–93)
≤60	26 (51.0)
>60	25 (49.0)
Gender	
Male	23 (45.1)
Female	28 (54.9)
ASA status	
1	8 (15.7)
2	18 (35.3)
3	21 (41.2)
4	4 (7.8)
Premorbid condition	
Hypertension	22 (43.1)
Diabetes mellitus	6 (11.8)
Hyperlipidemia	8 (15.7)
Ischemic heart disease	4 (7.8)
History of cerebrovascular accident	5 (9.8)
Number of premorbid condition	
0–1	39 (76.5)
2–5	12 (23.5)
Immunosuppression	
No	47 (92.2)
Yes	4 (7.8)
One patient who is HIV positive	
One patient with systemic lupus erythematosus and two patients with rheumatoid arthritis on corticosteroids	
Preoperative CT scan	
Performed	30 (58.8)
Not performed	21 (41.2)

Operative Findings

As shown in Table 4, diverticulitis accounted for majority of the perforations in 24 (47.1%) patients, with malignancy in another 19 (37.3%). Ten of these patients had perforation at the tumor site, while the other nine had perforation of the right colon due to a distal obstructing tumor. Some of the other causes included ischemic colitis (n=3, 5.9%), severe appendicitis causing cecal perforation (n=4, 7.8%) and tuberculosis (n=1, 2.0%).

The commonest site of perforation was at the cecum (n=30, 58.8%), followed by the ascending colon (11, 21.6%; Table 4). The median MPI score was 15 (0–37), with 10 (19.6%) patients having a score of >26. There were a total of 36 (70.6%) colonic anastomoses for which 32 (88.9%) were stapled, with the remaining four (11.1%) handsewn. Right hemicolectomy without diverting stoma (n=34, 66.7%) was performed most commonly while ileocolic resection with stoma was created in 14 (27.5%) patients. Of these 14 patients, only one had perforated diverticulitis, while the rest had either malignant perforation (n=8) or ischemic colitis (n=3). The time from symptoms or admission to surgery and the median duration of surgery were also described in Table 4.

Outcome

Significant proportion (74.5%) of our patients had associated perioperative morbidity, with 19 (37.3%) of them having GOC III or worse complications (Table 4). The majority of these arose from respiratory and wound complications. Five (9.8%) patients died in our series. There was no patient with postoperative anastomotic leak, but there was one patient with ischemic stoma that necessitated revision. The median length of stay was 8 days (range, 3–141 days).

Analysis—Complications

Worse complications (GOC III or IV) occurred more commonly in patients who had a higher ASA score (3–4), ≥2 premorbid conditions, MPI >26, raised preoperative creatinine levels, and in patients who had stoma created. Factors such as age, gender, site, and pathology of perforation were not shown to be significant. Duration from symptoms or admission to surgery and the median

Table 4 Surgical observations and procedures of the study group

	n (%)
Site of perforation	
Cecum	30 (58.8)
Ascending colon	11 (21.6)
Hepatic flexure and transverse colon	10 (19.6)
Cause of perforation	
Diverticulitis	24 (47.1)
Hinchey II	15
Hinchey III	8
Hinchey IV	1
Malignancy	19 (37.3)
Perforation at tumor	10
Perforation proximal to tumor	9
Stage II	5
Stage III	6
Stage IV	8
Severe appendicitis causing cecal perforation	4 (7.8)
Ischemic colitis	3 (5.9)
Tuberculosis	1 (2.0)
Median MPI	15 (0–37)
≤26	41 (80.4)
>26	10 (19.6)
Nature of anastomosis	
Handsewn	4 (7.8)
Stapled	32 (62.7)
No anastomosis (no stoma)	1 (2.0)
No anastomosis (stoma created)	14 (27.5)
Surgery performed	
Right hemicolectomy without stoma	34 (66.7)
Right hemicolectomy with stoma	10 (19.6)
Total colectomy with end ileostomy	4 (7.8)
Total colectomy with ileorectal anastomosis	2 (3.9)
Appendectomy and primary closure of perforation	1 (2.0)
Time from symptoms to surgery	
Within 48 h	28 (54.9)
After 48 h	23 (45.1)
Time from admission to surgery (h)	
<24	33 (64.7)
≥24	18 (35.3)
Median duration of surgery (min)	125 (60–315)
≤120	24 (47.1)
>120	27 (52.9)
GOC	
No complications	13 (25.5)
Grade I	7 (13.7)
Grade II	12 (23.5)
Grade III	6 (11.8)
Grade IV	8 (15.7)
Death or grade V	5 (9.8)
Median length of stay (days)	8 (3–141)

duration of surgery were also not related. ASA score was the only independent variable related to significant morbidity (GOC III or IV) after multivariate analysis (Table 5).

Analysis—Mortality

Mortality from perforated right colon was more likely in patients who had a higher ASA score (3–4), higher MPI, lower hematocrit (<33.0%), and raised preoperative urea and creatinine levels. Malignant perforation and creation of stoma were the only independent variables associated with higher mortality after multivariate analysis (Table 6).

Comparison—Malignancy Versus Diverticulitis

Patients with malignant perforation were older and had a higher ASA score compared to those with perforated diverticulitis. Lower white blood cell and hematocrit were also associated with malignant perforation. Factors such as MPI, site of perforation, and the grading of complications were not associated. Lower hematocrit was the only independent variable predictive for malignancy after multivariate analysis. However, patients with malignant perforation were more likely to have stoma created and perish from their conditions (Table 7).

Comparison—Stoma Versus No Stoma

Creation of stoma was more likely in patients with higher ASA scores and raised creatinine level. Both higher MPI and low hematocrit were the only independent variables associated with stoma creation. Patients with stoma also fared worse than those without (Table 8).

Discussion

Even though our series showed that diverticulitis and malignancy are responsible for majority of right colonic perforation, the distribution is vastly different compared to the West. Malignant perforation accounted for the majority of right colonic perforation in the West, while diverticulitis is the main pathology in our series.[2,14] This has been attributed to the genetic differences between Asians and the Western population.[5–7]

In the acute setting, differentiation between malignant and diverticular-related perforation is difficult and may only be evident after resection. Some of the differences between the two groups included advanced age and higher ASA score in malignant perforation. This is not surprising as cancer patients are typically older and associated with more premorbid conditions, while right-sided diverticular disease are more common in younger Asians. Another important

Table 5 Analysis of patients who developed serious versus minor or no complication

Characteristics	GOC 0–II (n=32), n (%)	GOC III–IV (n=14), n (%)	OR (95%CI)	p value
>60 years old	14 (43.8)	8 (57.1)	1.71 (0.48–6.09)	>0.05
ASA score 3–4	8 (25.0)	12 (85.7)	18.00 (3.30–98.27)[a]	<0.001[a]
≥2 premorbid conditions	4 (12.5)	7 (50.0)	7.00 (1.59–30.80)	0.010
MPI >26	1 (3.13)	6 (42.9)	23.25 (2.44–221.73)	0.002
WBC >10.0×10^9/L	24 (75.0)	10 (71.4)	0.83 (0.20–3.41)	>0.05
Hematocrit <33.0%	7 (21.9)	6 (42.9)	2.68 (0.69–10.31)	>0.05
Serum creatinine >110 μmol/L	1 (3.1)	4 (28.6)	12.4 (1.24–124.22)	0.025
Perforated diverticulitis	18 (56.3)	6 (42.9)	0.58 (0.16–2.07)	>0.05
Malignant perforation	9 (28.1)	5 (35.7)	1.42 (0.37–5.41)	>0.05
Creation of stoma	3 (9.4)	6 (42.9)	7.25 (1.47–35.71)	0.015

[a] Statistically significant on multivariate analysis

clue that our series highlighted was that lower hematocrit of <33.0% was more suggestive of malignant perforation.

Hinchey classification has often been used to predict operative intervention and the associated morbidity and mortality.[9,15] In our series, patients with Hinchey III and IV (four out of nine patients) had more severe complications than patients with Hinchey II (two out of 15 patients). While the ideal surgical procedure for perforated left colonic diverticulitis remains controversial, our series showed that right hemicolectomy with primary anastomosis (23 out of 24 patients, 95.8%) for perforated right colonic diverticulitis was associated with good outcome and minimal complications.[16,17]

Perforation in colorectal cancers occurs due to either direct perforation from tumor necrosis or proximally to an obstructing tumor from a resultant closed-loop syndrome. Recent data has suggested that factors such as perforation proximal to the cancer and number of metastatic lymph nodes were associated with higher perioperative morbidity and mortality.[18–20] In our series, though there were no differences seen in the perioperative outcome between patients who had proximal or tumor site perforation, this could be because of our small numbers.

Mortality rate from perforated colorectal cancers has been reported to be over 40%.[20,21] In our series, the mortality rate was 26.3%. Similar to other studies, the majority of our malignant perforations were either stage 3 or stage 4. Furthermore, malignant perforation has been shown to be associated with an increased risk of local recurrence and carcinomatosis peritonei.[22,23] In these patients, apart from managing the peritoneal contamination and the resultant septicemia, complete oncologic surgery should be attempted to offer the best long-term outcome, but only if the patient's condition allows.

ASA score has been used for decades and is highly predictive of morbidity and mortality in surgical patients.[24–26] In our series, a higher ASA score was the only independent variable predicting severe complications. However, ASA score has been criticized for its failure to include the impact of numerous comorbidities and age. Though our patients with two or more comorbid conditions were associated with worse complications, an increased age

Table 6 Comparison of patients who died and the rest

Characteristics	Alive (n=46), n (%)	Death (n=5), n (%)	OR (95%CI)	p value
>60 years old	22 (47.8)	3 (60.0)	1.64 (0.25–10.73)	>0.05
ASA score 3–4	20 (43.4)	5 (100.0)	NA	0.023
≥2 premorbid conditions	11 (23.9)	1 (20.0)	0.80 (0.08–7.88)	>0.05
MPI >26	7 (15.2)	3 (60.0)	8.36 (1.18–59.43)	0.046
WBC >10.0×10^9/L	34 (73.9)	1 (20.0)	0.09 (0.01–0.87)	0.029
Hematocrit <33.0%	13 (28.3)	4 (80.0)	10.20 (1.04–100.00)	0.037
Serum creatinine >110 μmol/L	5 (10.9)	3 (60.0)	12.30 (1.64–92.33)	0.023
Malignant perforation	14 (30.4)	5 (100.0)	NA	0.005[a]
Creation of stoma	9 (19.6)	5 (100.0)	NA	0.001[a]

[a] Statistically significant on multivariate analysis

Table 7 Comparison of patients with diverticulitis against malignancy

Characteristics	Diverticulitis (n=24), n (%)	Malignancy (n=19), n (%)	OR (95%CI)	p value
>60 years old	8 (33.3)	14 (73.7)	5.6 (1.48–21.13)	0.014
ASA score 3–4	6 (25.0)	15 (78.9)	11.25 (2.67–47.43)	0.001
≥2 premorbid condition	5 (20.8)	6 (31.6)	1.75 (0.44–6.98)	>0.05
MPI >26	3 (12.5)	5 (26.3)	2.50 (0.51–12.18)	>0.05
WBC >10.0×10^9/L	20 (83.3)	9 (47.4)	0.18 (0.04–0.73)	0.021
Hematocrit <33.0%	1 (4.2)	10 (52.6)	25.64 (2.84–250.00)	<0.001[a]
Serum creatinine >110 μmol/L	2 (8.3)	5 (26.3)	3.93 (0.67–23.10)	>0.05
Creation of stoma	1 (4.2)	8 (42.1)	16.67 (1.86–142.86)	0.006
Death	0 (0.0)	5 (26.3)	NA	0.012

[a] Statistically significant on multivariate analysis

did not have a similar relationship. It has been shown in many studies that chronological age is not an independent predictor, but it is logical to deduce that patients who are older are more likely to have more comorbid conditions and a higher ASA score.[27,28]

The severity of peritonitis, and not the surgical procedure or the underlying diagnoses, has also been shown to be directly accountable for the surgical outcome;[2,29–30] however, these data were predominantly based on left colonic pathologies in the Western population.[29] In our series, MPI was used as it is easy to apply, can be used for all diagnoses, and is able to prognosticate the patients according to the severity of the peritonitis.[2,8,29,30] To our knowledge, MPI has never been used for right-sided colonic perforation in an Asian population. Our series concurred with the others that a higher MPI is associated with stoma creation, severe complications, and death.[2,8,29,30] Some of its criticisms included the difficulty in determining the exact timing from perforation to operation and the neglect of patients' hemodynamic and physiological derangement.[31] Nonetheless, even though our series supported the usage of MPI in patients with colonic perforation, a prospective study would be required to further validate its usefulness in Asians.

Though emergency resection for right-sided colonic pathologies has been shown to be technically easier, it still carries an overall morbidity of up to 44%.[32,33] The method of anastomosis, be it handsewn or stapled, has not been shown to be significantly related to the development of an anastomotic leak or other complications in emergency right hemicolectomy.[33–35] This is supported in our series as there was no patient with primary anastomosis from either method that had any anastomotic complications. In addition, right colectomy is associated with a lower rate of anastomotic leakage compared to colocolic or colorectal anastomosis, especially in the presence of an unprepared colon.[36–38]

In our series, stoma was created more often in patients with more severe peritoneal contamination. Patients who required stoma also had worse perioperative outcome. This is not surprising, as diverting stoma has always been advocated in patients who are hemodynamically unstable or in those who are suspected to fare worse.[3,16] However, as

Table 8 Comparison of patients who had stoma created against those who did not

Characteristics	No stoma (n=37), n (%)	Stoma created (n=14), n (%)	OR (95%CI)	p value
>60 years old	18 (48.6)	7 (50.0)	1.06 (0.31–3.61)	>0.05
ASA score 3–4	12 (32.4)	13 (92.9)	27.08 (3.16–231.87)	<0.001
≥2 premorbid conditions	8 (21.6)	4 (28.6)	1.45 (0.36–5.87)	>0.05
MPI >26	2 (5.4)	8 (57.1)	23.33 (3.95–137.68)	<0.001[a]
WBC >10.0×10^9/L	28 (75.6)	7 (50.0)	0.32 (0.09–1.17)	>0.05
Hematocrit <33.0%	7 (18.9)	10 (71.4)	10.75 (2.58–43.48)	0.001[a]
Serum creatinine >110 μmol/L	3 (8.1)	5 (35.7)	6.30 (1.26–31.47)	0.028
Noncecal perforation	14 (37.8)	7 (50.0)	1.64 (0.48–5.68)	>0.05
Malignant perforation	11 (29.7)	8 (57.1)	3.15 (0.88–11.24)	>0.05
GOC 3–4	8 (21.6)	6 out of 9 (66.7)	7.25 (1.48–35.61)	0.015
Mortality	0 (0.0)	5 (35.7)	NA	0.001

[a] Statistically significant on multivariate analysis

the morbidity rate from the complications of a diverting stoma is not negligible,[32,39,40] the authors opined that the optimal choice of surgical intervention should remain at the discretion of the primary surgeon with paramount considerations given to the general condition of the patient and degree of contamination.

As with most studies, there were several limitations in the present study. This series of patients was enrolled from a single institution and any retrospective study has inherent flaws. Even though our study is the largest series in the literature analyzing the consequences of right colonic perforation in an Asian population, the sample size is still very small with only 51 patients. This may mask several other important factors that could be accountable for the outcomes measured. More importantly, there were no standard guidelines or protocol in our institution governing the indications of surgery and the ideal operative techniques to adopt in right colonic perforation with special considerations given to the degree of peritoneal contamination and the patient's general condition. In addition, patients that were managed conservatively for right colonic perforations were not included in our series as our focus was to uncover factors that could predict perioperative outcome.

Although these limitations are significant, this study remains important in highlighting the various issues pertinent in right colonic perforation that are considerably different and rarely seen in the Western population. Our study also identified various factors that could be predictive of a worse perioperative outcome after surgical resection for right colonic perforation.

Conclusions

Diverticulitis is the commonest cause of right colonic perforation in Asians. Anemia is predictive of a malignant perforation in these patients. Patients with higher ASA score and malignant perforation are at risk of higher morbidity and mortality. Resection with primary anastomosis is safe in the majority, and patients who require stomas are more likely to do worse.

References

1. Nespoli A, Ravizzini C, Trivella M, Segala M. The choice of surgical procedure for peritonitis due to colonic perforation. Arch Surg 1993;128(7):814–818.
2. Bielecki K, Kamiński P, Klukowski M. Large bowel perforation: morbidity and mortality. Tech Coloproctol 2002;6(3):177–182.
3. Breitenstein S, Kraus A, Hahnloser D, Decurtins M, Clavien PA, Demartines N. Emergency left colon resection for acute perforation: primary anastomosis or Hartmann's procedure? A case-matched control study. World J Surg. 2007;31(11):2117–2124.
4. Lee YS. Diverticular disease of the large bowel in Singapore: an autopsy survey. Dis Colon Rectum. 1986;29(5):330–335.
5. Sugihara K, Muto T, Morioka Y, Asano A, Yamamoto T. Diverticular disease of the colon in Japan. A review of 615 cases. Dis Colon Rectum. 1984;27(8):531–537.
6. Schoetz DJ Jr. Diverticular disease of the colon: a century-old problem. Dis Colon Rectum. 1999;42:703–709.
7. Wu X, Chen VW, Martin J, Roffers S, Groves FD, Correa CN, Hamilton-Byrd E, Jemal A. Subsite-specific colorectal cancer incidence rates and stage distributions among Asians and Pacific Islanders in the United States, 1995 to 1999. Cancer Epidemiol Biomarkers Prev. 2004;13(7):1215–1222.
8. Billing A, Fröhlich D, Schildberg FW. Prediction of outcome using the Mannheim peritonitis index in 2003 patients. Peritonitis Study Group. Br J Surg. 1994;81(2):209–213.
9. Hinchey EJ, Schaal PGH, Richards GK. Treatment of perforated diverticular disease of the colon. Adv Surg. 1978;12:85–109.
10. American Joint Committee on Cancer. AJCC Cancer Staging Manual. 6th ed. Berlin: Springer, 2002.
11. Clavien PA, Sanabria JR, Mentha G, Borst F, Buhler L, Roche B, Cywes R, Tibshirani R, Rohner A, Strasberg SM. Recent results of elective open cholecystectomy in a North American and a European center. Comparison of complications and risk factors. Ann Surg. 1992;216(6):618–626.
12. Clavien PA, Camargo CA Jr, Croxford R, Langer B, Levy GA, Greig PD. Definition and classification of negative outcomes in solid organ transplantation. Application in liver transplantation. Ann Surg. 1994;220(2):109–120.
13. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205–213.
14. Kriwanek S, Armbruster C, Beckerhinn P, Dittrich K. Prognostic factors for survival in colonic perforation. Int J Colorectal Dis. 1994;9(3):158–162.
15. Antolovic D, Reissfelder C, Koch M, Mertens B, Schmidt J, Büchler MW, Weitz J. Surgical treatment of sigmoid diverticulitis—analysis of predictive risk factors for postoperative infections, surgical complications, and mortality. Int J Colorectal Dis. 2009;24(5):577–584.
16. Constantinides VA, Heriot A, Remzi F, Darzi A, Senapati A, Fazio VW, Tekkis PP. Operative strategies for diverticular peritonitis: a decision analysis between primary resection and anastomosis versus Hartmann's procedures. Ann Surg. 2007;245(1):94–103.
17. Salem L, Flum DR. Primary anastomosis or Hartmann's procedure for patients with diverticular peritonitis? A systematic review. Dis Colon Rectum. 2004;47(11):1953–1964.
18. Carraro PG, Segala M, Orlotti C, Tiberio G. Outcome of large-bowel perforation in patients with colorectal cancer. Dis Colon Rectum. 1998;41(11):1421–1426.
19. Khan S, Pawlak SE, Eggenberger JC, Lee CS, Szilagy EJ, Margolin DA. Acute colonic perforation associated with colorectal cancer. Am Surg. 2001;67(3):261–264.
20. Runkel NS, Schlag P, Schwarz V, Herfarth C. Outcome after emergency surgery for cancer of the large intestine. Br J Surg. 1991;78(2):183–188.
21. Kriwanek S, Armbruster C, Dittrich K, Beckerhinn P. Perforated colorectal cancer. Dis Colon Rectum. 1996;39(12):1409–1414.
22. Willett C, Tepper JE, Cohen A, Orlow E, Welch C. Obstructive and perforative colonic carcinoma: patterns of failure. J Clin Oncol. 1985;3(3):379–384.
23. Obrand DI, Gordon PH. Incidence and patterns of recurrence following curative resection for colorectal carcinoma. Dis Colon Rectum. 1997;40(1):15–24.
24. Biondo S, Ramos E, Deiros M, Ragué JM, De Oca J, Moreno P, Farran L, Jaurrieta E. Prognostic factors for mortality in left

colonic peritonitis: a new scoring system. J Am Coll Surg. 2000;191(6):635–642.
25. Anwar MA, D'Souza F, Coulter R, Memon B, Khan IM, Memon MA. Outcome of acutely perforated colorectal cancers: experience of a single district general hospital. Surg Oncol. 2006;15(2):91–96.
26. Longo WE, Virgo KS, Johnson FE, Oprian CA, Vernava AM, Wade TP, Phelan MA, Henderson WG, Daley J, Khuri SF. Risk factors for morbidity and mortality after colectomy for colon cancer. Dis Colon Rectum. 2000;43(1):83–91.
27. Gurevitch AJ, Davidovitch B, Kashtan H. Outcome of right colectomy for cancer in octogenarians. J Gastrointest Surg. 2009;13(1):100–104.
28. Basili G, Lorenzetti L, Biondi G, Preziuso E, Angrisano C, Carnesecchi P, Roberto E, Goletti O. Colorectal cancer in the elderly. Is there a role for safe and curative surgery? ANZ J Surg. 2008;78(6):466–470.
29. Biondo S, Ramos E, Fraccalvieri D, Kreisler E, Ragué JM, Jaurrieta E. Comparative study of left colonic Peritonitis Severity Score and Mannheim Peritonitis Index. Br J Surg. 2006;93 (5):616–622.
30. Kologlu M, Elker D, Altun H, Sayek I. Validation of MPI and PIA II in two different groups of patients with secondary peritonitis. Hepatogastroenterology 2001;48(37):147–151.
31. Shinkawa H, Yasuhara H, Naka S, Yanagie H, Nojiri T, Furuya Y, Ariki K, Niwa H. Factors affecting the early mortality of patients with nontraumatic colorectal perforation. Surg Today. 2003;33 (1):13–17.
32. Miller FB, Nikolov NR, Garrison RN. Emergency right colon resection. Arch Surg. 1987;122:339–343.
33. Wyrzykowski AD, Feliciano DV, George TA, Tremblay LN, Rozycki GS, Murphy TW, Dente CJ. Emergent right hemicolectomies. Am Surg. 2005;71(8):653–656.
34. Lee YM, Law WL, Chu KW, Poon RT. Emergency surgery for obstructing colorectal cancers: a comparison between right-sided and left-sided lesions. J Am Coll Surg 2001;192(6):719–725.
35. Hsu TC. Comparison of one-stage resection and anastomosis of acute complete obstruction of left and right colon. Am J Surg. 2005;189(4):384–387.
36. Veyrie N, Ata T, Muscari F, Couchard AC, Msika S, Hay JM, Fingerhut A, Dziri C. Anastomotic leakage after elective right versus left colectomy for cancer: prevalence and independent risk factors. J Am Coll Surg. 2007;05(6):785–793.
37. Konishi T, Watanabe T, Kishimoto J, Nagawa H. Risk factors for anastomotic leakage after surgery for colorectal cancer: results of prospective surveillance. J Am Coll Surg. 2006;202(3):439–444.
38. Lipska MA, Bissett IP, Parry BR, Merrie AE. Anastomotic leakage after lower gastrointestinal anastomosis: men are at a higher risk. ANZ J Surg. 2006;76(7):579–585.
39. Duchesne JC, Wang YZ, Weintraub SL, Boyle M, Hunt JP. Stoma complications: a multivariate analysis. Am Surg. 2002;68:961–966.
40. Arumugam PJ, Bevan L, Macdonald L, Watkins AJ, Morgan AR, Beynon J, Carr ND. A prospective audit of stomas—analysis of risk factors and complications and their management. Colorectal Dis 2003;**5**(1):49–52.

J Gastrointest Surg (2009) 13:2260–2267
DOI 10.1007/s11605-009-0987-3

ORIGINAL ARTICLE

Routine Evaluation of the Distal Colon Remnant Before Hartmann's Reversal is Not Necessary in Asymptomatic Patients

Nikiforos Ballian · Barbara Zarebczan · Alejandro Munoz · Bruce Harms · Charles P. Heise · Eugene F. Foley · Gregory D. Kennedy

Received: 15 June 2009 / Accepted: 4 August 2009 / Published online: 2 September 2009

Abstract
Background Reversal of Hartmann's is a common surgical procedure. Routine preoperative evaluation of the distal colonic/rectal remnant (DCRR) with contrast and/or endoscopic studies is frequently performed despite lack of evidence to support this practice. We hypothesize that asymptomatic patients can safely undergo Hartmann's reversal without preoperative DCRR evaluation.
Methods Adult patients undergoing reversal of Hartmann's at a single institution were retrospectively identified. Operative characteristics and outcomes in patients with and without preoperative DCRR evaluation were compared.
Results Between 1993 and 2008, 203 patients underwent reversal of Hartmann's at a tertiary referral center. Sixty-eight patients (33%) did not undergo preoperative DCRR evaluation and had comparable demographic characteristics, comorbidities, DCRR length, and perioperative outcomes to 135 patients who underwent preoperative contrast and/or endoscopic studies. After evaluation, 125 (93%) patients had normal findings, seven (5%) patients had abnormal studies that did not impact their management, and three (2%) patients underwent additional procedures.
Conclusion Hartmann's reversal without previous DCRR evaluation is acceptable in selected asymptomatic patients, without increased risk of complications.

Keywords Hartmann's procedure · Colostomy · Enema · Endoscopy

Introduction

Hartmann's procedure involves segmental colonic resection with end-colostomy or end-ileostomy and closure of the distal colonic/rectal remnant (DCRR), which remains in the pelvis or abdomen as a blind-ending pouch (Hartmann's pouch). This procedure is commonly performed in emergency situations in patients who require partial colectomy and are deemed to be at high risk of complications from a primary bowel anastomosis. The number of patients who undergo takedown of their stoma as a second-stage procedure varies between 56% and 100%.[1–5]

Preoperative DCRR evaluation by means of contrast and/or endoscopic studies is routinely requested by many surgeons to exclude leak, stricture, inflammation, and tumors, which could preclude Hartmann's reversal. DCRR evaluation is safe and has only minor disadvantages including cost, radiation exposure, and patient discomfort. However, there is no clear evidence that this practice affects surgical management or benefits patients. A previous study reported abnormalities in 16% of routine contrast DCRR studies, although these altered treatment in only a small minority of cases.[6] In addition, the role of endoscopy in this setting has not been defined.

We undertook this study to evaluate our use of preoperative evaluation of the DCRR. We were specifically interested to determine if the findings of these routine studies changed our management of asymptomatic patients. We hypothesize that Hartmann's reversal can be safely

N. Ballian · B. Zarebczan · A. Munoz · B. Harms · C. P. Heise · E. F. Foley · G. D. Kennedy (✉)
Department of Surgery, University of Wisconsin,
G4/701 Clinical Science Center, 600 Highland Avenue,
Madison, WI 53792-7375, USA
e-mail: kennedyg@surgery.wisc.edu

performed without routine preoperative DCRR evaluation in asymptomatic patients lacking other indications for preoperative investigation of the DCRR.

Materials and Methods

Patients undergoing Hartmann's reversal at the University of Wisconsin were retrospectively identified after institutional review board approval. We were unable to retrospectively identify patients undergoing preoperative DCRR endoscopic and/or contrast studies due to lack of specific codes for these procedures. Hartmann's procedure was defined as segmental colectomy, with or without resection of contiguous distal ileum, with proximal end-colostomy or end-ileostomy and closure of the DCRR. Defunctionalized distal colon and rectum extending proximal to the rectosigmoid junction was defined as long DCRR. Patients younger than 18 years of age and those undergoing DCRR contrast or endoscopic studies more than 180 days prior to takedown were excluded from the study. Patients undergoing additional surgical procedures at the time of Hartmann's reversal were analyzed separately.

Medical records were reviewed for patient demographic characteristics, indications for Hartmann's procedure, operative characteristics, length of hospital stay, and procedure-related morbidity and mortality. Anesthesia records were retrieved to determine American Society of Anesthesiologists (ASA) score, estimated blood loss (EBL), and operative time. The ASA score was used to compare patient preoperative overall physical health.[7] Operative time was defined as the time from skin incision to closure. When EBL was reported as "minimal," a value of 50 ml was arbitrarily assigned to allow quantitative comparison between groups. Length of hospital stay (LOS) was defined as the time from operation to discharge from hospital. Return of bowel function was defined as the time to initiation of an oral diet consisting of unlimited liquids.

Radiology and endoscopy reports were reviewed to determine study indications, results, and type of contrast used. For contrast studies, a Foley catheter was inserted though the patient's anus and contrast was infused to distend the DCRR for adequate visualization. The presence of pouch diverticulosis or polyps not requiring treatment before Hartmann's reversal were defined as normal findings as they did not affect surgical management.

Complication grade was assigned using a scale ranging from 1 to 5 according to the system proposed by Mazeh et al.[8] Briefly, this system grades inpatient and outpatient complications in the first 21 days after colorectal surgery. In order to allow comparison of patient groups, we recorded only the highest complication grade for each patient.

Student's t test, Fisher's exact test, and the Cochran–Armitage test were used to compare continuous variables, noncontinuous variables, and trends in ordinal variables, respectively, with $p<0.05$ representing statistical significance. Means are represented ± standard deviation.

Results

Patient Characteristics

Between 1993 and 2008, 214 adult patients underwent reversal of Hartmann's procedure at the University of Wisconsin. Eleven patients underwent pouch contrast or endoscopic studies more than 180 days prior to takedown and were excluded, yielding 203 patients for analysis. One hundred thirty-five patients (67%) underwent pouch contrast and/or endoscopic studies prior to takedown and 68 (33%) did not. There were no significant differences in age, gender distribution, time interval from Hartmann's procedure to Hartmann's reversal, DCRR length, or ASA score in patients with and without preoperative DCRR evaluation (Table 1). The proportion of patients undergoing takedown after Hartmann's procedure for complications of diverticulitis was higher in patients with contrast/endoscopic studies of their DCRR but did not reach statistical significance ($p=0.052$). Fourteen of 135 patients (10.4%) who underwent DCRR evaluation and 12 of 68 (17.6%) of those who did not, had a long DCRR ($p=0.18$). There was no difference in the proportion of patients undergoing Hartmann's reversal by a surgeon other than the one who performed their Hartmann's procedure ($p=0.10$).

Sixty-seven of 203 (33%) patients underwent additional surgical procedures at the time of Hartmann's reversal (Table 2). Fifty-five percent of these patients ($n=37$) had preoperative investigation of the DCRR prior to reversal while the remaining 45% ($n=30$) did not. There were no significant differences in age, gender, interval of time from Hartmann's procedure to reversal, DCRR length, or ASA score in those patients with and without preoperative DCRR evaluation (Table 1). Similarly, there were no differences in surgeon ($p=0.46$) between these groups. We did find that the proportion of patients with a diagnosis of diverticulitis was significantly higher in patients with contrast/endoscopic studies of their DCRR ($p=0.01$).

Contrast/Endoscopic Studies

In 135 patients undergoing DCRR evaluation prior to takedown, 117 contrast studies and 22 endoscopic studies were performed (Table 3). Four patients (3%)

Table 1 Demographic Characteristics and Surgical Indications in Patients Undergoing Hartmann's Reversal With and Without Preoperative DCRR Study (n=203)

	Study	No study	p value
Age [mean years±SD (n)]			
All patients	57±16 (135)	55±16 (68)	0.41
HR only	57±16 (98)	57±16 (38)	0.90
HR+additional procedure	57±14 (37)	55±12 (30)	0.50
Gender [Male : Female]			
All patients	72:63 (135)	37:31 (68)	1
HR only	56:42 (98)	21:17 (38)	0.85
HR+additional procedure	16:21 (37)	16:14 (30)	0.47
Time to reversal[a] [mean days±SD (n)]			
All patients	254±343 (126)	190±162 (65)	0.16
HR only	237±233 (93)	159±91 (35)	0.06
HR+additional procedure	303±549 (33)	227±213 (30)	0.48
Long DCRR[b]			
All patients	14/135 (10.4%)	12/68 (17.6%)	0.18
HR	11/98 (11.2%)	6/38 (15.8%)	0.56
HR+additional procedure	3/37 (8.1%)	6/30 (20.0%)	0.28
Different surgeon[c]			
All patients	67/135 (49.6%)	25/68 (36.8%)	0.10
HR	48/98 (49.0%)	13/38 (34.2%)	0.13
HR+additional procedure	19/37 (51.4%)	12/30 (40.0%)	0.46
ASA score (1-5)			
All patients			
n	129	68	
1	4	5	0.32
2	74	28	
3	49	33	
4	2	2	
HR only			
n	94	38	
1	3	2	0.84
2	54	19	
3	36	17	
4	1	0	
HR+ additional procedure			
n	35	30	
1	1	3	0.23
2	20	9	
3	13	16	
4	1	2	
Indications for Hartmann's procedure			
All patients	135	68	
Diverticulitis	80 (59%)	30 (44%)	0.05
Trauma	9	7	
Perforation	8	4	

Table 1 (continued)

	Study	No study	p value
Ischemia	6	5	
Iatrogenic injury	5	6	
Obstruction	4	7	
Anastomotic leak	6	4	
Crohn's	3	1	
Clostridium difficile colitis	4	1	
Hemorrhage	2	1	
Unknown/other	8	2	
HR only	98	38	
Diverticulitis	53 (54%)	18 (47%)	0.57
Trauma	9	6	
Perforation	7	2	
Ischemia	6	0	
Iatrogenic injury	5	3	
Obstruction	4	4	
Anastomotic leak	5	2	
Crohn's	2	1	
Clostridium difficile colitis	3	1	
Hemorrhage	2	0	
Unknown/other	2	1	
HR+ additional procedures	37	30	
Diverticulitis	27 (73%)	12 (40%)	0.01
Trauma	0	1	
Perforation	1	2	
Ischemia	0	5	
Iatrogenic injury	0	3	
Obstruction	0	3	
Anastomotic leak	1	2	
Crohn's	1	0	
Clostridium difficile colitis	1	0	
Hemorrhage	0	1	
Unknown/other	6	1	

SD standard deviation, *HR* Hartmann's reversal, *ASA* American Society of Anesthesiologists, *DCRR* distal colon/rectal remnant

[a]Interval between Hartmann's procedure and Hartmann's reversal

[b]Long DCRR is defined as defunctionalized distal colon and rectum extending proximal to the rectosigmoid junction

[c]Attending surgeon(s) performing Hartmann's procedure and Hartmann's reversal

underwent both procedures. No patients had symptoms suggestive of DCRR pathology. Specific indications for performing DCRR evaluation were identified in very few patients. Mean time to surgery was 39 days after contrast study and 48 days after endoscopy ($p=0.36$). In all cases where DCRR evaluation was performed, this was as a routine preoperative study in asymptomatic patients, without any clinical or laboratory indications of DCRR abnormalities.

Barium and water-soluble contrast were used for 69 (59%) and 30 (26%) contrast studies, respectively. The type of contrast used was not specified in 18 of 117 studies (15%). There were no complications related to pouch contrast or endoscopic studies. Overall, only 7% of all patients undergoing preoperative evaluation had findings on preoperative DCRR investigation. Clinical management was affected by the findings of DCRR investigation in 2% of all studies obtained (Table 4). Takedown was delayed in one case of pouch stricture and one case of active Crohn's disease. One additional patient underwent stricture dilation prior to colostomy reversal.

Perioperative Outcomes

One patient who self-discharged against medical advice on postoperative day 3 and one patient who underwent

Table 2 Additional Surgical Procedures at the Time of Hartmann's Reversal in Patients Undergoing Hartmann's Reversal With and Without Preoperative DCRR Study (n=67)

	Study (n=37)[a]	No study (n=30)[a]
Hernia repair	12	7
Resection of proximal colon	8	3
Small bowel resection	3	1
Gynecological procedures	4	3
Cholecystectomy	1	2
Liver resection	0	3
Other procedures	16	16
Total	44	35

[a] Number of patients

thoracoabdominal aneurysm repair during the same hospital stay were not included in the LOS and complication analyses. There were no significant differences in EBL, operative time, time to return of bowel function, complication grade, mortality, and LOS between patients with and without pouch studies prior to takedown (Table 5). This did not change when patients undergoing additional procedures were excluded from analysis. There was one death on postoperative day 21 as a result of an anastomotic leak in a patient with metastatic pituitary adenocarcinoma.

Three patients who did not have contrast or endoscopic studies of their DCRR were found to have previously unrecognized intra-abdominal abscesses at the time of takedown. All three underwent abscess drainage and washout with reanastomosis in the same setting. The complication rate of ten patients with abnormal DCRR studies was 100%, significantly higher compared to patients with normal DCRR results (50%; p=0.002). With the exception of one patient who underwent a negative exploratory laparotomy for persistent unexplained hypotension, these were all grade 1–3 complications.

Discussion

Reversal of Hartmann's is a common surgical procedure with significant morbidity.[9] Previous reports have identified a number of abnormalities that can affect the DCRR and could potentially cause significant complications after Hartmann's reversal, such as leak, fistula, stricture, malignancy, and diversion colitis.[3,6,10,11] These studies have generally been small retrospective series that, in many cases, have included patients with symptomatic conditions of their DCRR and/or those who were not candidates for reversal.[3,6,10,11] The largest report of asymptomatic patients revealed a low incidence of radiographic DCRR abnormalities.[6] Therefore, in the absence of symptoms, the role of DCRR contrast and/or endoscopic studies before Hartmann's reversal is unclear. In this study, we found that the postoperative outcomes of 68 asymptomatic patients undergoing Hartmann's reversal without preoperative DCRR evaluation were equivalent to those of 135 patients cleared for surgery after contrast and/or endoscopic studies. This shows that DCRR evaluation prior to Hartmann's reversal can safely be omitted in asymptomatic patients.

One of the controversies of using rectal contrast and endoscopy to evaluate the DCRR before Hartmann's reversal is that their accuracy in this setting has not been studied. Although the present series did not specifically assess the accuracy of either type of study, no evidence of a leak was found intraoperatively in those patients with contrast studies suspicious for a leaking DCRR. Cherukuri et al. have also reported false-positive results with rectal contrast studies in the same setting. In another study, Da Silva et al. reviewed 84 preoperative contrast studies in patients scheduled for closure of diverting ileostomy after colonic J-pouch anal anastomoses and reported four false-positive results (three strictures and one leak) in a total of six abnormal studies.[12] Despite the differences in anatomy between a J-pouch anal anastomosis and a DCRR, this is additional evidence that rectal contrast studies are not

Table 3 Contrast Used and Time from Study to Hartmann's Reversal in Patients with Contrast and/or Endoscopic DCRR Studies

	N (%)	Days to reversal [mean±SD (n)]	p value
Contrast type	117	39±42 (114)	
Barium	69 (59%)		
Water-soluble	30 (26%)		
Gastrografin	21		
Hypaque	3		0.36
Not specified	6		
Unknown	18 (15%)		
Endoscopic study	22	48±46 (22)	
Contrast and endoscopic studies	4	N/A	

DCRR distal colon/rectal remnant, *SD* standard deviation, *N/A* not applicable

Table 4 Characteristics of Ten Patients with 13 Abnormal DCRR Studies

Patient	Age	Sex	Indication for Hartmann's	Study type/result	Change in management	Complication grade/type
1	66	M	Diverticulitis	E/diversion proctitis	None	1/atelectasis
2[a]	78	M	Ischemic colitis	E/ischemia	None	N/A
				C/stricture	Dilation	1/atelectasis
3	79	M	Diverticulitis	E/diversion proctitis	None	2/wound bleeding
4[a]	26	F	Anastomotic leak	C/stricture	Reversal delayed	N/A
				E/diversion proctitis	None	2/pancreatitis
5	77	F	Diverticulitis	C/possible leak	None	2/delirium
6	28	M	Diverticulitis	C/possible stricture	None	1/wound dehiscence
7[a]	25	M	Crohn's colitis	E/active Crohn's disease	Reversal delayed	N/A
				E/diversion proctitis	None	3/wound abscess
8	68	M	*Clostridium difficile* colitis	C/presacral abscess	None	2/ileus
9	62	F	Diverticulitis	E/diversion proctitis	None	2/atelectasis
10	62	F	Ischemic colitis	E/diversion proctitis	None	4/hypotension

DCRR distal colonic/rectal remnant, *M* male, *F* female, *E* endoscopic study, *C* contrast study, *N/A* not applicable

[a] Patient with more than one abnormal study

accurate in identifying leaks and strictures. In addition to the risk of false-positive results, true-positive findings can sometimes negatively impact patients. Diversion proctocolitis, an inflammatory condition that affects defunctionalized bowel, can be misdiagnosed as inflammatory bowel disease and unnecessarily delay colostomy takedown. [13] Diversion proctocolitis commonly affects the DCRR, but it is not an indication for preoperative endoscopy nor should it affect the management of asymptomatic patients who are candidates for Hartmann's reversal.[10,13]

Furthermore, the clinical significance of abnormal DCRR radiographic or endoscopic findings and their value in patient management is unclear. In 135 patients undergoing Hartmann's reversal, preoperative DCRR evaluation by means of contrast and/or endoscopic studies revealed abnormalities in ten (7%) patients and altered the management of only three of them (Table 4). Our findings are corroborated by the report of Cherukuri et al. who found that, in 70 asymptomatic patients with 11 abnormal contrast studies of their DCRR, patient management was changed in three cases.[6] Similar to our study, all three patients subsequently underwent successful Hartmann's reversal.[6]

In the absence of findings on preoperative DCRR investigation that impact management, a DCRR study may still be indicated if preoperative planning leads to decreased complications. In fact, we found no difference in complication rate between those patients with and without DCRR investigation. Interestingly, all patients with abnormal DCRR studies had postoperative complications. Nevertheless, all these complications were minor and, given the small number of patients with abnormal studies, we do not believe that a cause-and-effect relationship between an abnormal DCRR study and postoperative complications can be inferred. Therefore, we do not believe that DCRR investigation is warranted for either decreasing complications or for changing management in the asymptomatic patient.

However, we do believe that DCRR evaluation prior to Hartmann's reversal has a role in the management of some patients. Certainly, any patient with symptoms or signs of DCRR abnormalities should have DCRR investigation prior to reversal. In a previous report, five of 14 patients with symptoms indicating abnormalities of the DCRR were found to have abnormal DCRR contrast studies, which in all five cases affected patient management.[6] In 24 patients with bleeding and/or pain affecting the DCRR, Haas et al. diagnosed 11 cases of severe proctitis, two polyps, and eight carcinomas, which were not further described in their series.[10]

We also believe that endoscopy of the remaining colon and rectum should be offered preoperatively to all patients who meet screening criteria for colorectal cancer. In their series of 25 asymptomatic patients who underwent DCRR evaluation at 1 year or longer after Hartmann's procedure, Haas et al. diagnosed two polyps and one carcinoma.[10] Due to the retrospective nature of this study and the changes in colonoscopic screening criteria, we were unable to determine the number of patients in our study population who met the screening criteria at the time of their operation.

A third group of patients who may have indications for routine preoperative DCRR evaluation is those patients with a diagnosis which carries a high risk of DCRR abnormalities. For example, a DCRR study in the Crohn's

Table 5 Outcomes in Patients Undergoing Hartmann's Reversal

	Study [mean±SD (n)]	No study [mean±SD (n)]	p value
Estimated blood loss (ml)			
All patients	238±228 (134)	272±269 (68)	0.35
HR only	223±229 (97)	215±197 (38)	0.86
HR + additional procedures	278±223 (37)	343±328 (30)	0.34
Operative time (min)			
All patients	183±70 (124)	203±98 (65)	0.10
HR only	170±62 (91)	182±74 (36)	0.38
HR + additional procedures	219±78 (33)	231±117 (29)	0.65
Time to liquid diet (days)			
All patients	5.2±3.5 (129)	5.1±2.6 (66)	0.88
HR only	5.2±3.7 (95)	5.6±2.9 (38)	0.68
HR + additional procedures	4.9±2.9 (34)	4.4±2.0 (28)	0.40
LOS (days)			
All patients	8.4±4.6 (132)	8.2±5.0 (67)	0.83
HR only	8.1±4.4 (96)	8.5±6.3 (37)	0.73
HR + additional procedures	9.1±5.1 (36)	8.0±3.0 (30)	0.29
30-day mortality			
All patients	1 (0.7%)	0	-
HR only	0	0	-
HR + additional procedures	1 (2.7%)	0	-
Complications			
All patients			
None	62/135 (45.9%)	33/68 (48.5%)	
Grade[a]			
1	16	2	
2	36	22	0.67
3	17	6	
4	3	5	
5	1	0	
HR only			
None	48/98 (49.0%)	18/38 (47.4%)	
Grade[a]			
1	13	1	
2	23	13	0.34
3	11	2	
4	3	4	
5	0	0	
HR + additional procedures			
None	14/37 (37.8%)	15/30 (50.0%)	
Grade[a]			
1	3	1	
2	13	9	0.53
3	6	4	
4	0	1	
5	1	0	

DCRR distal colon/rectal remnant, *SD* standard deviation, *LOS* length of hospital stay, *HR* Hartmann's reversal

[a] As defined by Mazeh et al.,[8] only the highest complication grade recorded

patient is warranted to ensure disease in the distal remnant is controlled. In our study, one patient of three with Crohn's disease was found to have acute inflammation requiring medical therapy. Similarly, a previous leak from a colonic anastomosis requiring Hartmann's procedure may increase risk of DCRR stenosis and evaluation before takedown may be warranted. In this study, one of six patients with a history of anastomotic leak was found to have a DCRR stricture at the time of DCRR evaluation.

Finally, DCRR evaluation may be indicated in some cases to assist operative planning by defining its anatomy, especially in patients who had their Hartmann's procedure by a different surgeon. Surgeons who are not comfortable performing low pelvic anastomoses would be more likely to refer patients with short DCRR to a surgeon with more experience. In our series, 45% of patients had Hartmann's reversal by a different surgeon than the one who performed their Hartmann's procedure. These patients were not more likely to have a preoperative DCRR contrast or endoscopic study.

A potential limitation of this retrospective series is that it may have not captured patients with abnormal DCRR studies who subsequently did not undergo reversal due to an abnormal study result or other reasons. However, patients who do not undergo reversal after Hartmann's procedure are usually unfit for surgery or have a poor prognosis due to known malignancy and are unlikely to undergo DCRR endoscopic or contrast studies in the absence of symptoms.[14] Furthermore, abnormalities of the DCRR do not preclude Hartmann's reversal. In the study of Cherukuri et al., none of the 16 patients with abnormal DCRR contrast studies were turned down for Hartmann's reversal as a result of their contrast study results.[6] Similarly, we found that all patients with abnormalities on preoperative DCRR investigation were ultimately reversed. Furthermore, the retrospective nature of our study did not permit accurate identification of the indications for DCRR evaluation. Due to the lack of guidelines for asymptomatic patients, we believe this is largely determined by personal preference. DCRR length, time since Hartmann's procedure, and previous Hartmann's procedure by a different surgeon greatly influence the decision to study the DCRR preoperatively. Finally, lack of differences in patient outcomes could be related to small sample size, particularly in subgroup analyses.

Conclusion

Hartmann's reversal without previous DCRR evaluation is acceptable in selected asymptomatic patients, without increased risk of complications. Contrast and/or endoscopic studies should be reserved for patients with symptoms indicating potential DCRR pathology, those patients who have situations predisposing them to complications of the DCRR, and those who meet the screening criteria for specific colorectal pathology.

References

1. Haas PA, Haas GP. A critical evaluation of the Hartmann's procedure. Am Surg 1988;54:380–385.
2. Belmonte C, Klas JV, Perez JJ, Wong WD, Rothenberger DA, Goldberg SM, et al. The Hartmann procedure. First choice or last resort in diverticular disease? Arch Surg 1996;131:612–615.
3. Schein M, Decker G. The Hartmann procedure. Extended indications in severe intra-abdominal infection. Dis Colon Rectum 1988;31:126–129.
4. Sweeney JL, Hoffmann DC. Restoration of continuity after Hartmann's procedure for the complications of diverticular disease. Aust N Z J Surg 1987;57:823–825.
5. Salem L, Anaya DA, Roberts KE, Flum DR. Hartmann's colectomy and reversal in diverticulitis: a population-level assessment. Dis Colon Rectum 2005;48:988–995.
6. Cherukuri R, Levine MS, Maki DD, Rubesin SE, Laufer I, Rosato EF. Hartmann's pouch: radiographic evaluation of postoperative findings. AJR Am J Roentgenol 1998;171:1577–1582.
7. American Society of Anesthesiologists. ASA physical status classification system. Available at http://www.asahq.org/clinical/physicalstatus.htm.
8. Mazeh H, Samet Y, Abu-Wasel B, Beglaibter N, Grinbaum R, Cohen T, et al. Application of a novel severity grading system for surgical complications after colorectal resection. J Am Coll Surg 2009;208:355–361.
9. Aydin HN, Remzi FH, Tekkis PP, Fazio VW. Hartmann's reversal is associated with high postoperative adverse events. Dis Colon Rectum 2005;48:2117–2126.
10. Haas PA, Fox TA Jr. The fate of the forgotten rectal pouch after Hartmann's procedure without reconstruction. Am J Surg 1990;159:106–110.
11. Thaemert BC, Kisken WA. Neoplasms in long-term Hartmann's pouches. Wis Med J 1996;95:105–107.
12. da Silva GM, Wexner SD, Gurland B, Gervaz P, Moon SD, Efron J, Nogueras JJ, Weiss EG, Vernava AM, Zmora O. Is routine pouchogram prior to ileostomy closure in colonic J-pouch really necessary? Colorectal Dis 2004;6:117–120.
13. Orsay CP, Kim DO, Pearl RK, Abcarian H. Diversion colitis in patients scheduled for colostomy closure. Dis Colon Rectum 1993;36:366–367.
14. Chua CL. Surgical considerations in the Hartmann's procedure. Aust N Z J Surg 1996;66:676–679.

J Gastrointest Surg (2009) 13:2268–2275
DOI 10.1007/s11605-009-0977-5

ORIGINAL ARTICLE

Perioperative Risk Assessment for Hepatocellular Carcinoma by Using the MELD Score

Spiros G. Delis · Andreas Bakoyiannis · Christos Dervenis · Nikos Tassopoulos

Received: 17 May 2009 / Accepted: 21 July 2009 / Published online: 7 August 2009

Abstract
Background/aims The aim of this study was to evaluate the ability of Model for End-Stage Liver Disease (MELD) in predicting post hepatectomy outcome for hepatocellular carcinoma (HCC).
Methods Between 2001 and 2005, 94 cirrhotic patients with HCC underwent hepatectomy and were analyzed retrospectively. MELD score associated with postoperative mortality and morbidity, hospital stay, and 3-year survival.
Results Twenty-eight major and 66 minor resections were performed. Thirty-day mortality rate was 6.4%. MELD≤9 was associated with no perioperative mortality vs 15.3% when MELD>9 (p=0.01). Overall morbidity rate was 32%; 21% when MELD≤9 vs 42% when MELD>9 (p=0.01). Median hospital stay was 11 days (7 days, when MELD≤9 and 14 days when MELD>9; p=0.03). Three-year survival reached 48% (63% when MELD≤9; 30% when MELD>9; p<0.01). In multivariate analysis, MELD>9 (p=0.01), clinical tumor symptoms (p=0.04), and American Society of Anesthesiologists score (p=0.04) were independent predictors of perioperative mortality; MELD>9 (p=0.01), tumor size >5 cm (p=0.01), presence of tumor symptoms (p=0.02), high tumor grade (p=0.01), and absence of tumor capsule (p=0.01) were independent predictors of decreased long-term survival.
Conclusion MELD score seems to predict outcome of cirrhotic patients with HCC after hepatectomy.

Keywords Hepatocellular carcinoma · MELD score · Hepatectomy · Cirrhosis · Liver resection outcome

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide with an incidence of 1:500,000 and is strongly correlated with cirrhosis.1 The mainstay of treatment in patients with solitary HCC and good liver function is hepatic resection.[2] Evolution in surgical techniques and perioperative care have improved postoperative outcome in patients with severe underlying liver disease undergoing hepatectomy.

However, the risk of hepatic failure in a cirrhotic patient undergoing hepatectomy remains high due to compromised function of the liver remnant.[3,4] Therefore, a thorough evaluation of the hepatic function reserve is necessary prior to surgical intervention in order to select among cirrhotic patients the best candidates for hepatic resection with reasonable postoperative morbidity and mortality.

Child–Turcotte–Pugh (CTP) classification was the first systematic approach for determining the severity of cirrhosis and selecting patients that could tolerate hepatic resection.[5] CTP class C is considered an absolute contraindication for surgical treatment, while only few hepatectomies are performed in class B cirrhosis.[5]–7 CTP class A patients are generally considered good candidates for hepatic resection with good postoperative outcome. How-

S. G. Delis
Division of Liver and GI Transplantation,
University of Miami Miller School of Medicine,
Miami, FL 33136, USA

S. G. Delis (✉) · A. Bakoyiannis · C. Dervenis
Liver Surgical Unit, 1st Surgical Department,
Kostantopouleio-"Agia Olga" Hospital,
3-5 Agias Olgas str.,
142 33 Athens, Greece
e-mail: sgdelis55@yahoo.gr

N. Tassopoulos
First Department of Medicine, Western Attica Gen. Hospital,
Athens, Greece

ever, more refined evaluation of the liver function reserve is often needed due to limitations in the discriminatory ability of CTP system, since it uses subjective parameters such as ascites and encephalopathy.[8–11] Many tests have been applied for the assessment of dynamic hepatic function, such as indocyanine green clearance test,[9] lidocaine test,[10] and galactose elimination capacity,[11] and showed that these could provide a more refined estimate of hepatic function than CTP score.[9]

Recently, Model for End-Stage Liver Disease (MELD) score was introduced for the evaluation of hepatic function reserve in cirrhotic patients.[12–17] It has the advantage of using three objective and easily measured parameters: creatinine levels, international normalized ratio, and total bilirubin.

The original intent of MELD was to predict survival in patients with cholestatic liver disease.[12,13] Using the statistical methods that have been successful in predicting the survival of patients with primary biliary cirrhosis[12] and primary sclerosing cholangitis,[13] Malinchoc et al. used MELD score to predict survival in cirrhotic patients receiving transjugular intrahepatic portosystemic shunt.18 MELD score is also used to determine priority on the waiting list for liver transplantation[19] and to predict postoperative outcome of cirrhotic patients undergoing surgical procedures.[14–17]

The aim of this study was to examine whether preoperative MELD score can predict postoperative mortality, morbidity, hospital stay, and 3-year survival in cirrhotic Child A patients undergoing hepatectomy for HCC. An effort to subcategorize the low- from the high-risk Child A patients is provided along with a thorough review of the current literature.

Materials and Methods

We retrospectively analyzed the clinical records of all patients with HCC on chronic liver disease who underwent hepatic resection in our institution between January 2001 and January 2005. Patients who were anticoagulated and those with chronic renal insufficiency requiring hemodialysis were excluded from the study. HCC was pathologically confirmed in all patients included in the study. We identified 69 patients fulfilling the above criteria. Clinical and pathological features of the patients are reported in Tables 1 and 2.

CTP class was calculated using prothrombin time, albumin, bilirubin, and clinical findings of ascites and encephalopathy.20 CTP score was stratified as class A (5–6), B (7–9), and C (10–15). Eighty-two patients were classified as CTP class A (87.2%) and 12 patients as CTP class B, score 7 (12.7%).

MELD score was calculated by using preoperative values of three laboratory tests: international normalized ratio (INR) for prothrombin time, serum total bilirubin (TBil), and serum creatinine (Cr). MELD score was calculated using the following formula: $\mathrm{MELD} = 9.57\times \log_e(\mathrm{Cr\ mg/dL}) + 3.78 \times \log_e(\mathrm{TBil\ mg/dL}) + 11.20\times \log_e(\mathrm{INR}) + 6.43$.[18] We used the MELD score of the patient upon admission to our clinic, since it represents more accurately the severity of cirrhosis before surgery. Median MELD score prior to surgery was 9 (range, 6–15). The distribution of MELD score in our population is shown in Fig. 1.

Patients with CTP class A cirrhosis showed a median MELD score of 8, ranging from 6 to 14, significantly lower than patients with CTP class B cirrhosis who had a median MELD score of 11 (range, 9–15, $p<0.05$).

During hospitalization and prior to surgery, many patients received blood products such as fresh frozen plasma (FFP) in order to improve their laboratory values before surgery. Hepatitis activity and cirrhosis were evaluated by the Ishak fibrosis score.21 Necrosis and inflammatory changes characteristic of hepatitis were scored as mild (0–5), moderate (6–12), or severe (13–18), and fibrosis was scored as cirrhosis vs noncirrhosis. Operative data are shown in Tables 1 and 2. Major hepatic resection was defined as the removal of three or more segments.22 Portal vein embolization was performed 6 to 8 weeks before operation whenever the future liver remnant was expected to be less than 40% of the total liver volume with the tumor volume subtracted as calculated by three-dimensional CT volumetry. Tumor histological grading was assessed according to the criteria of Edmondson and Steiner[23] based on the areas of the tumor having the highest grade. Tumors were classified accordingly to the sixth edition of American Joint Committee on Cancer (AJCC) Cancer Staging Manual.[24]

Postoperative mortality was defined as any death occurring within 30 days after surgery. The primary end point of the study was the investigation of the relationship existing between the preoperative MELD score and the development of irreversible liver failure after hepatectomy of cirrhotic patients. It was defined as a growing impairment of liver function after resection that led to patient death or required transplantation. The relationship between the MELD score and postoperative complications (morbidity), length of hospital stay, and 3-year patient survival represented secondary end points. Postoperative jaundice was defined as serum bilirubin level above 5 mg/dL, alteration of coagulation factors was defined as considerable or severe when fresh frozen plasma infusion was required in order for those to be corrected, and renal impairment was defined as an increase of blood urea nitrogen above 2 g/L and/or an increase of serum creatinine above 2 mg/dL.

Table 1 Univariate Analysis of Perioperative Mortality in Patients with Cirrhosis with Hepatocellular Carcinoma

Variable	Number of patients	Perioperative mortality, *n* (%)	*p* value
Age (year)			0.7
≤65	59	3 (5.1%)	
>65	35	3 (8.6%)	
Gender			0.7
Male	63	4 (6.3%)	
Female	31	2 (6.4%)	
Symptoms			0.04
Present	33	5 (15%)	
Absent	61	1 (1.6%)	
CTP class			0.3
A	82	5 (6.1%)	
B	12	1 (8.3%)	
MELD score			0.01
≤9	55	0	
>9	39	6 (15.3%)	
Tumor size			0.09
≤5	58	4 (6.9%)	
>5	36	2 (5.5%)	
Grade			0.07
1	9	0	
2	51	4 (7.8%)	
3	34	2 (5.8%)	
4	0		
Stage			0.1
1	33	2 (6%)	
2	39	3 (7.7%)	
3	22	1 (4.5%)	
Extent of resection			0.1
Minor	66	3 (4.5%)	
Major	28	3 (10.7%)	
ASA class			0.04
1	23	0	
2	41	2 (4.8%)	
3	30	4 (13%)	

CTP Child–Turcotte–Pugh, *MELD* Model for End-Stage Liver Disease, *ASA* American Society of Anesthesiologists

Hospital stay was computed from the day of surgery until discharge at home. Patient survival was computed from the day of surgery until the most recent follow-up. Controls and patients still alive after the first year after surgery were censored at this time point; patients transplanted for postoperative liver failure were censored the day prior to transplantation, and patients dead for causes not related to liver failure were censored the day prior to the event.

Long-term follow up included serum a-fetoprotein and CT scan of the abdomen every 3 months during the first year after surgery and at 6-month intervals thereafter. CT, MRI, and PET scan or angiography were performed selectively when recurrence was suspected.

Statistical Analysis

Continuous variables were expressed as median and range. The values in the different subgroups were compared using the Kruskal–Wallis test. Normal distribution was not able to be proved for the clinical variables available (Kolmogorov–Smirnov test, $p<0.05$). Nonparametric tests were applied to all the data analysis. Categorical variables were expressed as prevalence, and subgroups were compared using the χ^2 test with Yates's correction. Survival probabilities were constructed using Kaplan–Meier survival estimates and compared using the log-rank test.

The prognostic value of MELD in predicting postoperative liver failure and complications was assessed using

Table 2 Univariate Analysis of Clinicopathologic Factors Associated with Survival After Hepatectomy for Hepatocellular Carcinoma in Patients with Cirrhosis

Variable	1-year survival (%)	3-year survival (%)	P value
Age (year)			0.2
≤65	60	50	
>65	68	41	
Gender			0.7
Male	68	49	
Female	66	53	
Symptoms			0.02
Present	39	14	
Absent	83	72	
CTP class			0.3
A	68	41	
B	48	46	
MELD score			0.01
≤9	88	63	
>9	42	30	
Tumor size			0.01
≤5	76	64	
>5	40	29	
Grade			0.01
1	100	100	
2	71	60	
3	50	31	
4	0	0	
Stage			0.6
1	68	61	
2	79	31	
3	44	29	
Extent of resection			0.06
Minor	74	52	
Major	43	31	
Capsule			0.01
Yes	69	49	
No	31	12	

MELD Model for End-Stage Liver Disease

receiver operating characteristic (ROC) curve analysis. A significance level of 0.05 was used in all analyses. ROC analysis was performed using MedCalc version 7.2.1.0 (Med-Calc Software, Mariakerke, Belgium). The statistical analysis was done using SPSS Version 10.0 software (SPSS, Chicago, IL, USA).

Results

Surgery consisted of 66 (70.2%) minor hepatic resections and 28 (29.7%) major hepatic resections. Serum α-fetoprotein was elevated in 64% of patients with a mean level of 1,981 ng/ml (range 1–25,000 ng/ml). There were performed 12 right hepatectomies (12.7%), 16 left hepatectomies (17%), 29 wedge resections (30.8%), 25 segmentectomies (26.6%), and 12 left lateral sectionectomies (12.7%). Resection was performed by the conventional method with hepatic inflow dissection and selective vascular pedicle ligation followed by outflow short hepatic vein ligation in a piggyback fashion. Intraoperative ultrasound was performed routinely in patients undergoing hepatectomy. Median operating time was 190 min (range 140 to 310 min). In nine patients, ischemic preconditioning by vascular inflow occlusion was performed during resection.

The mean size of HCC was 6.1 cm (range 1.5 to 14 cm). AJCC stage was I in 33 patients, II in 39 patients, and III in 22 patients.

All resections were performed with a tumor-free margin of at least 1 cm.

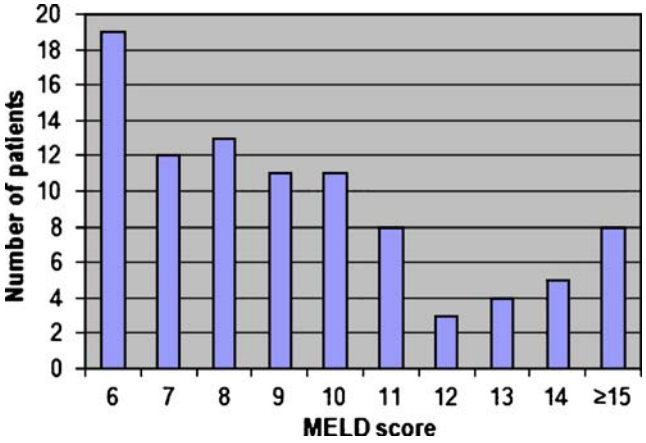


Figure 1 Distribution of MELD in patients with cirrhosis. *MELD* Model for End-Stage Liver Disease.

Six patients (6.39%) developed irreversible postoperative liver failure and died within 30 days after surgery. Five of these patients were classified as CTP class A and underwent left hepatectomy in two cases, wedge resections in two cases, and a right posterior sectionectomy. One patient, classified as CTP class B, developed postoperative liver failure after a wedge resection.

Patients who experienced postoperative liver failure had a median MELD score of 11 (range, 9–15), significantly higher in comparison to patients in which this event did not occur (median, 7; range, 6–13; $p=0.01$). ROC analysis identified a MELD score above 9 as satisfactory cutoff value for predicting postoperative liver failure (area under curve (AUC)=0.91, 95% confidence interval (CI)=0.86–0.96; sensitivity=82%; specificity=86%; Fig. 2).

Univariate analysis identified MELD score >9 ($p<0.01$), presence of clinical tumor symptoms ($p<0.05$), and American Society of Anesthesiologists (ASA) score ($p<0.05$) as significantly associated with perioperative mortality.

The overall perioperative mortality was 6.3%.

The perioperative mortality for patients with MELD score >9 (15.3%) was significantly greater than that for patients with MELD score ≤9 (0%; $p=0.01$). Other patients' demographics and pathological factors were not associated with perioperative mortality (Table 1). Multivariate analysis demonstrated that MELD score >9 ($p=0.01$), clinical tumor symptoms ($p=0.04$), and ASA score ($p<0.04$) are independent predictors of perioperative mortality.

Other less life-threatening than liver failure postoperative complications included the occurrence of intractable ascites, requiring intensive therapy with diuretics for its remission, elevation of INR>2; 24 h post surgery requiring FFP transfusion, and elevation of total bilirubin >5 mg/dl. Thirty patients (32%) experienced at least one postoperative complication. Refractory ascites developed in 13 cases (13.8%), jaundice in seven cases (7.4%), and alteration of coagulation factors in 15 cases (16%).

Patients who experienced postoperative complications had higher MELD score (median, 10; range, 7–15) in comparison to patients who did not experience any complication (median, 8; range, 6–11; $p=0.001$). ROC analysis again identified MELD score above 9 as the best cutoff value for predicting occurrence of postoperative complications (AUC 0.84, 94% CI=0.77–0.88; sensitivity=85%; specificity=61%; Fig. 3).

Patients were divided according to the cutoffs of the MELD scores obtained by ROC analysis in two groups: MELD below or equal to 9 and MELD above 9. MELD score was ≤9 in 55 patients (58.5%) and >9 in 39 patients (41.5%). The prevalence of postoperative liver failure and the morbidity in relationship with MELD score prior to

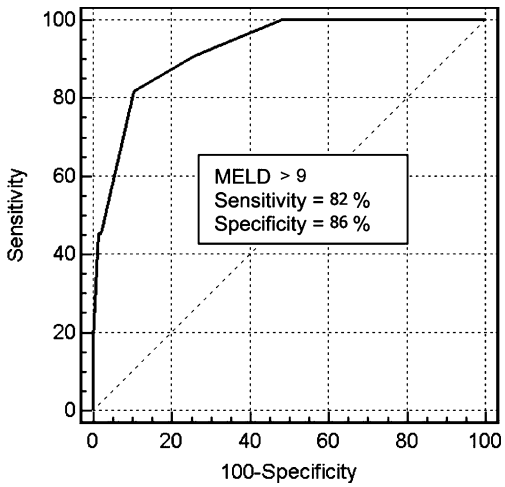


Figure 2 ROC curve of the MELD score in predicting postoperative liver failure after hepatic resection in patients with cirrhosis (AUC=0.91, 95% CI=0.86–0.96).

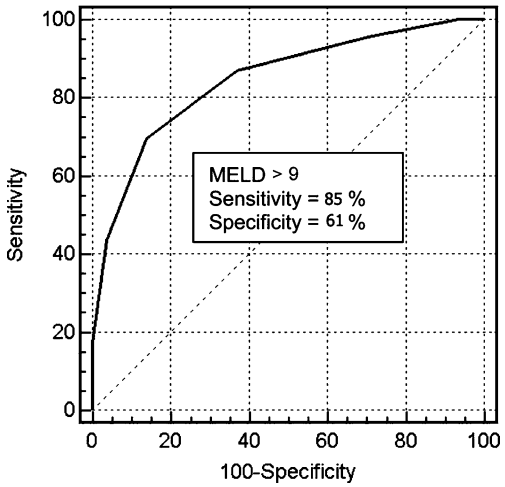


Figure 3 ROC curve of the MELD score in predicting occurrence of postoperative complication after hepatic resection in patients with cirrhosis (AUC=0.84, 94% CI=0.77–0.88).

surgery as well as 3-year survival rates are reported in Tables 1 and 2. Patients with a MELD score below or equal to 9 did not experience postoperative liver failure; they had zero 30-day mortality and showed the lowest morbidity (21%) in contradistinction to patients with a score above 9 who had the highest prevalence of postoperative liver failure and 30-day mortality (15.3%) and the highest morbidity (42%; $p=0.01$ in both cases).

Mean hospital stay was 11 days. Patients with a MELD score below or equal to 9 were discharged from the hospital after a median of 7 days (range, 5–13 days). When MELD score was above 9, the median hospital stay reached 14 days (range 8–21 days; $p=0.03$). The 3-year survival for the entire cohort reached 48%. The 3-year survival was 63% when MELD≤9 and 30% when MELD>9; $p<0.01$ (Table 2). Multivariate analysis revealed that MELD>9 ($p=0.01$), tumor size >5 cm ($p=0.01$), high tumor grade ($p=0.01$), presence of tumor symptoms ($p=0.02$), and absence of tumor capsule ($p=0.01$) are independent predictors of decreased long-term survival (Table 2).

Discussion

Preoperative assessment of liver function and prediction of postoperative functional reserve are of paramount importance to minimize surgical risk of liver resection, especially in cirrhotic patients.

MELD score seems to have the ability to stratify cirrhotic patients more accurately than CTP classification.[16,17] Teh et al.[16] examined whether MELD was predictive of perioperative mortality and correlated MELD with other potential clinicopathologic factors to overall survival in patients with cirrhosis undergoing hepatic resection for HCC. They reviewed 82 patients who underwent liver resection for HCC and concluded that MELD score was a strong predictor of both perioperative mortality and long-term survival in patients with cirrhosis undergoing hepatic resection for HCC.[16]

Cucchetti et al.,[17] in their study, presented a way to predict postoperative liver failure and morbidity after hepatectomy for hepatocellular carcinoma with cirrhosis. One hundred fifty-four cirrhotic patients resected in a tertiary care setting for HCC were retrospectively analyzed. They concluded that cirrhotic patients with MELD score below 9 had no postoperative liver failure and low morbidity (8.1%) and that the MELD score can accurately predict postoperative liver failure and morbidity of cirrhotic patients referred for resection of HCC and should be used to select the best candidates for hepatectomy.[17]

A cirrhotic patient eligible for resection on the basis of CTP score may not be resectable on the basis of MELD. Such patients should be referred to nonsurgical approaches such as radiofrequency ablation or transarterial chemoembolization. In our study, most patients were class A (82 out of 94 patients—87.2%) according to CTP system. MELD classification, however, managed to identify pre-operatively those Child A patients with higher 30-day mortality rate, greater risk in developing a post hepatectomy complication, and longer hospital stay and poorer long-term outcome.

Several reports from different groups, including ours, consider partial hepatectomy a good option in well-compensated CTP class A patients.[25–28] Otherwise, liver resection has been considered as a bridge to liver transplantation in order to reduce the dropout rate in patients with HCC on cirrhosis on the waiting list.[29]

Patients with a MELD score equal to or above 11 probably represent the ideal patients to refer for nonsurgical approaches such as thermal ablation or chemoembolization and, whenever possible, for liver transplantation.

In particular, in the setting of liver transplantation, Merion et al.[30] showed the threshold score of 11 patients in whom, independent of HCC, transplantation is justified (above 11) or futile (below 11); in particular, cirrhotic patients with a MELD score between 6 and 11 were shown to have a posttransplant mortality significantly higher than waiting list mortality. Therefore, the results from recent studies may give support to a systematic transplantation policy in small HCC patients with a MELD score exceeding 11 as well as partial hepatectomy in patients with lower MELD scores.17 Even in patients with MELD score between 9 and 10, strict care must be taken in intraoperative and postoperative management, and major hepatectomies should be avoided.

Our findings show that MELD score >9 is strongly predictive of increased perioperative mortality in patients with cirrhosis undergoing hepatic resection for HCC. No other clinical and pathologic factors except for clinical tumor symptoms and ASA score were predictive of perioperative mortality. This is in agreement with other reports in the field.[16,17]

We agree with the hypothesis that the high recurrence rate in patients with higher MELD score can be explained by the different immunologic status of these patients (cytokines).[31–33]

Although Schroeder et al.[34] in their recent paper criticized the reliability of MELD score to predict morbidity and mortality after elective liver resection, 91% of the patients with HCC in their study had minimal or no evidence of liver disease. In our study, all patients had histologically proved cirrhosis.

Recently, another study identified MELD score <10 as an independent predictor of survival and showed that MELD was a more reliable predictor of survival than CTP class, but only 12 patients underwent resection.35 Three current staging systems for HCC, Barcelona Clinic Liver

Cancer staging system,[36] Cancer of the Liver Italian Program (CLIP),[37] and Japan Integrated Staging[38] use CTP class as a primary component for determining prognosis. Although each staging system is predictive of survival for patients with HCC, only CLIP has been externally validated.[39]

There is no consensus on which staging system is best.[40,41] Minagawa et al.[42] compared in a large series the accuracy of the Japanese tumor–node–metastases (TNM) staging system for predicting patient survival (Liver Cancer Study Group of Japan (LCSGJ)) with that of the TNM staging system of the American Joint Committee on Cancer/International Union Against Cancer (UICC), using the cross-validation method. They concluded that, while both staging systems allow for the clear stratification of patients into prognostic groups, the LCSGJ staging may be more appropriate for stratifying patients with early-stage HCC.

Cho et al.[43] analyzed 184 patients who underwent primary complete resection of HCC between 1989 and 2002 and constructed a novel prognostic nomogram using prognostically relevant variables. They concluded that contemporary staging systems for HCC do not accurately predict postoperative outcomes, while on the other hand, the prognostic nomogram they describe provides a mechanism for accurate prediction of survival and risk stratification. Their nomogram has not been validated yet by other hepatobiliary centers.

Conclusion

MELD score can accurately predict mortality, morbidity, and long-term survival in patients with HCC and cirrhosis undergoing hepatic resection. Cirrhotic patients with high MELD score have increased risk of postoperative liver failure and complications; they are expected to have poorer long-term survival after liver resection and should be referred for other treatments. Cirrhotic patients with low MELD score treated with minor hepatic resections achieve no 30-day mortality and low morbidity rates, while expected long-term survival is promising. Application of MELD score in the preoperative assessment of liver function prior to hepatic resection is recommended, as this facilitates identification of high-risk Child A patients prior to hepatic resection and selection of the best candidates for hepatectomy. A multi-institutional study is required to better define selection criteria for hepatic resection in HCC patients with cirrhosis.

Conflict of interest statement All authors declare to have no financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work.

The authors: Spiros G Delis, Andreas Bakoyiannis, Nikos Tassopoulos, Christos Dervenis.

Role of the funding source All authors declare that no sponsors had any involvement in the study.

The authors: Spiros G Delis, Andreas Bakoyiannis, Nikos Tassopoulos, Christos Dervenis.

References

1. El-Serag HB. Epidemiology of hepatocellular carcinoma. Clin Liver Dis 2001;5:87–107.
2. Poon RT, Fan ST, Lo CM, Ng IO, Liu CL, Lam CM, Wong J. Improving survival results after resection of hepatocellular carcinoma: a prospective study of 377 patients over 10 years. Ann Surg 2001;234:63–70.
3. Belghiti J, Regimbeau JM, Durand F, Kianmanesh AR, Dondero F, Terris B, Sauvanet A, Farges O, Degos F. Resection of hepatocellular carcinoma: a European experience on 328 cases. Hepatogastroenterology 2002;49:41–46.
4. Bilimoria MM, Lauwers GY, Doherty DA, Nagorney DM, Belghiti J, Do KA, Regimbeau JM, Ellis LM, Curley SA, Ikai I, Yamaoka Y, Vauthey JN. Underlying liver disease, not tumor factors, predicts long-term survival after resection of hepatocellular carcinoma. Arch Surg 2001;136(5):528–535.
5. Franco D, Capussotti L, Smadja C, Bouzari H, Meakins J, Kemeny F, Grange D, Dellepiane M. Resection of hepatocellular carcinomas. Results in 72 European patients with cirrhosis. Gastroenterology 1990;98:733–738.
6. Paquet KJ, Gad HA, Lazar A, Koussouris P, Mercado MA, Heine WD, Jachman-Jahn V, Ruppert W. Analysis of factors affecting outcome after hepatectomy of patients with liver cirrhosis and small hepatocellular carcinoma. Eur J Surg 1998;164:513–519.
7. Wayne JD, Lauwers GY, Ikai I, Doherty DA, Belghiti J, Yamaoka Y, Regimbeau JM, Nagorney DM, Do KA, Ellis LM, Curley SA, Pollock RE, Vauthey JN. Preoperative predictors of survival after resection of small hepatocellular carcinomas. Ann Surg 2002; 235:722–731.
8. Miyagawa S, Makuuchi M, Kawasaki S, Kakazu T. Criteria for safe hepatic resection. Am J Surg 1995;169:589–594.
9. Lau H, Man K, Fan ST, Yu WC, Lo CM, Wong J. Evaluation of preoperative hepatic function in patients with hepatocellular carcinoma undergoing hepatectomy. Br J Surg 1997;84:1255–1259.
10. Ercolani G, Grazi GL, Callivà R, Pierangeli F, Cescon M, Cavallari A, Mazziotti A. The lidocaine (MEGX) test as an index of hepatic function: its clinical usefulness in liver surgery. Surgery 2000;127:464–471.
11. Redaelli CA, Dufour JF, Wagner M, Schilling M, Hüsler J, Krähenbühl L, Büchler MW, Reichen J. Preoperative galactose elimination capacity predicts complications and survival after hepatic resection. Ann Surg 2002;235:77–85.
12. Dickson ER, Grambsch PM, Fleming TR, Fisher LD, Langworthy A. Prognosis in primary biliary cirrhosis: model for decision making. Hepatology 1989;10(1):1–7.
13. Dickson ER, Murtaugh PA, Wiesner RH, Grambsch PM, Fleming TR, Ludwig J, LaRusso NF, Malinchoc M, Chapman RW, Kaplan MM et al. Primary sclerosing cholangitis: refinement and validation of survival models. Gastroenterology 1992;103(6):1893–1901.
14. Northup PG, Wanamaker RC, Lee VD, Adams RB, Berg CL. Model for end-stage liver disease (MELD) predicts nontransplant surgical mortality in patients with cirrhosis. Ann Surg 2005; 242:244–251.
15. Befeler AS, Palmer DE, Hoffman M, Longo W, Solomon H, Di Bisceglie AM. The safety of intra-abdominal surgery in patients with cirrhosis: model for end-stage liver disease is superior to Child–Turcotte–Pugh classification in predicting outcome. Arch Surg 2005;140:650–654.

16. Teh SH, Christein J, Donohue J, Que F, Kendrick M, Farnell M, Cha S, Kamath P, Kim R, Nagorney DM. Hepatic resection of hepatocellular carcinoma in patients with cirrhosis: model for end-stage liver disease (MELD) score predicts perioperative mortality. J Gastrointest Surg 2005;9:1207–1215.
17. Cucchetti A, Ercolani G, Vivarelli M, Cescon M, Ravaioli M, La Barba G, Zanello M, Grazi GL, Pinna AD. Impact of model for end-stage liver disease (MELD) score on prognosis after hepatectomy for hepatocellular carcinoma on cirrhosis. Liver Transpl 2006;12(6):966–971.
18. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000;31:864–871.
19. Freeman RB Jr, Wiesner RH, Harper A, McDiarmid SV, Lake J, Edwards E, Merion R, Wolfe R, Turcotte J, Teperman L. The new liver allocation system: moving toward evidence-based transplantation policy. Liver Transpl 2002;8:851–858.
20. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60(8):646–649.
21. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, Denk H, Desmet V, Korb G, MacSween RN, Phillips MJ, Portmann BG, Poulsen H, Scheuer P, Schmid M, Thaler H. Histological grading and staging of chronic hepatitis. J Hepatol 1995;22:696–699.
22. Committee of the International Hepato-Pancreato-Biliary Association. IHPBA Brisbane 2000 Terminology of Liver Anatomy and Resections. Abingdon: Taylor & Francis, 20002:333–339.
23. Edmondson HA, Steiner PE. Primary carcinoma of the liver. A study of 100 cases among 48,900 necropsies. Cancer 1954;7:462–503.
24. American Joint Committee on Cancer. AJCC Cancer Staging Manual. 6th ed. New York: Springer, 2002, pp 145–153.
25. Grazi GL, Ercolani G, Pierangeli F, Del Gaudio M, Cescon M, Cavallari A, Mazziotti A. Improved results of liver resection for hepatocellular carcinoma on cirrhosis give the procedure added value. Ann Surg 2000;234:71–78.
26. Poon RT, Fan ST. Hepatectomy for hepatocellular carcinoma: patient selection and postoperative outcome. Liver Transpl 2004;10(suppl):S39–S45.
27. Song TJ, Ip EW, Fong Y. Hepatocellular carcinoma: current surgical management. Gastroenterology 2004;127(suppl):S248–S260.
28. Ikai I, Arii S, Kojiro M, Ichida T, Makuuchi M, Matsuyama Y, Nakanuma Y, Okita K, Omata M, Takayasu K, Yamaoka Y. Reevaluation of prognostic factors for survival after liver resection in patients with hepatocellular carcinoma in a Japanese nationwide survey. Cancer 2004;101:796–802.
29. Belghiti J, Cortes A, Abdalla EK, Régimbeau JM, Prakash K, Durand F, Sommacale D, Dondero F, Lesurtel M, Sauvanet A, Farges O, Kianmanesh R. Resection prior to liver transplantation for hepatocellular carcinoma. Ann Surg 2003;238:925–928.
30. Merion RM, Schaubel DE, Dykstra DM, Freeman RB, Port FK, Wolfe RA. The survival benefit of liver transplantation. Am J Transplant 2005;5:307–312.
31. Imai H, Nakano Y, Kiyosawa K, Tan EM. Increasing titers and changing specificities of antinuclear antibodies in patients with chronic liver disease who develop hepatocellular carcinoma. Cancer 1993 1;71(1):26–35.
32. Ledesma F, Echevarria S, Casafont F, Lozano JL, Pons-Romero F. Natural killer cell activity in alcoholic cirrhosis: influence of nutrition. Eur J Clin Nutr 1990;44(10):733–740.
33. Pang RW, Joh JW, Johnson PJ, Monden M, Pawlik TM, Poon RT. Biology of hepatocellular carcinoma. Ann Surg Oncol 2008;15 (4):962–971.
34. Schroeder RA, Marroquin CE, Bute BP, Khuri S, Henderson WG, Kuo PC. Predictive indices of morbidity and mortality after liver resection. Ann Surg 2006;243(3):373–379.
35. Marrero JA, Fontana RJ, Barrat A, Askari F, Conjeevaram HS, Su GL, Lok AS. Prognosis of hepatocellular carcinoma: comparison of 7 staging systems in an American cohort. Hepatology 2005;41 (4):707–716.
36. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19 (3):329–338.
37. The Cancer of the Liver Italian Program (CLIP) Investigators. Prospective validation of the CLIP score: a new prognostic system for patients with cirrhosis and hepatocellular carcinoma. Hepatology 2000;31(4):840–845.
38. Kudo M, Chung H, Osaki Y. Prognostic staging system for hepatocellular carcinoma (CLIP score): its value and limitations, and a proposal for a new staging system, the Japan Integrated Staging Score (JIS score). J Gastroenterol 2003;38(3):207–215.
39. Henderson J, Sherman M, Tavill A, Abecassis M, Chejfec G, Gramlich T. AHPBA/AJCC consensus conference on staging of hepatocellular carcinoma: consensus statement. HPB (Oxford) 2003;5(4):243–250.
40. Wildi S, Pestalozzi BC, McCormack L, Clavien PA. Critical evaluation of the different staging systems for hepatocellular carcinoma. Br J Surg 2004;91(4):400–408.
41. Chung H, Kudo M, Takahashi S, Hagiwara S, Sakaguchi Y, Inoue T, Minami Y, Ueshima K, Fukunaga T. Review of current staging systems for hepatocellular carcinoma. Hepatol Res 2007;37(Suppl 2):S210–S215.
42. Minagawa M, Ikai I, Matsuyama Y, Yamaoka Y, Makuuchi M. Staging of hepatocellular carcinoma: assessment of the Japanese TNM and AJCC/UICC TNM systems in a cohort of 13,772 patients in Japan. Ann Surg 2007;245(6):909–922.
43. Cho CS, Gonen M, Shia J, Kattan MW, Klimstra DS, Jarnagin WR, D'Angelica MI, Blumgart LH, DeMatteo RP. A novel prognostic nomogram is more accurate than conventional staging systems for predicting survival after resection of hepatocellular carcinoma. J Am Coll Surg 2008;206(2):281–291.

J Gastrointest Surg (2009) 13:2276–2283
DOI 10.1007/s11605-009-0993-5

ORIGINAL ARTICLE

Laparoscopic versus Open Liver Resection: A Matched-Pair Case Control Study

Kaori Ito · Hiromichi Ito · Chandrakanth Are · Peter J. Allen · Yuman Fong · Ronald P. DeMatteo · William R. Jarnagin · Michael I. D'Angelica

Received: 30 May 2009 / Accepted: 10 August 2009 / Published online: 2 September 2009

Abstract
Background Laparoscopic liver resection (LLR) has become an increasingly popular operation; however, its theoretical benefits remain unproven. The aim of this study was to conduct a comparative outcome study between LLR and matched-pair open liver resections (OLR).
Methods Sixty five patients underwent attempted LLR from 1998 through 2008; 52 of which were completed laparoscopically. Patients who underwent OLR prior to 1998 were matched to laparoscopic cases for demographics, comorbidities, diagnosis, tumor characteristics, procedure, and background liver. Perioperative and oncologic outcomes were compared between the two groups. Analyses were performed excluding and including conversion cases.
Results Characteristics were comparable between both groups. LLR was associated with significant reductions in estimated blood loss, frequency of transfusion, frequency of Pringle maneuver, postoperative morbidity, time to recovery, length of hospital stay, and incidence of incisional hernia. For patients with malignant tumors, there were no positive surgical margins or local recurrence in either group and the overall pattern of recurrence was similar.
Conclusion For well-selected patients, LLR is a feasible operation that does not compromise operative or oncologic outcomes. While LLR was associated with some benefits, these can only be definitively proven in a randomized controlled trial.

Keywords Laparoscopic liver resection · Minimal invasive surgery · Case control study

Abbreviations

LLR	Laparoscopic liver resection
OLR	Open liver resection
EBL	Estimated blood loss
CVP	Central venous pressure
HALLR	Hand-assisted laparoscopic liver resection

Introduction

Therapeutic laparoscopy has revolutionized general surgery with many operations now routinely performed (cholecystectomy, Nissen fundoplication, bariatric surgery, colectomy, etc.). Laparoscopic liver resection (LLR) has been slow to develop due to its technically challenging nature (retraction, instruments to transect parenchyma, control of vessels, etc.). Due to improvements in technology and increasing surgeon's experience, LLR has recently in-

Author contributions
Conception and design: K. Ito, D'Angelica
Acquisition of data: K. Ito, Are
Analysis and interpretation of data: K. Ito, H. Ito, D'Angelica
Drafting of the manuscript: K. Ito, Are, D'Angelica
Critical revision of the manuscript: D'Angelica, H. Ito, Allen, Fong, DeMatteo, Jarnagin
Statistical expertise: K. Ito, H. Ito
Supervision: D'Angelica

This study was presented at the 24th Annual SSAT Research Conference on May 30th, 2009, Chicago, IL and at the 50th Annual SSAT Meeting on June 2, 2009, Chicago, IL.

K. Ito · H. Ito · P. J. Allen · Y. Fong · R. P. DeMatteo · W. R. Jarnagin · M. I. D'Angelica (✉)
Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue,
New York, NY 10065, USA
e-mail: dangelim@mskcc.org

C. Are
Surgical Oncology, University of Nebraska Medical Center, Omaha, Nebraska

creased in popularity. We published the results of our initial experience with hand-assisted LLR and suggested the safety of this approach for selected patients in 2000.[1]

Since no randomized trials have been published to date, the benefits of LLR are often assumed but remain unproven. In 2007, a meta-analysis based on eight non-randomized studies demonstrated the feasibility of LLR compared to open liver resection (OLR).[2–10] Many other studies have been published; however, these were limited by small sample size and plagued by selection bias as most LLR were done in small peripheral tumors. Case control studies typically control for the type of resection along with tumor size and number; however, they fail to control for the accessibility and location of tumors (inaccessible segments, proximity to major vessels) or histopathology of background liver.[11–18] Therefore, we conducted this study to update our experience and perform a comparative analysis. OLR patients were individually matched to LLR patients for demographics, diagnosis, tumor characteristics (size, number, and location), histopathology of background liver, and extent of resection (type of procedures and number of segment resected) to assess the potential benefit of LLR.

Materials and Methods

Subjects

The study was approved by the Institutional Review Board. In general, LLR was restricted to patients in whom tumors were free of major vessels, in accessible segments of the liver, and amenable to R0 resection with a resection of ≤2 segments. Sixty five patients underwent attempted LLR from 1998 through 2008, 80% of whom were completed laparoscopically. Cyst fenestrations were not included in this study. Matched-pair control patients were selected from 238 patients who underwent OLR prior to the laparoscopic era (1995–1998). We excluded OLR patients with concurrent extrahepatic procedures and resection of more than two segments. Candidates for control were matched to LLR cases for age, gender, comorbidities, body mass index, pathological diagnosis, size and number of tumors, histopathology of background liver, location of tumors (the segment in which tumors were located and the proximity to major vessels), and type of procedures (wedge vs segmental resection and number of resections). First, tumor pathological diagnosis, number, and size were matched. During this process, OLR patients who had tumors close to the major vessels were excluded from candidates. After the first step of the selection, the segments in which tumors were located and type of procedure were matched. If we could not find OLR candidates with tumors in exactly the same segments, patients with tumors in neighbor segments were selected. Among these candidates, OLR patients whose histopathology of background liver was different from a LLR patient were excluded. Then an OLR candidate who was best matched for demographics and comorbidity to an LLR patient was selected. Through the selection process, the investigators were blinded to outcome data. Peri- and postoperative outcomes were compared between the LLR group (n=65) and the matched-pair OLR group (n=65).

Postoperative complications were recorded prospectively into a departmental database and graded in severity using a score of 1 to 5, as described previously.[19] In this grading system, grade 1 complications are those requiring minor interventions such as oral antibiotics, bowel rest, or basic monitoring. Grade 2 complications are those requiring moderate interventions such as intravenous medication, total parenteral nutrition, prolonged tube feeding, or chest tube insertion. Grade 3 complications are those requiring hospital readmission, surgical, or radiologic interventions. Grade 4 complications are those producing chronic disability, organ resection, or enteral diversion. Grade 5 complications are those resulting in death.

Operative procedures, pathological diagnosis, radiology findings (tumor location and vessel proximity), and postoperative course (time to recovery and length of hospital stay) were obtained from a prospective data base with additional retrospective medical record review. Comparisons between LLR and OLR groups were performed in two different ways. An intent-to-treat analysis compared LLR including conversion cases (n=65) to matched-pair OLR cases (n=65). A separate analysis compared LLR cases excluding conversion (n=52) to matched-pair OLR (n=52).

Operative Procedure

Our general approach to LLR has been described previously.[1] The patient is placed in the supine position. Central lines for central venous pressure (CVP) monitoring were not routinely placed as measurement of the CVP can be unreliable with pneumoperitoneum. Some patients were placed into the low lithotomy position to allow assistants to stand between the patients legs. Some patients with right-sided tumors were positioned with the right side lifted up by a cushion. An initial 12-mm port is placed to gain access to the abdomen and establish pneumoperitoneum that is maintained at 15 mm Hg pressure. Additional ports are placed based on the body habitus, position of the tumor, degree of adhesions, location, and size of tumor. When utilized, the hand port is generally placed ipsilateral to the tumor with two to three additional ports placed contralaterally in the line of

transection. In patients in whom a hand port is not utilized, three to five ports are placed according to the location of the tumor. All ports are placed to obtain triangulation towards the line of transection. A thorough diagnostic laparoscopy is performed to exclude the presence of extra hepatic disease. Laparoscopic ultrasound is utilized to confirm the extent of liver disease and to establish and guide adequate margins. In general, the parenchyma is transected with an ultrasonic dissector and major inflow pedicle and venous branches are divided with endovascular staplers. Hemostasis is obtained with the laparoscopic argon beam coagulator.

Statistical Analysis

Categorical variables are summarized using proportions and continuous variables are presented as median and range. Comparison between groups was performed using the chi-square test or Fisher's exact test for categorical variables and the Mann Whitney *U* test for continuous variables. Kaplan–Meier and log-rank statistics were used for survival analyses. Statistical significance was defined as $p < 0.05$. All analyses were performed using SPSS 16.0 (SPSS, Chicago, IL, USA).

Table 1 Comparison of Demographics and Tumor Characteristics between Laparoscopic Liver Resection (LLR) Group versus Matched-Pair Open Liver Resection (OLR) Group

	LLR including conversion (n=65)				Matched-pair OLR (n=65)				p value
	Median	Range	*N*	%	Median	Range	*N*	%	
Demographics									
Age, years	61	21–87			64	27–80			0.572
Male			23	35.4			29	44.6	0.283
Comorbidity, overall			29	44.6			23	35.4	0.283
DM			11	16.9			5	7.7	0.109
HTN			21	32.3			16	24.6	0.331
IHD			2	3.1			4	6.2	0.403
CVA			2	3.1			0	0.0	0.154
COPD			7	10.8			5	7.7	0.545
Hepatitis			8	12.3			9	13.8	0.795
Cirrhosis			2	3.1			2	3.1	1.000
Alcohol abuse			1	1.5			0	0.0	0.339
History of abdominal surgery			26	40.0			28	43.1	0.611
BMI	24.7	18.1–39.9 0.0			25.0	18.0–39.0 0.0			0.234
Characteristics of tumors									
Size, cm	3.3	0.4–14.4			3.4	0.9–13.0			0.215
Number	1	1–6			1	1–3			0.807
Pathology									
Benign			28	43.1			18	27.7	0.067
Malignancy			37	56.9			47	72.3	0.067
Primary			12	18.5			15	23.1	0.517
Metastatic			25	38.5			32	49.2	0.517
Background liver histology									
Chronic hepatitis			3	4.6			1	1.5	0.310
Cirrhosis			5	7.7			8	12.3	0.380
Portal fibrosis			4	6.2			3	4.6	0.698
Steatosis			13	20.0			7	10.8	0.145
Inflammation			5	7.7			4	6.2	0.730
Cholestasis			1	1.5			2	3.1	0.559
Unremarkable			43	66.2			41	63.1	0.714

DM diabetes mellitus, *HTN* hypertension, *IHD* ischemic heart disease, *CVA* cerebrovascular accident, *COPD* chronic pulmonary disease, *BMI* body mass index

Results

Characteristics of LLR Patients

Characteristics of LLR patients including patients who underwent complete LLR and patients who required conversion are shown in Table 1. Median follow-up was 22 months (range 0.1–106). Final pathological diagnoses included 28 benign tumors (five adenoma, six hemangioma, six focal nodular hyperplasia, and six cysts) and five tumors preoperatively suspected to be malignant but turned out to be benign (two necrotic nodules, two normal parenchyma, and one angiomyolipoma) and 37 malignant tumors (ten hepatocellular carcinoma, one intrahepatic cholangiocarcinoma, and one primary sarcoma and 25 metastatic tumors including 13 colorectal, four breast, two lung, one ovarian, three melanoma, one neuroendocrine, and one sarcoma). A hand port was utilized in 37 (56.1%) patients. The median number of ports in patients without a hand port was 3 (range 1–4) and with a hand port was 3 (2–4). Thirteen patients (20.0%) required conversion to an open procedure. Reasons for conversion were as follows: extent of tumor (n=5), adhesions (n=4), poorly defined lesions and inability to assess margins (n=2), vascular proximity (n=1), and bleeding (n=1).

LLR Including Conversion versus Matched-Pair OLR (Intent-to-Treat Analysis)

Patient demographics, tumor characteristics, and operative procedures were comparable in LLR and the matched-pair OLR groups (Tables 1 and 2). Since patients in the OLR group were selected from an older time period (before 1998) than the LLR group (1998–2008), the median follow-up time was shorter in the LLR group (median 22 months [range 0.1–106.1] vs 32.6 months [range 0.1–154.2], p=0.048). The comparison in operative outcomes between LLR with conversions versus the matched-pair OLR is shown in Table 3. Operative time was longer in the LLR group. LLR was associated with significant reductions in median estimated blood loss (EBL), frequency of transfusion, frequency of Pringle maneuver, postoperative morbidity rate including the frequency of major complications (grade 3 and 4), time to regular diet, time to oral analgesia, length of hospital stay, and incidence of incisional hernia. Readmission rates were similar between the two groups. No patients required reoperation. There were no surgical deaths in either group.

Thirty seven LLR patients with malignant tumors were compared to OLR patients matched for histology. There were no patients with a positive surgical margin or local

Table 2 Comparison of Tumor Location and Operative Procedures between LLR and Matched-Pair OLR Group

	LLR including conversion (n=65)		Matched-pair OLR (n=65)		p value
	N	%	N	%	
Operative procedures					
Wedge resection	26	40.0	28	43.1	0.859
Wedge >1	5	7.7	5	7.7	1.000
Location					
Left lobe	13	20.0	13	20.0	1.000
Right lobe	17	26.2	19	29.2	0.840
Right anterior	7	10.8	9	13.8	0.593
Posterior sector	10	15.4	10	15.4	1.000
Segmental resection	39	60.0	37	56.9	0.722
Single segmentectomy	49	75.4	47	72.3	0.690
Bisegmentectomy	16	24.6	18	27.7	0.690
Location					
II	15	23.1	12	18.5	0.517
III	20	30.8	13	20.0	0.158
IV	7	10.8	2	3.1	0.084
V	6	9.2	10	15.4	0.286
VI	6	9.2	13	20.0	0.082
VII	1	1.5	3	4.6	0.310
VIII	1	1.5	0	0.0	0.315
Left lateral sectorectomy	11	16.9	9	13.8	0.627
Right posterior sectorectomy	1	1.5	1	1.5	1.000

Table 3 Perioperative Outcomes: LLR Group versus Matched-Pair OLR

	Analysis including conversion (intent-to-treat analysis)									Analysis excluding conversion								
	LLR including conversion (n=65)				Matched-pair OLR (n=65)				p value	LLR excluding conversion (n=52)				Matched-pair OLR excluding conversion (n=52)				p value
	Median	Range	N	%	Median	Range	N	%		Median	Range	N	%	Median	Range	N	%	
Perioperative outcomes																		
OR time, min	170	50–478			138	67–378			0.006	170	50–478			140	67–378			0.019
EBL, ml	100	0–500			200	0–2,500			<0.0001	100	0–500			200	0–2,500			<0.0001
Pringle time (min)	30	15–60			22.5	3–75			0.015	31	15–60			26	3–75			0.035
Pringle performed			31	47.7			54	83.1	<0.0001			21	40.4			46	88.5	<0.0001
Transfusion performed			1	1.5			19	29.2	<0.0001			1	1.9			13	25.0	0.001
Time to regular diet, days	2	1–7			4	2–10			<0.0001	2	1–6			4	3–8			<0.0001
Time to oral analgesia, days	3	1–7			4	1–8			<0.0001	2	1–7			4	1–7			<0.0001
Length of hospital stay, days	4	1–14			6	4–15			<0.0001	4	1–14			6	4–15			<0.0001
LOS ≥7 days			16	24.6			29	44.6	0.017			8	15.4			23	44.2	0.001
Patients with complications			9	13.8			28	43.1	<0.0001			6	11.5			23	44.2	<0.0001
Complication score 3 or more			4	6.2			4	6.2	0.848			2	3.8			3	5.8	0.647
Infectious complications			7	10.8			2	3.1	0.084			3	5.8			2	3.8	0.647
Short-term complications																		
Wound infection			3	4.6			2	3.1	0.648			1	1.9			2	3.8	0.558
Ascitis leakage			1	1.5			1	1.5	1.000			1	1.9			0	0.0	0.315
Intraabdominal abscess			2	3.1			0	0.0	0.154			1	1.9			0	0.0	0.315
Ileus			5	7.7			9	13.8	0.258			1	1.9			5	9.6	0.093
Urinary tract infection			2	3.1			1	1.5	0.559			2	3.8			1	1.9	0.558
Colitis			1	1.5			1	1.5	1.000			0	0.0			1	1.9	0.315
Anemia			0	0.0			1	1.5	0.315			0	0.0			1	1.9	0.315
Hypertension			1	1.5			1	1.5	1.000			1	1.9			1	1.9	1.000
Arrythmia			0	0.0			2	3.1	0.154			0	0.0			2	3.8	0.153
Pulmonary complications			0	0.0			3	4.6	0.080			0	0.0			3	5.8	0.079
Fever			0	0.0			11	16.9	0.001			0	0.0			11	21.2	<0.0001
Seizure			1	1.5			0	0.0	0.315			1	1.9			0	0.0	0.315
Long term complications																		
Incisional hernia			0	0.0			6	9.2	0.011			0	0.0			6	11.5	0.012
Surgical deaths			0	0.0			0	0.0	NA			0	0.0			0	0.0	NA
Readmission			2	3.1			3	4.6	0.636			1	1.9			3	5.8	0.308
Reoperation			0	0.0			0	0.0	NA			0	0.0			0	0.0	NA

OR operation, *EBL* estimated blood loss, *LOS* length of hospital stay

recurrence in either group. The pattern of recurrence was similar between LLR and OLR groups. Median disease-free survival, disease-specific survival, and 3-year survival rate were not different between groups (Table 4).

Comparison between the LLR Excluding Conversion Group and Matched-Pair OLR

After exclusion of conversion cases, LLR was associated with less blood loss, less frequency of Pringle maneuver, less frequency of transfusion, less intervals to regular diet and oral analgesia, less length of hospital stay, and less morbidity (Table 3). Oncologic outcomes were also similar in both groups (Table 4).

Hand-Assisted LLR versus Pure LLR

Excluding conversions, there were 31 patients who underwent hand-assisted LLR (HALLR) and 21 patients who underwent LLR without hand assist. Compared to patients undergoing LLR without hand assist, HALLR patients had more previous abdominal surgery (61.3% vs 23.8%, $p=0.011$), higher proportion of abnormal histopathology of background liver (48.4% vs 9.5%, $p=0.006$), and more malignant tumors (67.7% vs 33.3%, $p=0.023$). Segmentectomies were more frequently performed in HALLR group (74.2% vs 33.3%, $p=0.005$). The overall morbidity rate was not different between groups (16.1% vs 4.8%, $p=0.328$). The frequency of transfusion was not different between groups (3.2% vs 0%, $p=1.000$); however, the median EBL was higher in the HALLR (100 [range 5–500] vs 50 [0–400], $p=0.038$). The median operation time (181.0 min [range 100–478] vs 141.5 min [range 50–400], $p=0.018$), time to regular diet (3 days [range 1–6] vs 2 days [range 1–4], $p<0.0001$), time to oral analgesia (3 days [range 1–6] vs 1 day [range 1–7], $p<0.0001$), and length of hospital stay (5 days [range 3–14] vs 2 days [range 1–8], $p<0.0001$) were longer in the HALLR.

Discussion

Therapeutic laparoscopy has revolutionized how many operations are performed over the last few decades. LLR, however, has been slow to develop. Hepatic resection is a complex procedure and is fraught with several limitations making laparoscopic approaches difficult. Liver parenchyma has a tendency to bleed and instrumentation has only recently made hepatic transection feasible laparoscopically. Retraction and assessing tumor and margins is also challenging compared to standard open hepatic resection. Advances in instrumentation, use of the hand port and laparoscopic ultrasound have helped overcome

Table 4 Oncologic Outcomes for Patients with Malignancy: LLR Group versus OLR Group

	Analysis including conversion (intent-to treat analysis)								Analysis excluding conversion							
	LLR for malignancy including conversion ($n=37$)				Matched-pair OLR ($n=37$)				p value	LLR for malignancy excluding conversion ($n=28$)				Matched-pair OLR ($n=28$)				p value
	Median	SD	N	%	Median	SD	N	%		Median	SD	N	%	Median	SD	N	%	
Margin positive			0	0.0			0	0.0	NA			0	0.0			0	0.0	NA
Recurrence																		
Overall			16	43.2			19	51.4	0.238			12	42.8			15	53.6	0.422
Local (at surgical margin)			0	0.0			0	0.0	NA			0	0.0			0	0.0	NA
Liver			10	27.0			13	35.1	0.45			6	21.4			10	35.7	0.237
Distant			6	16.2			6	16.2	0.916			6	21.4			5	17.9	0.737
Follow-up time	27.9	0.9–106.1			39	0.2–154.2			0.042	29.7	0.9–106.1			61.2	7.5–154.2			0.004
Median disease-free survival, months	18.4	4.7			15.9	2.2			0.486	13.3	1.8			13.9	1.4			0.389
Median disease-specific survival, months	NR				41.8	15.4			0.178	NR				57.9	47.2			0.067
3-year survival		9.4		72.3		8.8		56.2	0.178		8.6		84.4		9.1		64.3	0.067

NR not reached

many of these barriers. Experience with LLR in well-selected patients has recently increased at several centers.[3–18] We also previously published the results of our initial experience with 11 patients confirming initial feasibility in our own hands.[1]

The theoretical benefit of LLR over conventional OLR has been assessed by small retrospective case series and some non-randomized case control studies. A recent meta-analysis concluded that LLR is potentially beneficial for well-selected patients and is associated with less blood loss and earlier postoperative recovery.[2] Previously published matched-pair case control studies comparing LLR and OLR are shown in Table 5.[3,4,6,12–15] These reports are limited in that they generally contain small numbers of patients and often inadequately control for the most important technical issues related to perioperative outcomes. These studies did not generally consider the specific location of tumor or the proximity to major vessels. Patients elected for LLR tend to have tumors in favorable locations, such as peripheral portions of the liver or distant from major vessels. Matching only to the type of procedures or size/number of tumors does not eliminate the bias due to the actual location. Furthermore, the histopathology of background liver (i.e., the presence of cirrhosis, steatosis, etc.) which could influence blood loss during parenchymal transection has seldom been matched.[4,14,15] In our study, control OLR cases were matched for the location of tumors (segments in which tumors were located and the proximity to the major vessels), background liver histology in addition to the factors taken into consideration in previous studies (demographics, comorbidities, BMI, pathological diagnosis, size/number of tumors, and type of procedures).

There are several limitations to LLR, one of which is the prolonged operative time. In our study, the operative time difference, although statistically significant, was only 30 min longer (170 vs 140 min, $p=0.019$). This minimal increase in operative times is generally not clinically significant and is similar to findings reported by other authors.[9,12] Operative times for LLR may decrease with increasing experience.

The compromise in tactile feedback during laparoscopic procedures can make handling the liver parenchyma difficult. This can hinder the ability to provide adequate retraction and to obtain appropriate margins. In our study, we were able to obtain negative margins in all patients with malignancy undergoing LLR. Laparoscopic ultrasound is very useful in guiding resections to obtain adequate margins and was an integral part of our laparoscopic resections. Hand assistance is also helpful to retract the liver safely and palpate margins in selected cases.

In our study, HALLRs were performed more frequently in patients with previous abdominal surgery, abnormal histopathology of background liver, malignant tumors, and required segmentectomies more frequently than in patients who did not have hand-assisted operations. HALLR was associated with a higher EBL, longer OR time, and slower recovery than pure LLR. Since HALLRs were applied for more challenging cases, these findings do not necessarily show a disadvantage to HALLR but rather demonstrate a technique that may be helpful in dealing with more complex cases.

There were 13 conversions (20%) in our study and this rate is higher than other studies (range 0–10%).[3,11,12,18] We feel that this is because of our relatively low threshold to convert to an open case if there were any questions about safety or the oncologic adequacy of the operation. Interestingly, the associated benefits of LLR were not altered by the intent to treat analysis including the converted cases which likely reflects the large differences in outcome found between the groups.

Table 5 Matched-Pair Case Control Studies of LLR versus OLR

Author/year	*N*	Disease	Operative time, min	Blood loss, ml	Length of stay, days	Morbidity, %
Farges[6]/02	21 vs 21	Benign	177 vs 156	218 vs 285	5 vs 7*[a]	10 vs 10
Lesurtel[4]/03	18 vs 20	Mixed	202 vs 145	236 vs 429*	8 vs 10	11 vs 15
Morino[3]/03	30 vs 30	Mixed	150 vs 140	320 vs 479	6 vs 8*	7 vs 7
Belli[12]/07	23 vs 23	HCC	148 vs 125*	NA	8 vs 12*	13 vs 48*
Troisi[13]/08	20 vs 20	Benign	220 vs 241	NA	7 vs 10*	20 vs 45
Aldrighetti[14]/08	20 vs 20	Mixed	260 vs 220	165 vs 214*	5 vs 6*	10 vs 25
Polignano[15]/08	25 vs 25	Mixed	362 vs 366	135 vs 420*	7 vs 13*	12 vs 40*
Ito/09 (present series)	65 vs 65	Mixed	170 vs 138*	100 vs 200*	4 vs 6*	14 vs 43*

LLR laparoscopic liver resection, *OLR* open liver resection, *CRCLM* colorectal cancer liver metastasis, *HCC* hepatocellular carcinoma, *NA* not available

*$p<0.05$

[a] Mean

An important aspect of analyzing the potential benefit of LLR is cost effectiveness. We did not perform a cost analysis in this study; however, Polignano et al.[15] reported in their case-matched intent-to-treat analysis that LLR group was associated with fewer cost than OLR group due to earlier recovery and shorter hospital stay.

Despite extensive matching, our study is still limited by its retrospective nature and somewhat small sample size. Unmeasurable bias certainly had an impact on our outcomes and the results must be interpreted in this context. Nonetheless, this study is the largest comparative study using matched-pair controls and the extensive matching is beyond that of previous reports. The associated benefits of LLR found in this study are hypothesis generating and support the idea that LLR has significant short-term benefits. Further studies with larger numbers of patients, particularly randomized controlled trials, are required to validate the true benefit of LLR.

In summary, our data suggest that LLR in patients in whom tumors were free of major vessels, in accessible segments of the liver and amenable to R0 resection with a resection of ≤2 segments, is safe and feasible. When accounting for selection bias, the laparoscopic approach is associated with better postoperative outcomes and comparable oncologic outcomes. These results reflect operations performed by experienced liver surgeons and we feel that a high level of expertise in both open and laparoscopic liver surgery is a prerequisite for performing LLR.

Conclusion

For well-selected patients, LLR is a feasible procedure that does not compromise peri- and postoperative outcomes including early oncologic outcomes for malignancy. This study suggests that LLR is associated with a more rapid recovery as well as less intraoperative blood loss. Despite the extensive case matching, this potential benefit can only be proven in a randomized controlled trial.

References

1. Fong Y, Jarnagin W, Conlon KC et al. Hand-assisted laparoscopic liver resection: lessons from an initial experience. Arch Surg 2000;135(7):854–859.
2. Simillis C, Constantinides VA, Tekkis PP et al. Laparoscopic versus open hepatic resections for benign and malignant neoplasms—a meta-analysis. Surgery 2007;141(2):203–211.
3. Morino M, Morra I, Rosso E et al. Laparoscopic vs open hepatic resection: a comparative study. Surg Endosc 2003;17(12):1914–1918.
4. Lesurtel M, Cherqui D, Laurent A et al. Laparoscopic versus open left lateral hepatic lobectomy: a case–control study. J Am Coll Surg 2003;196(2):236–242.
5. Mala T, Edwin B, Gladhaug I et al. A comparative study of the short-term outcome following open and laparoscopic liver resection of colorectal metastases. Surg Endosc 2002;16 (7):1059–1063.
6. Farges O, Jagot P, Kirstetter P et al. Prospective assessment of the safety and benefit of laparoscopic liver resections. J Hepatobiliary Pancreat Surg 2002;9(2):242–248.
7. Buell JF, Thomas MJ, Doty TC et al. An initial experience and evolution of laparoscopic hepatic resectional surgery. Surgery 2004;136(4):804–811.
8. Kaneko H, Takagi S, Otsuka Y et al. Laparoscopic liver resection of hepatocellular carcinoma. Am J Surg 2005;189(2):190–194.
9. Laurent A, Cherqui D, Lesurtel M et al. Laparoscopic liver resection for subcapsular hepatocellular carcinoma complicating chronic liver disease. Arch Surg 2003;138(7):763–769. discussion 769.
10. Rau HG, Buttler E, Meyer G et al. Laparoscopic liver resection compared with conventional partial hepatectomy—a prospective analysis. Hepatogastroenterology 1998;45(24):2333–2338.
11. Koffron AJ, Auffenberg G, Kung R et al. Evaluation of 300 minimally invasive liver resections at a single institution: less is more. Ann Surg 2007;246(3):385–392. discussion 392–4.
12. Belli G, Fantini C, D'Agostino A et al. Laparoscopic versus open liver resection for hepatocellular carcinoma in patients with histologically proven cirrhosis: short- and middle-term results. Surg Endosc 2007;21(11):2004–2011.
13. Troisi R, Montalti R, Smeets P et al. The value of laparoscopic liver surgery for solid benign hepatic tumors. Surg Endosc 2008;22(1):38–44.
14. Aldrighetti L, Pulitano C, Catena M et al. A prospective evaluation of laparoscopic versus open left lateral hepatic sectionectomy. J Gastrointest Surg 2008;12(3):457–462.
15. Polignano FM, Quyn AJ, de Figueiredo RS et al. Laparoscopic versus open liver segmentectomy: prospective, case-matched, intention-to-treat analysis of clinical outcomes and cost effectiveness. Surg Endosc 2008;22(12):2564–2570.
16. Tsinberg M, Tellioglu G, Simpfendorfer CH et al. Comparison of laparoscopic versus open liver tumor resection: a case-controlled study. Surg Endosc 2009;23(4):847–853.
17. Cho KJ, Suk SI, Park SR et al. Arthrodesis to L5 versus S1 in long instrumentation and fusion for degenerative lumbar scoliosis. Eur Spine J 2009;18(4):531–537.
18. Lai EC, Tang CN, Ha JP et al. Laparoscopic liver resection for hepatocellular carcinoma: ten-year experience in a single center. Arch Surg 2009;144(2):143–147. discussion 148.
19. Martin RC 2nd, Jaques DP, Brennan MF et al. Achieving RO resection for locally advanced gastric cancer: is it worth the risk of multiorgan resection. J Am Coll Surg 2002;194(5):568–577.

J Gastrointest Surg (2009) 13:2284–2291
DOI 10.1007/s11605-009-0990-8

ORIGINAL ARTICLE

Surgeon Volume is Predictive of 5-Year Survival in Patients with Hepatocellular Carcinoma after Resection: A Population-Based Study

Herng-Ching Lin · Chia-Chin Lin

Received: 23 June 2009 / Accepted: 10 August 2009 / Published online: 3 September 2009

Abstract
Background and Aim No study has examined associations between physician volume or hospital volume and survival in patients with liver malignancies in the hepatitis B virus-endemic areas such as Taiwan. This study was to examine the effect of hospital and surgeon volume on 5-year survival and to determine whether hospital or surgeon volume is the stronger predictor in patients with hepatocellular carcinoma after hepatic resection in Taiwan.
Methods Using the 1997–1999 Taiwan National Health Insurance Research Database and the 1997–2004 Cause of Death Data File, we identified 2,799 patients who underwent hepatic resection and 1,836 deaths during the 5-year follow-up period. The Cox proportional hazard regressions were performed to adjust for patient demographics, comorbidity, physician, and hospital characteristics when assessing the association of hospital and surgeon volume with 5-year survival.
Results When we examined the effect of physician and hospital volumes separately, both physician and hospital volumes significantly predicted 5-year survival after adjusting for characteristics of patient, surgeon, and hospital. However, after we adjusted for characteristics of physician and hospital, only physician volume remained a significant predictor of the 5-year survival.
Conclusions Physician volume is a stronger predictor of 5-year survival in hepatocellular carcinoma patients receiving hepatic resection.

Keywords Hepatocellular carcinoma · Survival · Hospital volume · Physician volume · Taiwan

Introduction

Hepatocellular carcinoma (HCC) is the most common cancer in Taiwan in terms of both incidence and mortality. HCC has been the second leading cause of cancer death in Taiwan.[1] The high-risk group for HCC in Taiwan includes patients chronically infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) and liver cirrhosis or a family history of HCC, HBV, or HCV chronic infections, which are the two major etiologies for HCC in Taiwan.[2] The last three decades has seen remarkable advances in hepatic surgery.[3] Hepatic surgeries are now a safe and effective therapy and one of the curative therapies for liver cancer.[4,5]

One of the most important issues of surgical oncology is to identify prognostic factors that influence the length of survival for cancer patients. Associations between hospital or physician volume and patient outcomes have been established for many surgical and other invasive procedures, with lower mortality among patients treated at hospitals or by physicians with higher procedural volumes.[6–8] Improved overall long-term survival in patients with HCC has resulted in an increased number of liver resection being performed with an increasingly aggressive surgical approach.[9] However, no study has examined

H.-C. Lin
School of Health Care Administration, Taipei Medical University, Taipei, Taiwan

C.-C. Lin (✉)
School of Nursing, Taipei Medical University,
Taipei Medical University-Wan Fang Hospital,
250 Wu-Hsing Street,
Taipei 110, Taiwan
e-mail: clin@tmu.edu.tw

associations between physician volume or hospital volume and survival in patients with liver malignancies in the HBV-endemic areas such as Taiwan. Most of the hepatic resections for malignancies are performed on an elective, rather than emergent, basis. If centers with superior patient outcomes could be identified, these procedures could be regionalized as a means of providing the most efficacious and cost-effective care.[10] Identification of factors contributing to better survival will help clinicians or policy makers to develop effective strategies to improve the quality care of HCC and survival.

A rapid rise in mortality from HCC has been observed in Taiwan since 1991 in patients aged greater than 20 years. Important efforts have been made to improve the survival rates of patients with HCC. However, despite scientific advances and the implementation of measures for early HCC detection in patients at risk, patient survival has not improved during the last three decades.[11] The 5-year survival for asymptomatic small HCC is approximately 50% after surgical resection.[12] To determine whether surgeon and hospital volumes are independent predictors of 5-year survival after resection of HCC, we examined the association of both volume elements with 5-year survival in a national sample in Taiwan. We also investigated whether physician or hospital volume was more strongly associated with 5-year survival.

Materials and Methods

Database

Two databases were used in this study. First, the Taiwan National Health Insurance Research Database (NHIRD), published by the Taiwan National Health Research Institute, was used to obtain hospitalization data. The NHIRD is possibly one of the largest and most comprehensive databases; it covers 96% of the Taiwanese population of some 23 million. The NHIRD included medical claims for inpatient expenditures by admissions, details of inpatient orders, and registry for contracted medical facilities, board-certified specialists, medical personnel, and beneficiaries. One principal diagnosis and procedure based on the 'International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM)' code and up to four secondary diagnoses and procedures using ICD-9-CM codes are listed for each patient.

Second, the mortality date was obtained from the Cause of Death Data File published by Taiwan's Department of Health (DOH) covering the years 1997–2004. The Cause of Death file provides data on marital status, the date of birth and death, place of legal residence, underlying cause of death (ICD-9-CM code), and employment status. The data are believed to be very accurate and complete because of mandatory registration of all births and deaths in Taiwan. The NHIRD was linked to the Cause of Death Data File with the assistance of Taiwan's DOH.

Study Subjects

All hospitalized patients from the NHIRD covering the period 1997–1999 by a principal diagnosis of malignant neoplasm of liver and intrahepatic bile ducts (ICD-9-CM codes 155.XX) were selected as our study sample (n= 34,158). We limited the cases to those who underwent a liver lobectomy (ICD-9-CM procedure code 50.3) or partial hepatectomy (ICD-9-CM procedure code 50.22), and 3,159 cases were left. In addition, those patients who were also diagnosed with secondary and unspecified malignant neoplasm (ICD-9-CM codes 196.XX–199.XX), malignant neoplasm of intrahepatic bile ducts (ICD-9-CM code 155.1), or malignant neoplasm of liver, not specified as primary or secondary (ICD-9-CM code 155.2), were all excluded from the study sample. Ultimately, we were left with a sample of 2,799 eligible subjects with primary liver malignancy and underwent hepatectomies during the period of the study.

Five-year follow-up were subsequently undertaken in order to determine whether any of the sampled patients were dead within a 5-year period after hepatic resections. All cause mortality was used except those who died of accidents (ICD-9-CM codes E800–E869, E880–E928, and E950–E999). In total, 1,836 deaths were identified, regardless of time of occurrence, during the 5-year follow-up period.

Surgeon and Hospital Hepatectomy Volume Groups

Since unique physician and hospital identifiers are available within the NHIRD for each medical claim submitted, this enabled us to identify the same physician, or the same hospital, carrying out one or more hepatectomies during our 3-year study period. Surgeons and hospitals were sorted, in ascending order of their total volume of liver cancer resections, with the cutoff points (high, medium, and low) being determined by the volume that most closely sorted the sample patients into three groups, which were roughly equivalent in size. The sample of 2,799 patients was divided into three surgeon volume groups: ≤19 cases (hereafter referred to as low volume), 20–95 cases (medium volume), and ≥96 cases (high volume), while the three hospital volume groups were ≤87 cases (low volume), 88–298 cases (medium volume), and ≥299 cases (high volume).

Key Variables of Interest

The key dependent variable of interest was "5-year survival," with "patient" as the unit of analysis, and the key independent variables were the "hepatectomy volume groups" for both surgeons and hospitals.

The characteristics of surgeon, hospital, and patient were taken into account in our study. Surgeon characteristics included the surgeon's age (as a surrogate for practice experience) and gender; hospital characteristics included hospital ownership, hospital level, teaching status, and geographical location, with the hospital ownership variable being recorded as one of three types, "public," "private not-for-profit" and "private for-profit" hospitals. Within the hospital level variable, each hospital was classified as a medical center (with a minimum of 500 beds), a regional hospital (minimum 250 beds), or a district hospital (minimum 20 beds); hospital level can therefore be used as a proxy for both hospital size and clinical service capabilities.

Patient characteristics comprised of age, gender, severity of illness, and type of operation. Age was not linearly associated with survival and was categorized into four groups (<50, 50–64, 65–74, and >74). Since no illness severity index is currently available in Taiwan, we used a modified Charlson's index, the Deyo–Charlson index, to adjust for the patients' clinical comorbidities; the Deyo–Charlson index has been used as a means of adjusting for the higher mortality risks associated with comorbidities and has been widely used since then for risk adjustment in administrative claims datasets. Higher scores on Charlson's index indicate more illness severity. The "type of operation" comprised of partial hepatectomy and liver lobectomy.

Statistical Analysis

The SAS statistical package (SAS System for Windows, Version 8.2) was used to perform the statistical analysis of the data in this study. The distribution of characteristics of surgeon, hospital, and patient according to surgeon and hospital hepatectomy volume groups were examined by χ^2 or ANOVA test. Five-year cumulative survival estimates and survival curves were calculated using the Kaplan–Meier method and compared by means of the log-rank test by surgeon and hospital volume. Survival time was computed from the date of hepatectomy to the date of death within the 5-year follow-up period. In order to account for possible clustering effects within each surgeon or hospital panel, we used stratified Cox regression models to evaluate the contributions of surgeon and hospital volume to 5-year survival while adjusting for the characteristics of surgeon, hospital, and patient. Hazard ratios and 95% confidence intervals are presented. A two-sided p value of less than or equal to 0.05 was considered statistically significant.

Results

Table 1 describes the distribution of the characteristics of surgeons and patients by surgeon hepatectomy volume group. Hepatectomies were performed by 286 surgeons between January 1997 and December 1999, at a mean volume per surgeon of 9.8 operations. Of the total of 2,799 patients, 996 (35.6%) had undergone liver lobectomy, and the other 1,803 (64.4%) had partial hepatectomy. The surgeons in the high-volume group were more likely to be older ($p<0.001$). Patients in the low-volume group, on average, had higher Charlson Comorbidity Index Score than their counterparts in other groups ($p<0.001$).

Table 2 presents the characteristics of hospital and patients, classified by three hospital hepatectomy volume group. Hepatectomies were carried out by 90 hospitals between 1997 and 1999, at a mean volume of 31.2 resections per hospital. The vast majority of the hospitals (92.2%) fell into the low-volume group; these hospitals were generally located in the northern part of Taiwan. All hospitals in the medium- and high-volume groups are medical centers and teaching hospitals. Patients treated by surgeons in low-volume group were more likely to undergo liver lobectomies ($p<0.001$).

Figures 1 and 2 illustrate the unadjusted 5-year survival of patients by surgeon and hospital volume. The log-rank tests show that patients treated by high-volume surgeons or hospitals had significantly greater 5-year survival (both $p<0.001$).

Table 3 provides the 5-year survival rate, crude hazard ratios and adjusted hazard ratios by hospital and surgeon volume group. Five-year survival rate increased with increasing surgeon volume group; it was 33.7%, 40.8%, and 46.8% for sampled patients in low-, medium-, and high-volume groups, respectively, while the 5-year survival rate was 34.0%, 45.1%, and 43.1% for sampled patients in low-, medium-, and high-volume hospital groups, respectively. Cox proportional hazard regressions show that patients treated by low-volume surgeons had a 51.6% higher risk of death than those treated by high-volume surgeons ($p<0.001$). Similarly, the risk of death for patients receiving resections in low-volume hospitals was 1.335 times as high as the risk of their counterparts in high-volume hospitals ($p<0.001$).

After adjusting for characteristics of patient, surgeon, and hospital and clustering effects of surgeon or hospital, the relationships between 5-year survival and surgeon volume group remains; the stratified Cox regression models

Table 1 Surgeon and Patient Characteristics in Taiwan, by Surgeon Liver Cancer Resection Volume Groups, 1997–1999

Variable	Surgeon liver cancer resection volume groups												*p* value
	Low (1–19)				Medium (20–95)				High (>95)				
	Number	Percent	Mean	SD	Number	Percent	Mean	SD	Number	Percent	Mean	SD	
Surgeon characteristics (n=286)													
Total number of surgeons	263				18				5				
Liver cancer resection volume			3.5	3.8			49.3	23.5			247.0	132.5	–
Age			40.8	7.6			42.7	7.0			43.6	4.1	–
Gender													
Male	258	98.1			18	100.0			5	100.0			0.805
Female	5	1.9			–	–			–	–			
Physician age													
<40	141	53.6			8	44.4			1	20.0			0.3424
41–50	96	36.5			8	44.4			4	80.0			
>51	26	9.9			2	11.2			–	–			
Patient characteristics (n=2,799)													
Total number of patients	910				887				1,002				
Patient age													
<50	249	27.4			255	28.8			305	30.4			0.0066
50–64	304	33.4			316	35.6			369	36.8			
65–74	264	29.0			263	29.7			259	25.9			
>74	93	10.2			53	6.0			69	6.9			
Patient gender													
Male	681	74.8			695	78.3			817	81.5			0.0018
Female	229	25.2			192	21.7			185	18.5			
Charlson Comorbidity Index score													
3	457	50.2			434	48.9			58	54.7			<0.001
4	279	30.7			336	37.9			360	35.9			
5 or more	174	19.1			117	13.2			94	9.4			
Surgery type													
Lobectomy	363	39.9			291	32.8			342	34.1			0.0036
Partial hepatectomy	547	60.1			596	67.2			660	65.9			

show that adjusted risk of death for patients operated by low-volume surgeons was 41.1% higher than those by high-volume surgeons ($p<0.001$). However, hospital case volume alone is not a significant predictor of 5-year survival for hepatectomies.

Discussion

The volume–outcome relationship has been rarely explored in liver cancer. Although few studies have examined the relationship between volume and outcomes of hepatic resection for HCC in the USA, these studies examined only in-hospital mortality and examined effects of hospital volume only. These studies did not examine effects of hospital and physician volume simultaneously.[10,13,14] This is the first study using population-based data to investigate whether physician or hospital volume was more strongly associated with long-term survival of hepatic resection for HCC.

A number of studies have correlated perioperative outcome to hospital volume or physician volume for some certain types of surgical procedures, including cardiac, vascular, and general surgeries.[15–18] These volume–outcome relationships serve as the basis for the argument that high-risk procedures should be regionalized to centers of excellence.[10,19–21] However, it is relatively unknown whether long-term survival after hepatic resections may be altered by such regionalization. These data in this current study further support regionalization of high-risk

Table 2 Hospital and Patient Characteristics in Taiwan, by Hospital Liver Cancer Operation Volume Groups, 1997–1999

Variable	Hospital Liver Cancer Resection Volume Groups												*p* value
	Low (1–87)				Medium (88–298)				High (>298)				
	Number	Percent	Mean	SD	Number	Percent	Mean	SD	Number	Percent	Mean	SD	
Hospital characteristics (n=90)													
Total number of hospitals	83				5				2				
Liver cancer operation volume			11.4	18.3			173.8	75.7			495.5	111.0	
Hospital level													
Medical center	7	8.4			5	100.0			2	100.0			<0.001
Regional hospital	46	55.4			–	–			–	–			
District hospital	30	36.1			–	–			–	–			
Hospital ownership													
Public	23	27.7			4	80.0			1	50.0			0.1336
Private (not-for-profit)	36	43.4			1	20.0			1	50.0			
Private (for-profit)	24	28.9			–	–			–	–			
Hospital location													
Northern	34	41.0			1	20.0			2	100.0			0.5404
Central	21	25.3			1	20.0			–	–			
Southern	25	30.1			3	60.0			–	–			
Eastern	3	3.6			–	–			–	–			
Teaching status													
Yes	75	90.4			5	100			2	100.0			0.69096
No	8	9.6			–	–			–	–			
Patient characteristics (n=2,799)													
Total number of patients	939				869				991				
Age													
<50	264	28.1			240	27.6			305	30.8			0.0013
50–64	335	35.7			276	31.8			378	38.1			
65–74	261	27.8			273	31.4			252	25.4			
>74	79	8.4			80	9.2			56	5.7			
Gender													
Male	722	76.9			707	81.4			764	77.1			0.0345
Female	217	23.1			162	18.6			227	22.9			
Charlson Comorbidity Index score													
3	426	45.4			487	56.1			526	53.1			<0.001
4	341	36.3			268	30.8			366	36.9			
5 or more	172	18.3			114	13.1			99	10.0			

Table 2 (continued)

Variable	Hospital Liver Cancer Resection Volume Groups								*p* value
	Low (1–87)				Medium (88–298)				High (>298)				
	Number	Percent	Mean	SD	Number	Percent	Mean	SD	Number	Percent	Mean	SD	
Surgery type													<0.001
Lobectomy	413	44.0			288	33.1			295	29.8			
Partial hepatectomy	526	56.0			581	66.9			696	70.2			

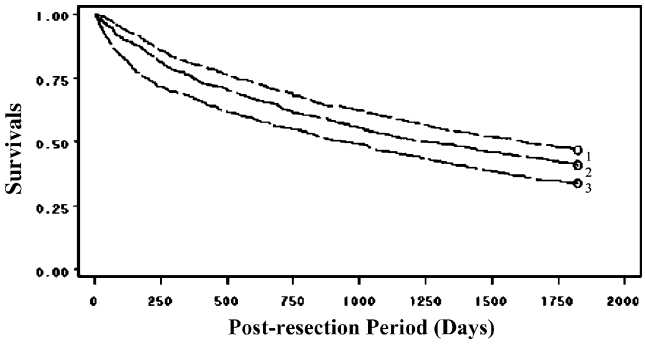


Figure 1 Liver cancer resection survival rates for patients hospitalized in Taiwan, by surgeon volume, 1997–1999. *Asterisk* Surgeon volume was defined as the number of liver cancer surgeries between the years 1997 and 1999 as follows: *1* high, *2* medium, and *3* low.

procedures, such as hepatectomy for HCC, in Taiwan. In the current study, we confirmed a relationship of long-term survival with hospital volume for liver resections using a large national database in Taiwan. If centers with superior patient outcomes, i.e., long-term survival, could be identified, the procedure of resection of HCC could be regionalized as a means of providing the most cost-effective care with optimal quality.

In this study, when we examined the effect of physician volume and hospital volume separately, both physician volume and hospital volume significantly associated with 5-year survival. However, after we adjusted for characteristics of physician and hospital, only physician volume remained a significant predictor to the 5-year survival. In those very few studies, which sought to identify the simultaneous contribution of hospital and physician volume to outcomes, they have generated similar results, i.e., physician volume is more significant than hospital volume on the relationship between volume and mortality. Halm et al.[22] conducted

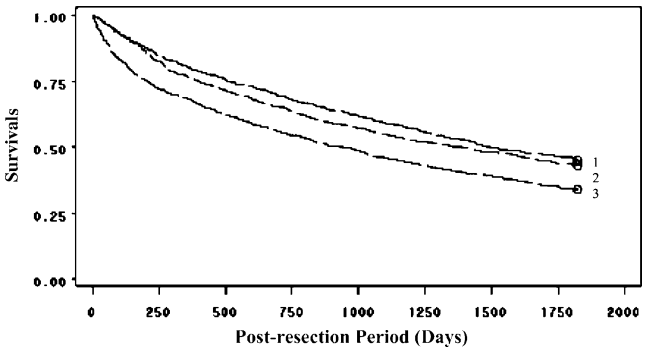


Figure 2 Liver cancer resection survival rates for patients hospitalized in Taiwan, by hospital volume, 1997–1999.*Asterisk* Hospital volume was defined as the number of liver cancer surgeries between the years 1997 and 1999 as follows: *1* high, *2* medium, and *3* low.

Table 3 Relative 5-Year Survival and Hazard Ratios by Surgeon and Hospital Liver Cancer Resection Volume Groups

Variables	Relative 5-year survival (%)	Crude hazard ratio/95% CI	Adjust hazard ratio[a]/95% CI
Surgeon hepatectomy volume			
≤19	33.7	1.516 (1.349–1.704)***	1.411 (1.232–1.617)***
20–95	40.8	1.203 (1.066–1.357)**	1.189 (0.871–1.620)
>95	46.8	1.000	1.000
Hospital hepatectomy volume			
≤87	34.0	1.335 (1.191–1.496)***	1.211 (0.832–1.751)
88–298	45.1	0.925 (0.819–1.045)	1.110 (0.834–1.452)
>298	43.1	1.000	1.000

Total sample No.=2,799

** $p<0.01$; *** $p<0.001$

[a] Odds ratios are adjusted for patient's age, gender, type of operation, the Charlson Comorbidity Index, and surgeon's age and gender and hospital characteristics including hospital ownership, hospital level, teaching status and geographical location and clustering effect of surgeon or hospital (by stratified Cox regression model)

a systematic review on volume–outcome relationship in health care and concluded that the surgeon seemed to be a more important determinant of outcomes than hospital volume in the case of coronary artery bypass surgeries, carotid endartectomy, surgery for ruptured abdominal aortic aneurysm, and surgery for colorectal cancer. Similarly, Hu et al.[23] found that hospital volume is not significantly associated with outcomes after adjusting for physician volume in male patients who underwent radical prostatectomy. Moreover, Hannan et al.[24] found that physician volume is more significant than hospital volume on the relationship between volume and mortality for coronary artery bypass surgeries, resection of abdominal aortic aneurysms, partial gastrectomies, and colectomies. Therefore, it appears that physician volume could be the mechanism that underlines the relationship between hospital volume and survival rates. More research efforts are needed to continue to clarify the impact of both hospital and surgeon volume on mortality rates simultaneously as well as the impact of the interaction of these two volume measures on mortality rates.

As documented in the literature, our results support the notion that high volume is often associated with better outcomes. Two major hypotheses have been proposed to explain these relationships.[22,25–28] First, "practice makes perfect," i.e., physicians and hospitals develop more effective skills if they treat more patients. Second is "selective referral", i.e., physicians and hospitals achieving better outcomes receive more referrals and thus accrue larger volumes. However, the relative contribution of physician versus hospital volume still remains unknown because there have been very few studies that examined both types of volume measures simultaneously.[22]

Although a compelling volume–outcome relationship was supported in our study, several limitations existed in this study. First, this study was adjusted for patient co-morbidities; nevertheless, the National Database lacked data on the severity of HCC, e.g., on MELD or Child scores, to account for differences in the severity of HCC among patients. Moreover, other variables that possibly affect patients' long-term survival rates were not comprehensively collected in the database, and therefore, we were not able to incorporate these possible confounding variables in the analyses. Lastly, this study used a cross-sectional design. We were not able to reveal the consequential relationship between volume and outcomes. Further longitudinal studies may be needed to explore whether hospitals or physicians with better outcomes would consequently acquire greater volume of patients.

In conclusion, this is the first population-based study examining associations between both physician volume and hospital volume and long-term survival in patients with liver malignancies in the HBV-endemic areas, Taiwan. We have demonstrated that higher volumes are associated with better long-term survival rates. Moreover, physician volume is more significant than hospital volume in predicting 5-year survival rates in HCC patients. If physicians or centers with superior patient outcomes could be identified, these procedures could be regionalized as a means of providing the most efficacious and cost-effective care. Furthermore, it is important to find out why some providers have substantially better outcomes than others, and the government should make systematic efforts to transfer this capability to all providers in order to improve the care and treatment outcome for all HCC patients.

References

1. Department of Health. Taiwan, ROC. Statistics of causes of death, Vol. I. http://www.doh.gov.tw/EN2006/DM/DM2_p01.aspx?class_no=390&now_fod_list_no=9256&level_no=2&doc_no=51991. Accessed August 12, 2008.
2. Chen CJ, Yu MW, Liaw YF. Epidemiological characteristics and risk factors of hepatocellular carcinoma. J Gastroenterol Hepatol 1997;12(9–10):S294–S308.
3. Fong Y, Gonen M, Rubin D, Radzyner M, Brennan MF. Long-term survival is superior after resection for cancer in high-volume centers. Ann Surg 2005;242(4):540–547.
4. Fong Y, Blumgart LH, Fortner JG, Brennan MF. Pancreatic or liver resection for malignancy is safe and effective for the elderly. Ann Surg 1995;222(4):426–437.
5. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 1999;230(3):309–321.
6. Luft HS, Garnick DW, Mark DH, McPhee SJ. Hospital Volume, Physician Volume, and Patient Outcomes. Ann Arbor, MI: Health Administrative Press, 1990.
7. Dudley RA, Johansen KL, Brand R, Rennie DJ, Milstein A. Selective referral to high-volume hospitals: estimating potentially avoidable deaths. JAMA 2000;283(9):1159–1166.
8. Gandjour A, Bannenberg A, Lauterbach KW. Threshold volumes associated with higher survival in health care: a systematic review. Med Care 2003;41(10):1129–1141.
9. Choti MA, Bowman HM, Pitt HA, Sosa JA, Sitzmann JV, Cameron JL, Gordon TA. Should hepatic resections be performed at high-volume referral centers? J Gastrointest Surg 1998;2(1):11–20.
10. Glasgow RE, Showstack JA, Katz PP, Corvera CU, Warren RS, Mulvihill SJ. The relationship between hospital volume and outcomes of hepatic resection for hepatocellular carcinoma. Arch Surg 1999;134(1):30–35.
11. Blum HE. Treatment of hepatocellular carcinoma. Best Pract Res Clin Gastroenterol 2005;19(1):129–145.
12. Lee CS, Sheu JC, Wang M, Hsu HC. Long-term outcome after surgery for asymptomatic small hepatocellular carcinoma. Br J Surg 1996;83(3):330–333.
13. Dimick JB, Cowan JA, Knol JA, Upchurch GR. Hepatic resection in the United States: indications, outcomes, and hospital procedural volumes from a nationally representative database. Arch Surg 2003;138(2):185–191.
14. Dimick JB, Pronovost PJ, Cowan JA, Lipsett PA. Postoperative complication rates after hepatic resection in Maryland hospitals. Arch Surg 2003;138(1):41–46.
15. Hannan EL, Kilburn H, Bernard H, O'Donnell JF, Lukacik G, Shields EP. Coronary artery bypass surgery: the relationship between inhospital mortality rate and surgical volume after controlling for clinical risk factors. Med Care 1991;29(11):1094–1107.
16. Khuri SF, Daley J, Henderson W, Hur K, Hossain M, Soybel D, Kizer KW, Aust JB, Bell RH, Chong V, Demakis J, Fabri PJ, Gibbs JO, Grover F, Hammermeister K, McDonald G, Passaro E, Phillips L, Scamman F, Spencer J, Stremple JF. Relation of surgical volume to outcome in eight common operations: results from the VA National Surgical Quality Improvement Program. Ann Surg 1999;230(3):414–432.
17. Steinberg EP, Tielsch JM, Schein OD, Javitt JC, Sharkey P, Cassard SD, Legro MW, Diener-West M, Bass EB, Damiano AM, et al. National study of cataract surgery outcomes. Variation in 4-month postoperative outcomes as reflected in multiple outcome measures. Ophthalmology 1994;101(6):1131–1141.
18. Lavernia CJ. Hemiarthroplasty in hip fracture care: effects of surgical volume on short-term outcome. J Arthroplasty 1998;13(7):774–778.
19. Luft HS, Bunker JP, Enthoven AC. Should operations be regionalized? The empirical relation between surgical volume and mortality. N Engl J Med 1979;301(25):1364–1369.
20. Gordon TA, Burleyson GP, Tielsch JM, Cameron JL. The effects of regionalization on cost and outcome for one general high-risk surgical procedure. Ann Surg 1995;221(1):43–49.
21. Wen HC, Tang CH, Lin HC, Tsai CS, Chen CS, Li CY. Association between surgeon and hospital volume in coronary artery bypass graft surgery outcomes: a population-based study. Ann Thorac Surg 2006;81(3):835–842.
22. Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. Ann Intern Med 2002;137(6):511–520.
23. Hu JC, Gold KF, Pashos CL, Mehta SS, Litwin MS. Role of surgeon volume in radical prostatectomy outcomes. J Clin Oncol 2003;21(3):401–405.
24. Hannan EL, O'Donnell JF, Kilburn H, Bernard HR, Yazici A. Investigation of the relationship between volume and mortality for surgical procedures performed in New York State hospitals. JAMA 1989;262(4):503–510.
25. Luft HS. The relation between surgical volume and mortality: an exploration of causal factors and alternative models. Med Care 1980;18(9):940–959.
26. Luft HS, Hunt SS, Maerki SC. The volume–outcome relationship: practice-makes-perfect or selective-referral patterns? Health Serv Res 1987;22(2):157–182.
27. Flood AB, Scott WR, Ewy W. Does practice make perfect? Part I: the relation between hospital volume and outcomes for selected diagnostic categories. Med Care 1984;22(2):98–114.
28. Flood AB, Scott WR, Ewy W. Does practice make perfect? Part II: the relation between volume and outcomes and other hospital characteristics. Med Care 1984;22(2):115–125.

J Gastrointest Surg (2009) 13:2292–2301
DOI 10.1007/s11605-009-0988-2

ORIGINAL ARTICLE

The National Mortality Burden and Significant Factors Associated with Open and Laparoscopic Cholecystectomy: 1997–2006

James P. Dolan · Brian S. Diggs · Brett C. Sheppard · John G. Hunter

Received: 4 June 2009 / Accepted: 4 August 2009 / Published online: 2 September 2009

Abstract
Introduction This study aims to determine the mortality rate and significant factors associated with laparoscopic (LC) and open cholecystectomies (OC) over a 10-year period.
Methods Using the Nationwide Inpatient Sample, we analyzed data for both LC and OC between 1997 and 2006. Cholecystectomies performed as part of another primary procedure were excluded. Using procedure-specific codes, we calculated annual national volumes for both open and laparoscopic cholecystectomies for the time period under review and the associated in-hospital mortality following both of these procedures. Using logistic regression modeling, we then analyzed selected patient and institutional characteristics to determine if a significant association existed between these factors and in-hospital mortality.
Results There was a 16% increase in the volume of LC and a corresponding decrease in open procedures over the 10 years under review. In 2006, 12% of cholecystectomies were still performed using an open approach and the associated mortality remained significantly higher than that seen with LC. Overall, after adjusting for patient and hospital characteristics, the mortality for OC was higher than that for LC (OR 4.57; 95% CI, 4.37–4.79, $p<0.001$). Age (>60 years), male gender, non-elective admission, admission source, and a primary diagnosis other than cholelithiasis were all independently associated with increased mortality. The average mortality rate associated with conversion from LC to OC was found to be 0.7%.
Conclusions These data indicate an increase in the proportion LCs performed over the years under study with a decrease in the proportion of OCs. However, OCs remain associated with a significant mortality burden when compared with the laparoscopic approach.

Keywords Open cholecystectomy · Laparoscopic cholecystectomy · Mortality · Cholecystectomy mortality · Mortality factors

Presented at the 50th annual meeting of the Society for Surgery of the Alimentary Tract, Chicago, Illinois, United States, 30 May–4 June 2009.

J. P. Dolan (✉) · B. S. Diggs · B. C. Sheppard · J. G. Hunter
Department of Surgery, Division of General Surgery,
Oregon Health and Science University,
3181 SW Sam Jackson Park Road, L223A,
Portland, OR 97239, USA
e-mail: dolanj@ohsu.edu

Introduction

Over the course of the last two decades, laparoscopic cholecystectomy (LC) has replaced open cholecystectomy (OC) as the standard operation to treat symptomatic gallbladder disease. Through refinement of techniques and instrumentation, the laparoscopic approach has evolved to offer significant reduction in pain and postoperative recovery time with low rates of morbidity and mortality.[1–3] The alternative open operation is now reserved for instances where the laparoscopic approach is not possible or where there is a need to convert from the laparoscopic approach due to severity of disease or complication. A large number of cholecystectomies are performed annually[4–6] and one recent report, investigating quality improvement in general surgery, found that inpatient cholecystectomy ranked third

and outpatient cholecystectomy ranked 22nd in contributing to morbidity and mortality among the 36 surgical procedures examined.[7] Indeed, there are numerous reports of high morbidity and mortality in certain groups undergoing OC[8] and low mortality and morbidity in those undergoing LC or partial LC,[9–11] even in the developing world,[12] but the magnitude of this mortality burden has not been fully reported over a sustained period of time. In addition, factors associated with mortality after either LC or OC have not been investigated under the same circumstances.

In a previous investigation on bile duct injury after LC, we noted that the percentage of cholecystectomies performed laparoscopically had increased between 1991 and 2000 but that the mortality rate had remained consistently low (ranging between 0.33% and 0.58%) over this period.[6] In this current study, we have returned to this issue and report our findings on the mortality associated with both OC and LC in the United States during the years 1997 to 2006 as derived from the largest all-payer administrative database currently available in this country. In addition, we also determined the major factors associated with mortality in patients undergoing both of these procedures.

Materials and Methods

Study Population

For this retrospective study, the population was drawn from discharge data contained in the Nationwide Inpatient Sample (NIS) compiled by the Healthcare Cost and Utilization Project (HCUP, Agency for Healthcare Research and Quality, Rockville, MD) for the years 1997 through 2006.[13] This sample represents the all-payer inpatient experience of a 20% stratified probability sample of American non-military, non-federal hospitals for each year under consideration. Each individual discharge abstract for this population of patients is statistically weighted to provide a national representation of diagnoses and procedure volume.

Data Extraction and Factors Impacting Analysis and Modeling

Using the appropriate procedure codes as defined by the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), patients undergoing open cholecystectomy (51.22), laparoscopic cholecystectomy (51.23), or laparoscopic partial cholecystectomy (51.24), for each year under review, were identified and extracted from the overall dataset. Specific ICD-9 coding for open cholecystectomy has been present in the database since its inception and was modified in October 1991 while the codes for laparoscopic cholecystectomy and laparoscopic partial cholecystectomy were introduced in October 1991 and October 1996, respectively. The specific ICD-9 coding for a case converted from a laparoscopic to an open procedure (converted) was introduced in October 1997 and was modified again in October 2003. Since no conversion data is available for the first three quarters of 1997, we do recognize that conversion rates for 1997 are underestimated. Cholecystectomies associated with pancreatic or biliary tract neoplasms, chronic pancreatitis, or liver transplantation were excluded. Patient comorbidities were analyzed individually using a subset of the comprehensive list defined and developed by Elixhauser for administrative data analysis.[14] Comorbidities present in at least 5% of cases and deemed clinically relevant were included in our analysis. The comorbidities of diabetes mellitus, renal failure, and liver disease did occur in less than 5% of our cohort but were included in the analysis due to their known association with adverse outcomes during or after surgical procedures.

For the purpose of our analysis, converted cases were considered to be part of our LC cohort on an intent-to-treat basis. Converted cases were analyzed separately in a subgroup univariate analysis of LC patients that compared these groups on how the procedure was completed (laparoscopically versus converted). Subsequently, conversion was examined as an independent variable within our multivariate model for LC.

Specific variables selected for univariate analysis were chosen based on our determination of their importance in contributing to the outcome of interest (death) after LC or OC. We did not include race as a variable for univariate or multivariate analysis due to our finding that 25% of all case abstracts in our study population were missing a race designation. This was due to several states (nine of 38 states in 2006) not reporting race data in any of their patient abstracts.

Data Analysis

Data extraction for the primary (OC, LC, and converted) procedures as well as calculation of national averages and statistical analysis was performed using SAS/STAT Software (SAS Institute Inc, Cary, NC; Release 9.1). For univariate analysis continuous variables were compared using the Mann–Whitney U test to compare medians given the nonparametric distribution of the data. Categorical variables were compared using the Chi square test to compare proportions. Variables found to be significant ($p<0.05$) under univariate analysis, or deemed clinically relevant, were included in a multivariate logistic regression model in order to examine the relationship between these variables and the outcome of interest (death). Separate models were created for all cholecystectomies, OC, LC, and for comorbidities.

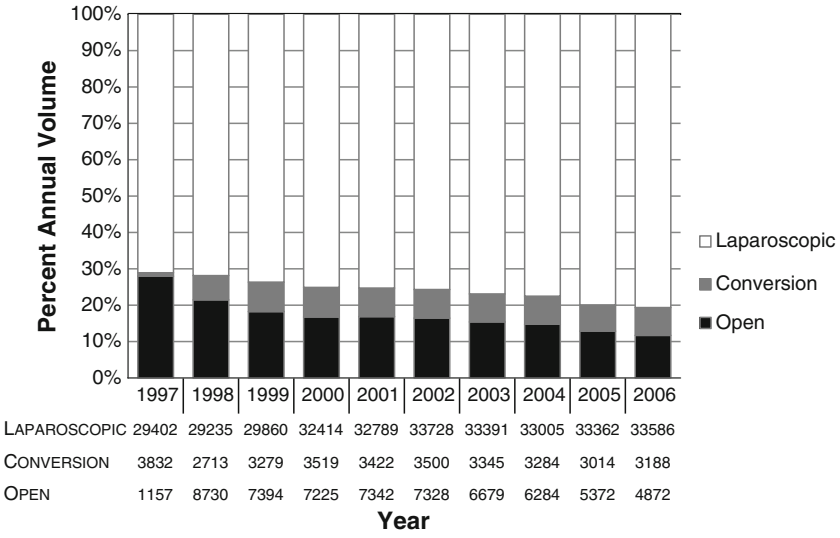


Figure 1 NIS-derived annual percent and numeric inpatient cholecystectomy volume: 1997–2006.

Results

For the study period, a total of 75,984,572 weighted NIS inpatient abstracts were surveyed in order to derive the study cohort of 4,232,329 cholecystectomy procedures. Of these cases, 3,504,248 were LCs and 728,081 were OCs. Within the LC group, 296,503 cases were converted.

There was a 16% increase in the proportion of LC and a corresponding decrease in open procedures over the 10 years under review (Fig. 1). The average conversion rate was 8.34% over the study period (range 1.29% in 1997 to 9.9% in 1999). If 1997 data is excluded, given that only last quarter conversion data was available for that particular year, the average conversion rate was 9.13%. In 1997, 297,855 cholecystectomies were attempted laparoscopically, representing 72% of all cholecystectomies performed during that year. For 2006, 367,748 LCs were attempted representing 88% of all cholecystectomies for that year. LC was associated with a low mortality (mean 0.52%, range 0.45–0.58%) over the study period while OC was associated with a significantly higher rate (mean 4.9%; range 4.04–5.65%). Conversion from LC to OC was associated with a mean mortality of 0.65% (range 0.50–0.80%; Fig. 2). If data from 1997 is excluded, the average mortality for LC, OC, and converted are 0.53%, 5.11%, and 0.66%, respectively.

Univariate analysis comparing the OC and LC groups are shown in Table 1. There was a statistical difference between the two groups in regard to all patient, institutional, and outcome characteristic that were chosen for comparison. For the OC group, larger clinical percentage differences were seen in the categories of age, sex, admission type and source, presence or absence of cholecystitis, primary payer, and disposition. A subset analysis of LC (intent-to-treat) cases was also performed in order to compare LC and converted cases (Table 2). Again, there was a statistical difference between the two groups in regard to all patient, institutional, and outcome characteristic examined. Compared to the OC group, large clinical percentage differences was only seen in the categories of age, sex, and primary payer.

The OC, LC, and conversion groups were further subjected to a multivariate logistic regression model

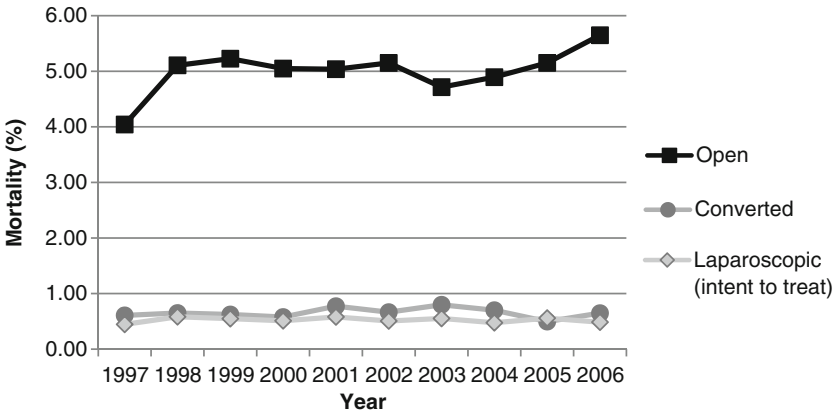


Figure 2 NIS-derived annual percent inpatient mortality following cholecystectomy: 1997–2006.

Table 1 Comparison of Patient, Institutional and Outcome Characteristics Between Patients Who Underwent OC and LC Between 1997 and 2006, NIS

	OC	LC[a]	*p* value	All cases
N[b] (%)	728,081 (12)	3,504,249 (88)		4,232,329 (100)
Patient characteristics				
Age			<0.001	
0–10 years	0.4%	0.1%		0.2%
11–20 years	1.3%	3.5%		3.2%
21–40 years	14.6%	27.2%		25.0%
41–60 years	28.2%	31.9%		31.3%
61–80 years	41.4%	29.5%		31.6%
>81 years	14.0%	7.7%		8.8%
Sex			<0.001	
Female	59.0%	70.0%		68.0%
Male	41.0%	30.0%		32.0%
Admission type			<0.001	
Elective	41.0%	25.7%		28.4%
Non-elective	52.4%	68.1%		65.4%
Unknown	6.6%	6.2%		6.3%
Admission source			<0.001	
Routine	57.2%	42.5%		45.0%
Other health facility	3.3%	2.2%		2.4%
Emergency department	36.9%	53.3%		50.5%
Unknown	2.6%	2.0%		2.1%
Primary diagnosis			<0.001	
Cholecystitis	37.7%	69.5%		64.0%
Cholelithiasis	1.3%	3.1%		2.8%
Other	61.0%	27.4%		33.2%
Primary payer			<0.001	
Medicare	48.4%	31.5%		35.3%
Medicaid	8.0%	11.2%		10.7%
Private insurance	36.1%	46.0%		44.3%
Self-pay	4.1%	6.3%		5.9%
No charge	0.3%	0.5%		0.5%
Other	2.7%	3.1%		3.0%
ZIP-based income level[c]			<0.001	
Lowest quartile	17.1%	16.5%		16.6%
Second lowest quartile	27.1%	26.3%		26.1%
Second highest quartile	24.6%	24.8%		24.8%
Highest quartile	28.1%	29.9%		29.6%
Institution characteristics				
Location/teaching status of facility			<0.001	
Rural	16.4%	17.6%		17.4%
Urban/non-teaching	41.3%	47.9%		46.8%
Urban/teaching	42.2%	34.4%		35.7%
Outcome characteristics				
LOS[d]	7 (4–11)	3 (2–5)	<0.001	3 (2–6)
Disposition			<0.001	
Routine (to home)	69.9%	91.4%		87.7%
Transfer to short-term hospital	1.0%	0.5%		0.6%
Transfer, other (including SNF)	13.8%	4.1%		5.8%

Table 1 (continued)

	OC	LC[a]	*p* value	All cases
Home health care	10.1%	3.3%		4.5%
Against medical advice	0.1%	0.1%		0.1%
Died during hospitalization	4.9%	0.5%		1.3%

LOS length of stay, *SNF* skilled nursing facility

[a] Category also includes converted cases on intent to treat basis

[b] National estimate based on NIS statistical weighting

[c] Quartiles are calculated and indexed annually

[d] Values are median with interquartile range

(Table 3). All groups differed significantly in regard to almost all variables examined. There was a significant overall risk of dying for patients undergoing OC (OR 4.57; 95% CI, 4.37–4.79; $p<0.001$) when all variables and comorbidities were controlled for. Older age was also an independent risk factor for mortality after either OC or LC. Patients in the 61–80 years age group and in the over 81 years age group who underwent LC had an even greater risk of dying (OR 2.34; 95% CI, 2.04–2.69; $p<0.001$ and OR 4.91; 95% CI, 4.21–5.73; $p<0.001$, respectively) than those comparable individuals undergoing OC (OR 1.97; 95% CI, 1.79–2.17; $p<0.001$ and OR 3.25; 95% CI, 2.91–3.64; $p<0.001$, respectively). Conversion did not significantly increase mortality risk (OR 1.12; 95% CI, 1.00–1.25; $p=0.05$). Other variables predictive of mortality after cholecystectomy included, transfer from another health facility for patients who had undergone OC and a primary diagnoses other than cholecystitis for both OC and LC groups. Primary payer had the largest impact on the LC group of patients.

The influence of comorbidities on mortality following cholecystectomy was examined using the multivariate regression models shown in Table 4. Liver disease, renal failure, congestive heart failure, and fluid and electrolyte disorders all had twofold or greater risk of morality for both OC and LC. Renal failure imparted the largest risk of dying (OR 3.86; 95% CI, 3.52–4.25; $p<0.001$ for OC and OR 4.96; 95% CI, 4.45–5.53; $p<0.001$ for LC).

Discussion

Gallbladder disease continues to have a major impact in western populations and its surgical treatment accounts for a large proportion of annual operations done in developed countries. In this population-based study we find that US national, nonfederal inpatient cholecystectomy volume has remained high over our study period while, as previously reported,[5,6] the laparoscopic approach continued to account for an increasing proportion of the annual operative volume. Schilling and Dimick, using data derived from the American College of Surgeons' National Surgery Quality Improvement Program (ACS-NSQIP),[7] have recently reported that inpatient cholecystectomy has an adverse event rate of 7.5%, third highest of the 36 procedures they examined. Our reported mortality rate after LC is comparable to that found by others,[3,15–17] but our reported mortality is higher for OC than that previously reported by other investigators using data derived from different patient samples.[15,18] Although it is clear that a number of factors also influence mortality,[8,16,19–21] our findings may be explained by the fact that they are aggregate data derived from a large dataset over a long period of time.

In comparing our OC and LC groups (Table 1) it is apparent that a larger proportion of the OC group was older than 61 years and male. While this is in keeping with the patterns seen by others,[15,19] we have also noted that a larger proportion of our patients were admitted on an elective basis from a routine source and with a diagnosis other than cholecystitis. Taken together, this suggests that these patients were admitted for another diagnosis or illness and were diagnosed with, or developed, gallbladder disease during the course of their hospitalization. A review of our dataset shows that 15% of our OC patients had chronic pulmonary disease, 14% had diabetes, 35% had hypertension, and 19% had fluid and electrolyte disorders as additional comorbidities. These patients were also significantly different from those patients undergoing LC ($p<0.001$, data not shown). Of these comorbidities, diabetes has been most closely associated with the development of gallbladder disease.[22,23] However, the NIS database is limited in clinical depth which makes it impossible to fully investigate the relationship between diabetes or any other admission diagnoses and the subsequent development of gallbladder disease over the course of a patient's hospitalization. A large proportion of our OC group were Medicare patients, as would be expected of this older age group, and

Table 2 Comparison of Patient, Institutional and Outcome Characteristics Between Patients Who Underwent Successful LC and Those Who Were Converted Between 1997 and 2006, NIS

	LC	Converted	*p* value
N[a] (%)	3,207,745 (91.5)	296,503 (8.5)	
Patient characteristics			
Age			<0.001
0–10 years	0.1%	0.1%	
11–20 years	3.7%	1.3%	
21–40 years	28.2%	16.4%	
41–60 years	31.8%	33.0%	
61–80 years	28.7%	38.8%	
>81 years	7.4%	10.5%	
Sex			<0.001
Female	71.0%	55.0%	
Male	29.0%	45.0%	
Admission type			<0.001
Elective	25.2%	31.5%	
Non-elective	68.6%	62.3%	
Unknown	6.2%	6.2%	
Admission source			<0.001
Routine	41.8%	49.2%	
Other health facility	2.2%	3.1%	
Emergency department	54.0%	45.6%	
Unknown	2.0%	2.1%	
Primary diagnosis			<0.001
Cholecystitis	68.8%	77.3%	
Cholelithiasis	3.1%	2.1%	
Other	28.1%	20.6%	
Primary payer			<0.001
Medicare	31.7%	42.0%	
Medicaid	11.4%	9.1%	
Private insurance	46.7%	39.1%	
Self-pay	6.3%	5.7%	
No charge	0.5%	0.6%	
Other	3.1%	3.2%	
ZIP-based income level[b]			<0.001
Lowest quartile	16.6%	16.1%	
Second lowest quartile	26.0%	27.2%	
Second highest quartile	24.7%	26.4%	
Highest quartile	30.1%	28.0%	
Institution characteristics			
Location/teaching status of facility			<0.001
Rural	17.5%	19.0%	
Urban/non-teaching	48.3%	43.3%	
Urban/teaching	34.1%	37.6%	
Outcome characteristics			
LOS[c]	3 (2–5)	5 (4–8)	<0.001
Disposition			<0.001
Routine (to home)	92.2%	83.4%	
Transfer to short-term hospital	0.5%	0.7%	
Transfer, other (including SNF)	3.8%	7.4%	

Table 2 (continued)

	LC	Converted	*p* value
Home health care	2.9%	7.7%	
Against medical advice	0.1%	0.1%	
Died during hospitalization	0.5%	0.7%	

LOS length of stay, *SNF* skilled nursing facility

[a] Category also includes converted cases on intent to treat basis

[a] National estimate based on NIS statistical weighting

[b] Quartiles are calculated and indexed annually

[c] Values are median with interquartile range

income level and institutional characteristics, although statistically significant, are clinically insignificant if the percentage difference between them are examined.

In comparing our LC and converted group, it is interesting to note that conversion did not impart an increase in mortality rate (Table 2) or increase the risk of mortality after cholecystectomy to any significant level (OR 1.12; 95% CI, 1.00–1.25; $p=0.05$). Wolf and Nijsse, have previously reported a mortality rate of 1.5% in their series of converted patients[15] and this is much higher than our findings. Their series, however, was relatively small. In our particular case, it is also interesting to note that the converted group shared some of the characteristics of the OC group, particularly in regard to age and sex (Table 2). The association between age and risk of conversion has been well established and it is usually high. Timmons and Chandio, as an example, report a conversion rate of 22% in patients over 65 years old.[24] Our converted cohort did differ from the OC group in regard to mortality, LOS and the finding that 83.4% had a routine disposition as opposed to 69.9% of the former group (Table 1). Taken together, these findings suggest that the converted group represent a different population of patients distinct from the OC group. They retain many of the characteristics of the LC group and resemble the OC group only in largely being elderly male Medicare beneficiaries. The average conversion rate of 8.3% found in this investigation is comparable with that found by others [2,18,22] but is considerably lower than the 15.6% reported during the 1990s.[3]

Patients undergoing OC have over a greater than fourfold risk of dying compared to those undergoing LC (Table 3). While conversion from LC to OC does not appear to impart significant risk of dying, there are other factors that clearly do. Almost all variables examined by our regression model reached statistical significance but it is evident that some impart considerably higher mortality risk for both OC and LC. In our model, the variables with the highest overall risk of death were age, admission from another health facility, and a primary diagnoses other than cholecystitis or cholelithiasis. A number of other investigators have found that age and sex are independent risk factors for mortality after OC and LC,[15,18] but the surprising finding here is that patients in the 61–80 years age group and in the over 81 years age group who underwent LC had an even greater risk of dying than those comparable individuals undergoing OC. In 1998, Maxwell and Tyler found a 1.8% mortality following LC in patients aged 80 and older.[8] Our findings, coupled with theirs, may suggest an adverse effect of carbon dioxide insufflation on the cardiopulmonary reserve of this segment of the population but this cannot be proven within the context of the current study. The NIS database includes all skilled nursing and rehabilitation facilities within the designation of "other health facility." This may explain the increased mortality risk (overall OR 2.12; 95% CI, 1.91–2.34; $p<0.001$) associated with this variable since it may represent elderly patients being admitted from skilled nursing or rehabilitation facilities with a primary diagnoses other than cholecystitis or cholelithiasis (OR 2.97; 95% CI, 2.83–3.12; $p<0.001$). Finally, it is interesting to note that mortality risk is decreased at urban teaching and rural hospitals as compared to urban teaching facilities. While we may speculate that adverse mortality may be attributable to case complexity at teaching facilities, it is not possible to ascertain the detailed factors responsible for this within the design of this study and further suggests the need for additional investigation.

In our second multivariate analysis, we examined the influence of ten common comorbidities on in-hospital mortality following cholecystectomy. It is interesting to note that the four conditions with the highest risk (renal failure, congestive heart failure, fluid and electrolyte disorders, and liver disease) all have the highest risk manifested in the LC group over the OC group of patients. Beyond consideration of the physiological effects of a carbon dioxide pneumoperitoneum, it is difficult to explain these findings. There have been a number of studies looking at the contribution of comorbidities to the risk of death following cholecystectomy. Skies and Nguyen's sophisticated analysis, also drawn from the NIS dataset,

Table 3 Multivariate Analysis of In-hospital Mortality Following All Cholecystectomies, OC and LC Between 1997 and 2006, NIS

	All cases		OC		LC	
Variable	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Approach						
Laparoscopic	Reference					
Open	4.57 (4.37–4.79)	<0.001				
Completed						
Laparoscopic					Reference	
Converted					1.12 (1.00–1.25)	0.05
Age						
0–10 years	0.97 (0.60–1.56)	0.890	0.81 (0.49–1.35)	0.422	0.96 (0.23–3.94)	0.957
11–20 years	0.37 (0.27–0.51)	<0.001	0.62 (0.44–0.88)	0.007	0.21 (0.12–0.39)	<0.001
21–40 years	0.42 (0.37–0.47)	<0.001	0.55 (0.47–0.63)	<0.001	0.35 (0.28–0.43)	<0.001
41–60 years	Reference		Reference		Reference	
61–80 years	2.17 (2.00–2.35)	<0.001	1.97 (1.79–2.17)	<0.001	2.34 (2.04–2.69)	<0.001
>81 years	3.98 (3.62–4.36)	<0.001	3.25 (2.91–3.64)	<0.001	4.91 (4.21–5.73)	<0.001
Sex						
Male	1.28 (1.23–1.35)	<0.001	1.23 (1.18–1.30)	<0.001	1.33 (1.25–1.42)	<0.001
Female	Reference		Reference		Reference	
Admission type						
Elective	Reference		Reference		Reference	
Non-elective	1.52 (1.42–1.64)	<0.001	1.87 (1.71–2.04)	<0.001	1.10 (0.98–1.22)	0.092
Unknown	1.49 (1.34–1.66)	<0.001	1.63 (1.42–1.86)	<0.001	1.24 (1.04–1.48)	0.016
Admission source						
Routine	Reference		Reference		Reference	
Other health facility	2.12 (1.91–2.34)	<0.001	2.31 (2.04–2.62)	<0.001	1.75 (1.49–2.06)	<0.001
Emergency department	1.25 (1.18–1.33)	<0.001	1.51 (1.40–1.63)	<0.001	0.99 (0.90–1.08)	0.784
Unknown	1.42 (1.21–1.67)	<0.001	1.54 (1.27–1.87)	<0.001	1.29 (1.03–1.62)	0.027
Primary diagnosis						
Cholecystitis	Reference		Reference		Reference	
Cholelithiasis	0.89 (0.70–1.14)	0.363	1.00 (0.67–1.50)	0.981	0.80 (0.60–1.09)	0.155
Other	2.97 (2.83–3.12)	<0.001	3.66 (3.41–3.92)	<0.001	2.35 (2.19–2.52)	<0.001
Primary payer						
Medicare	1.66 (1.54–1.79)	<0.001	1.45 (1.33–1.59)	<0.001	2.01 (1.75–2.29)	<0.001
Medicaid	1.59 (1.43–1.77)	<0.001	1.42 (1.25–1.62)	<0.001	1.87 (1.57–2.23)	<0.001
Private insurance	Reference		Reference		Reference	
Self-pay	1.26 (1.07–1.47)	0.004	1.26 (1.05–1.52)	0.013	1.19 (0.90–1.58)	0.225
No charge	1.57 (1.01–2.44)	0.004	1.25 (0.71–2.20)	0.444	2.16 (1.09–4.28)	0.027
Other	1.16 (0.97–1.38)	0.103	1.10 (0.89–1.37)	0.373	1.18 (0.85–1.64)	0.324
ZIP-based income level						
Lowest quartile	0.98 (0.91–1.05)	0.583	0.96 (0.88–1.04)	0.323	0.99 (0.89–1.11)	0.907
Second lowest quartile	0.98 (0.93–1.05)	0.616	1.01 (0.94–1.08)	0.878	0.93 (0.85–1.03)	0.185
Second highest quartile	1.06 (0.99–1.12)	0.075	1.03 (0.95–1.10)	0.476	1.08 (0.98–1.19)	0.127
Highest quartile	Reference		Reference		Reference	
Location/teaching status						
Urban teaching	Reference		Reference		Reference	
Urban nonteaching	0.88 (0.83–0.93)	<0.001	0.90 (0.85–0.96)	<0.001	1.01 (0.94–1.10)	0.745
Rural	0.71 (0.66–0.77)	<0.001	0.72 (0.66–0.78)	<0.001	0.85 (0.77–0.95)	0.003

Association between each variable and the outcome of interest (death) was modeled using stepwise logistic regression (backwards variable elimination method). The association between each variable and the outcome of interest was controlled for all other variables

Table 4 Multivariate Analysis of the Influence of Selected Comorbidities on In-hospital Mortality Following All Cholecystectomies, LCs and OCs Between 1997 and 2006, NIS

	All cases		OC		LC	
Variable	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Liver disease	2.42 (2.22–2.64)	<0.001	2.25 (2.01–2.53)	<0.001	2.53 (2.22–2.88)	<0.001
Renal failure	4.46 (4.15–4.80)	<0.001	3.86 (3.52–4.25)	<0.001	4.96 (4.45–5.53)	<0.001
Deficiency anemias	0.70 (0.64–0.76)	<0.001	0.63 (0.57–0.70)	<0.001	0.80 (0.70–0.90)	<0.001
Congestive heart failure	2.46 (2.33–2.59)	<0.001	2.03 (1.89–2.17)	<0.001	3.23 (2.97–3.51)	<0.001
Chronic pulmonary disease	1.31 (1.24–1.38)	<0.001	1.25 (1.17–1.34)	<0.001	1.40 (1.28–1.52)	<0.001
Diabetes, uncomplicated	0.78 (0.73–0.84)	<0.001	0.73 (0.67–0.80)	<0.001	0.84 (0.76–0.93)	<0.001
Hypertension	0.45 (0.42–0.47)	<0.001	0.44 (0.41–0.47)	<0.001	0.46 (0.42–0.49)	<0.001
Hypothyroidism	0.57 (0.51–0.64)	<0.001	0.51 (0.44–0.60)	<0.001	0.64 (0.55–0.74)	<0.001
Fluid and electrolyte disorders	2.38 (2.26–2.50)	<0.001	2.01 (1.90–2.13)	<0.001	3.09 (2.85–3.34)	<0.001
Obesity	0.50 (0.43–0.59)	<0.001	0.48 (0.39–0.60)	<0.001	0.56 (0.45–0.69)	<0.001

Association between each variable and the outcome of interest (death) was modeled using stepwise logistic regression (backwards variable elimination method). The association between each variable and the outcome of interest was controlled for all other variables

found a 3.4-fold increase in mortality in cirrhotic patients undergoing cholecystectomy. Their study relied on specific diagnosis codes for cirrhosis and portal hypertension, had a component of surgical selection bias associated with it and involved a specific group of patients with advanced liver dysfunction. In such case, our study could be viewed as applying to the general population with differing degrees of diagnosed liver disease. Others investigators have reported low mortality in patients with severe cardiovascular disease,[20] renal failure,[25] and chronic obstructive pulmonary disease[26] undergoing LC. However, these data were derived from relatively small studies and none have derived odds ratios as has been done here. It is also interesting to note that a number of our common comorbidities were associated with a significant decreased risk of mortality after either OC or LC. It is highly unlikely that deficiency anemias (overall OR 0.70), uncomplicated diabetes (overall OR 0.78), hypertension (overall OR 0.45), hypothyroidism (overall OR 0.57), or obesity (overall OR 0.50) are protective conditions in patients undergoing cholecystectomy. This lack of correlation with clinical expectations may indicate that patients with these conditions were under medical care and were better able to tolerate these procedures than individuals with unrecognized anemia, diabetes, hypertension, or hypothyroidism. This finding with regard to obesity is difficult to explain but may simply represent a selection bias towards the younger segment of the population, on which the majority of these procedures are performed and where mortality is lower, instead of the elderly segment where we have found mortality risk to be greater.

There are potential limitations of this study that may have an impact on our findings. First, the NIS does not include patient abstracts derived from US Military or Veteran's Affairs hospitals, or from stand-alone ambulatory surgery centers. While it is not likely that the federal government system would contribute a significant increase to the mortality rate of uncomplicated LC since these patients would simply discharged to home in a timely manner, it is not possible to assess the contribution of converted or OC patients to our national estimation of mortality. Ferreira and colleagues, reported a volume of 7,492 LCs performed within the Veterans Affairs Healthcare System between 1992 and 1995[27] so it is likely that a small percentage of cholecystectomies are lost to us from this source. In the case of ambulatory surgery centers, it is reasonable to assume, as we did with the federal healthcare system, that uncomplicated LCs were discharged to home while converted cases would be admitted to a healthcare facility as inpatients. Second, the introduction of a specific ICD-9 code for conversion in October 1997 makes it impossible to report actual conversions for that year thus impacting our average conversion rate for the study period. Although it would be convenient to predict a conversion rate between 8.3% (including 1997 data) and 9.1% (excluding 1997 data), we would still fail to take into consideration the contribution of ambulatory surgery center LC volume. Converted cases from this source would tend to overestimate our annual conversion rate. OC volume for 1997 also appears to be inflated due to the late introduction of the conversion code. Third, it is impossible to control for all potential ICD-9 coding errors at the hospital level that may have an impact on our ability to accurately extract patient abstracts. An example of this may be seen in mortality impacted by "fluid and electrolyte disorders" in our multivariate analysis of comorbidity factors. While this may be related to critical illness or sepsis, it may also simply represent overcoding on the part of the dataset.

Conclusion

In our current study, we have found that the proportion of LCs performed annually has continued to increase over our decade of study. The mortality rate associated with LC continues to be low. In contrast, a sizeable proportion of OCs are still being performed with an associated high mortality rate. Elderly male Medicare patients and patients with renal failure, congestive heart failure, and liver disease appear to represent a segment of the population that are at higher risk for death after cholecystectomy by either the open or laparoscopic approach.

References

1. Fogli L, Boschi S, Patrizi P, et al. Laparoscopic cholecystectomy without intraoperative cholangiography: audit of long-term results. J Laparoendosc Adv Surg Tech A 2009;19(2):191–193.
2. Livingston EH, Rege RV. A nationwide study of conversion from laparoscopic to open cholecystectomy. Am J Surg 2004;188 (3):205–211.
3. Suter M, Meyer A. A 10-year experience with the use of laparoscopic cholecystectomy for acute cholecystitis: is it safe? Surg Endosc 2001;15(10):1187–1192.
4. Flum DR, Dellinger EP, Cheadle A, et al. Intraoperative cholangiography and risk of common bile duct injury during cholecystectomy. JAMA 2003;289(13):1639–1644.
5. Shoemaker CP Jr. Changes in the general surgical workload, 1991–1999. Arch Surg 2003;138(4):417–426. discussion 426.
6. Dolan JP, Diggs BS, Sheppard BC, Hunter JG. Ten-year trend in the national volume of bile duct injuries requiring operative repair. Surg Endosc 2005;19(7):967–973.
7. Schilling PL, Dimick JB, Birkmeyer JD. Prioritizing quality improvement in general surgery. J Am Coll Surg 2008;207(5):698–704.
8. Maxwell JG, Tyler BA, Rutledge R, et al. Cholecystectomy in patients aged 80 and older. Am J Surg 1998;176(6):627–631.
9. Orlando R 3rd, Russell JC, Lynch J, Mattie A. Laparoscopic cholecystectomy. A statewide experience. The Connecticut laparoscopic cholecystectomy registry. Arch Surg 1993;128(5):494–498. discussion 498–9.
10. Deziel DJ, Millikan KW, Economou SG, et al. Complications of laparoscopic cholecystectomy: a national survey of 4,292 hospitals and an analysis of 77,604 cases. Am J Surg 1993;165(1):9–14.
11. Sharp CF, Garza RZ, Mangram AJ, Dunn EL. Partial cholecystectomy in the setting of severe inflammation is an acceptable consideration with few long-term sequelae. Am Surg 2009;75(3):249–252.
12. Manning RG, Aziz AQ. Should laparoscopic cholecystectomy be practiced in the developing world?: the experience of the first training program in Afghanistan. Ann Surg 2009;249(5):794–798.
13. Healthcare Cost and Utilization Project (HCUP). Agency for Healthcare Research and Quality 1997–2006.
14. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care 1998;36 (1):8–27.
15. Wolf AS, Nijsse BA, Sokal SM, et al. Surgical outcomes of open cholecystectomy in the laparoscopic era. Am J Surg 2009;197 (6):781–784.
16. Giger UF, Michel JM, Opitz I, et al. Risk factors for perioperative complications in patients undergoing laparoscopic cholecystectomy: analysis of 22,953 consecutive cases from the Swiss Association of Laparoscopic and Thoracoscopic Surgery database. J Am Coll Surg 2006;203(5):723–728.
17. Z'Graggen K, Wehrli H, Metzger A, et al. Complications of laparoscopic cholecystectomy in Switzerland. A prospective 3-year study of 10,174 patients. Swiss Association of Laparoscopic and Thoracoscopic Surgery. Surg Endosc 1998;12(11):1303–1310.
18. Csikesz N, Ricciardi R, Tseng JF, Shah SA. Current status of surgical management of acute cholecystitis in the United States. World J Surg 2008;32(10):2230–2236.
19. Uecker J, Adams M, Skipper K, Dunn E. Cholecystitis in the octogenarian: is laparoscopic cholecystectomy the best approach? Am Surg 2001;67(7):637–640.
20. Liu YY, Yeh CN, Lee HL, et al. Laparoscopic cholecystectomy for gallbladder disease in patients with severe cardiovascular disease. World J Surg 2009;33:1720–1726.
21. Csikesz NG, Nguyen LN, Tseng JF, Shah SA. Nationwide volume and mortality after elective surgery in cirrhotic patients. J Am Coll Surg 2009;208(1):96–103.
22. Lipman JM, Claridge JA, Haridas M, et al. Preoperative findings predict conversion from laparoscopic to open cholecystectomy. Surgery 2007;142(4):556–563. discussion 563–5.
23. Friedrich N, Volzke H, Hampe J, et al. Known risk factors do not explain disparities in gallstone prevalence between Denmark and northeast Germany. Am J Gastroenterol 2009;104(1):89–95.
24. Timmons S, Chandio A, Twomey A, Aftab F. Older patients have higher conversion rates for laparoscopic cholecystectomy than younger patients. J Am Geriatr Soc 2009;57(3):573–574. author reply 574.
25. Yeh CN, Chen MF, Jan YY. Laparoscopic cholecystectomy for 58 end stage renal disease patients. Surg Endosc 2005;19(7):915–918.
26. Hsieh CH. Laparoscopic cholecystectomy for patients with chronic obstructive pulmonary disease. J Laparoendosc Adv Surg Tech A 2003;13(1):5–9.
27. Ferreira MR, Bennett RL, Gilman SC, et al. Diffusion of laparoscopic cholecystectomy in the Veterans Affairs health care system, 1991–1995. Eff Clin Pract 1999;2(2):49–55.

J Gastrointest Surg (2009) 13:2302–2308
DOI 10.1007/s11605-009-0997-1

ORIGINAL ARTICLE

Sleeve Gastrectomy Provides a Better Control of Diabetes by Decreasing Ghrelin in the Diabetic Goto–Kakizaki Rats

Feng Li · Guangyong Zhang · Jianwei Liang · Xiangjiu Ding · Zhiqiang Cheng · Sanyuan Hu

Received: 20 July 2009 / Accepted: 11 August 2009 / Published online: 2 September 2009

Abstract
Aim Sleeve gastrectomy (SG) and modified duodenal jejunal bypass (MDJB) were compared as procedures for glucose control. We aim to form the initial conclusions with respect to the possibility of (1) whether gastric fundus exclusion is essential for the control of diabetes and (2) application as a low morbidity procedure.
Materials and Methods SG and MDJB were performed on 10- to 12-week-old Goto–Kakizaki rats that spontaneously develop type 2 diabetes. Rats were observed for 36 weeks after surgery, and glucose, insulin, glucagons-like peptide-1 (GLP-1), glucose tolerate, insulin sensitivity, cholesterol, triglycerides, and free fatty acid levels were measured.
Results Apart from distinct weight loss of SG and MDJB after 1 month compared with sham-operated rats ($P<0.001$), SG showed strikingly improved blood glucose levels and significantly decreased Ghrelin secretion ($P<0.001$). Furthermore, SG resulted in a shorter operative time ($P<0.01$) and postoperative recovery time ($P<0.01$) than MDJB group.
Conclusions SG shows better control in terms of glucose tolerance and other measurements. This study provides direct evidence that SG possesses better improvement of diabetes by reduction of Ghrelin.

Keywords Sleeve gastrectomy · Modified duodenal jejunal bypass · Glucagon-like peptide-1 · Insulin

Abbreviations

SG	Sleeve gastrectomy
GK	Goto–Kakizaki
MDJB	Modified duodenal jejunal bypass
OGTT	Oral glucose tolerance test
ITT	Insulin tolerance test
GLP-1	Glucagon-like peptide-1

Introduction

Diabetes mellitus (DM) presently affects more than 170 million people worldwide,[1] with an estimated increase of at least 50% by 2010. DM is expected to double to about 300 million by the year 2025.[2] As the population with Type 2 diabetes increases, so does the prevalence of life-threatening complications. By now, the disease has become a major cause of morbidity and mortality and places a huge strain on public health funding.[3] However, etiology and the best treatment remain elusive still.

Current therapies including diet, exercise, behavior modification, oral hypoglycemic agents, and insulin[4–6] rarely return patients to euglycemia. Investigators had found that a number of Type 2 diabetes patients achieved clinical resolution after surgical treatment of morbid obesity.[7] Moreover, recent reports that glycemic control often occurs long before significant weight loss[8,9] suggested that the control of diabetes may be a direct effect of the operations rather than a secondary outcome of the amelioration of obesity-related abnormalities.

It is reported that the SG and duodenal jejunal bypass (DJB) for the treatment of diabetes type 2 in patients are effective treatments for diabetes[10–12] and restore normal concentrations of plasma glucose, insulin, and glycosylated hemoglobin in 80% to 100% of patients.[8,13,14] Furthermore,

F. Li · G. Zhang · J. Liang · X. Ding · Z. Cheng · S. Hu (✉)
Department of General Surgery,
Qilu Hospital of Shandong University,
107#, Wenhua Xi Road,
Jinan 250012 Shandong, People's Republic of China
e-mail: husanyuan1962@hotmail.com

it was also demonstrated that other bariatric operations may result in significant clinical improvement in Type 2 diabetes.[7,15–21]

Since many of these procedures resulted in significant control of diabetes in obese and non-obese individuals, then which procedure is best? To find the answer, we studied the effect of SG and MDJB in Goto–Kakizaki (GK) rats, the most widely used animal model of non-obese Type 2 diabetes.[22, 23] We herein report the comparison of glycemic control outcomes between SG and MDJB in GK rats during a 36-week period.

Materials and Methods

SG and MDJB were compared as surgeries for glucose control. Initial conclusions might be formed with respect to the possibility of (1) whether gastric fundus exclusion is essential for the control of diabetes and (2) application as a low morbidity procedure.

Animals

Male 8- to 10-week-old GK rats were purchased from National Rodent Laboratory Animal Resources (Shanghai, China). All animals were housed in individual cages under constant ambient temperature and humidity in a 12-h light/dark cycle. Care and procedural protocols were evaluated to ensure compliance with National Institute of Health standards.[24]

Experimental Design

All the rats were acclimated for 1 week before the start of experiments. Then, 10 rats randomly underwent each one of the following groups: (1) SG, (2) Sham–SG, (3) MDJB, and (4) Sham–MDJB. Operations were performed after an overnight fast and the induction of ether anesthesia.

In all groups, weight, food intake, fasting glycemia, fasting insulin, glucose-stimulated glucagon-like peptide-1 (GLP-1), glucose tolerance, insulin tolerance test (ITT), and plasma lipids were measured before and at several time points after the intervention.

The surgery time of SG and MDJB groups was strictly recorded. The first defecation time, serving as an indication of postoperative recovery time, and the occurrence of postoperative complications were observed and recorded carefully.

Surgical Procedures

Rats undergoing any operation were made to fast overnight. Inhalation anesthesia with 2% isoflurane and air/oxygen was used during the surgery.

SG surgery was performed as described by de Bona Castelan J, et al.[10,11,25] First, a 4-cm mid-laparotomy was made, and the structures were identified. Gastric omentum was dissociated to disclose gastric cardium. To dissect the fundus and greater curve, ligation with 6/0 silk of the short vessels towards the spleen and of the gastroepiploic vessels in the region of the antrum was needed. Then, the vessels of the greater curvature were cauterized with a thermocautery, from the cardia all the way to the pylorus. This arrangement defined the line of incision for the longitudinal sleeve gastrectomy. This line covered the entire lumen and much of the gastric fundus in which 70% to 80% of total stomach was removed. After exeresis, the peritoneal cavity was cleaned with saline before the gastroraphy was conducted with an invaginating continuous polypropylene (Prolene 6–0; Ethicon) hand-sewn suture (Schimieden pattern) from the fundus to the antrum. Hemostasis and suture-line integrity were checked, and an additional stitch was applied when necessary. The details of the procedure are illustrated in Fig. 1a.

MGJB surgery, modified from prior techniques,[12,13] involved (1) a midline abdominal incision, (2) separation of the duodenum from the stomach, (3) transection at the level of the distal jejunum, (4) connection of the distal limb to the pylorus, (5) an anastomosis with the proximal limb and jejunum 12 cm distally. The gastric volume was preserved during the procedure. The details of the procedure are illustrated in Fig. 1b.

Sham surgeries involved the same incisions, transections and reanastomosis of the gastrointestinal tract at multiple sites corresponding to the SG and MDJB. After transection, the intestines were immediately anastomosed. When needed, operative time was prolonged to ensure an equivalent degree of anesthesiological stress as those rats that underwent SG or MDJB.

In all groups, weight and food intake were measured daily for the first 2 weeks after the intervention, twice a week for the following 2 weeks, and then monthly for 1 month after surgery.

Biochemical Tests

Biochemical measurements were tested by blood samples collected from the tail vein in conscious rats.

Fasting glycemia was measured, using a Sure-step plus blood glucose meter produced by Life Scan Company, USA, once a week for the first 4 weeks and then monthly for 1 month after surgery.

Ghrelin levels were measured by radioimmunoassay (Performed by Jingmei Biotech Company, USA), using I125-labelled Ghrelin as a tracer molecule, and a polyclonal antibody raised in rabbits against full-length octanoylated rat Ghrelin before (baseline) and then on day 1, 4, 12, 24, and 36 weeks following the operation.

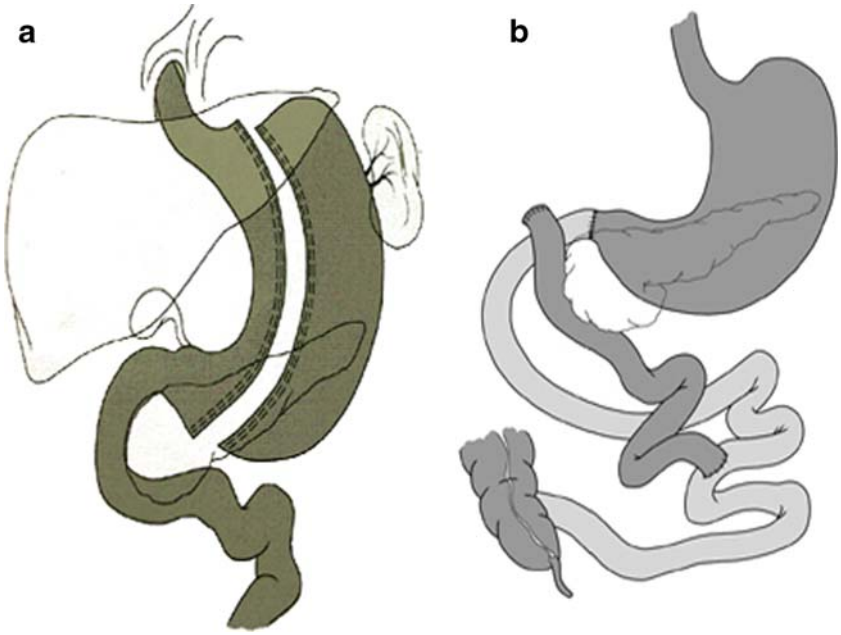


Figure 1 Surgical procedures: **A** Sleeve gastrectomy: remove 70% to 80% of total stomach from the cardia to the pylorus. **B** Modified duodenal jejunal bypass: separate the duodenum from the stomach and transect the distal jejunum 8 cm from the ligament of Treitz. Gastrojejunostomy and enteroenterostomy were conducted successively.

GLP-1 levels were measured 30 min after the administration of 1 g/kg glucose by oral gavages (as described below) before and 1, 4, 8, 24, and 36 weeks after surgery. Rat radioimmunoassay kits (Linco, USA) were used for measurement (Performed by Jingmei Biotech Company, USA).

Oral glucose tolerance test (OGTT) was performed before and 10 weeks postoperatively as a measure of the progress of the surgery and sugar control. After 12–14 h of fasting, blood glucose (analyzed by a glucometer) was measured in conscious rats before (baseline) and then 30, 60, 120, and 180 min after the administration of 1 g/kg glucose by oral gavages.

ITT was performed before and 10 weeks postoperatively by measuring glucose levels before and 30, 60, 90, and 120 min after injection of 0.5 IU/kg human insulin intraperitoneally in conscious rats.

Plasma lipid—plasma total cholesterol, triglycerides, and free fatty acids (FFA) were measured both after 12–14 h fasting and in the fed condition before and 10 weeks after surgery. Analytical testing of plasma lipids was performed by the biochemical laboratory of Qilu Hospital, China.

Statistical Analysis

All statistical procedures were performed using SPSS version 15.0. Data were expressed as mean ± SD. Trapezoidal integration was applied for calculating areas under curves for OGTT and ITT. Statistical analysis was performed using a two-way ANOVA for repeated measures and the Student's *t* test as appropriate. $P<0.05$ were considered to be statistically significant.

Results

Operative time was defined to begin at the midline abdominal incision and to end with the suturing of the abdominal incision. SG resulted in savings of time compared with MDJB surgery for less anastomosis (47.6±7.5 vs. 67.8±8.7 min; $P<0.01$). Postoperative recovery time was defined to begin at the end of the operation and to end with the first defecation. SG surgery needed a significant shorter postoperative recovery time compared with MDJB surgery (22.3±5.2 vs. 37.2±8.5 h; $P<0.01$). Two MDJB rats died from intestinal obstruction on the third and fifth postoperative day, respectively; no deaths or postoperative complications were observed in SG group.

Weight Loss Both SG and MDJB surgery lead to significant weight loss compared with the sham-operated rats ($P<0.001$) after 4 weeks postoperatively who started regaining body weight approximately the 14th postoperative day. The mean weights of SG and MDJB groups did not differ from one another at any period ($P>0.05$; Fig. 2a).

Glucose level Though all groups display a decline of fasting glucose level during week 1 and a slight rebound by week 4, SG and MDJB levels remained stable lower while the sham operations yield progressive raises ($P<0.001$). Glucose level remained consistently lower in the SG and MDJB animals ($P>0.05$; Fig. 2b).

Ghrelin The study displays that Ghrelin levels in SG group decreased dramatically on the first postoperative day and did not rise to the original level during the study period

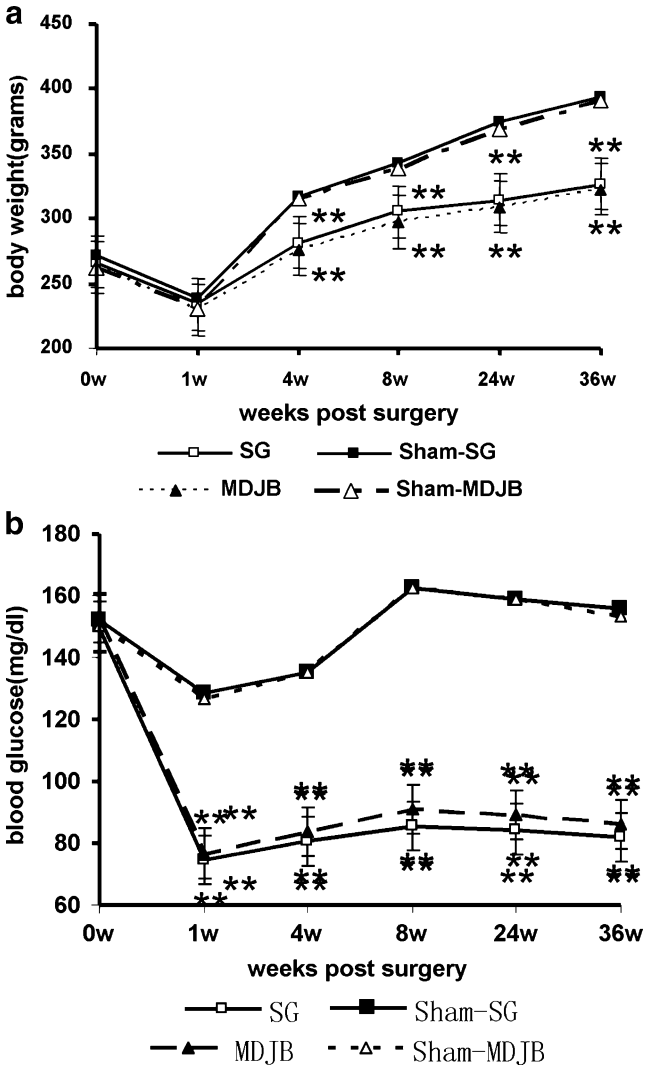


Figure 2 **A** Mean ± SD body weights of rats. Both SG and MDJB group show less weight gain compared with sham-operated animals ($P<0.001$). **B** Mean ± SD fasting glycemia. Mean fasting glycemia remained constantly lower in SG and MDJB rats compared with sham-operated animals ($P<0.001$). There were no significant differences between SG rats and MDJB rats ($P>0.05$; $^{**}P<0.001$).

(36 weeks). Ghrelin levels for SG were much lower than that for MDJB or sham groups ($P<0.001$) which was higher throughout the experiment (Fig. 3a).

GLP-1 It shows that GLP-1 levels for the sham groups were stable throughout the experiment. GLP-1levels for MDJB group increased promptly at week 4 and were higher than that for SG or sham groups ($P<0.001$). Postoperative GLP-1 levels were higher for SG group than S-SG group at weeks 4, 8, 24, and 36 ($P<0.01$; Fig. 3b).

OGTT The study shows that there were no statistical differences in OGTT between groups before surgery. However, at week 10 after surgery, OGTT was improved in both SG and MDJB rats compared with the sham-operated rats ($P<0.001$). Meanwhile, SG rats show a better improvement of OGTT than they were for MDJB rats ($P<0.001$; Fig. 4a).

ITT Whereas SG and MDJB groups display improvement in ITT compared with the sham-operated groups ($P<0.001$), no statistical differences were observed between SG and MDJB groups ($P>0.05$; Fig. 4b).

Insulin Neither SG nor MDJB had any effect on both fasting and after glucose-stimulated plasma insulin concentrations. The levels were not significantly different between each other and those of sham-operated rats ($P>0.05$).

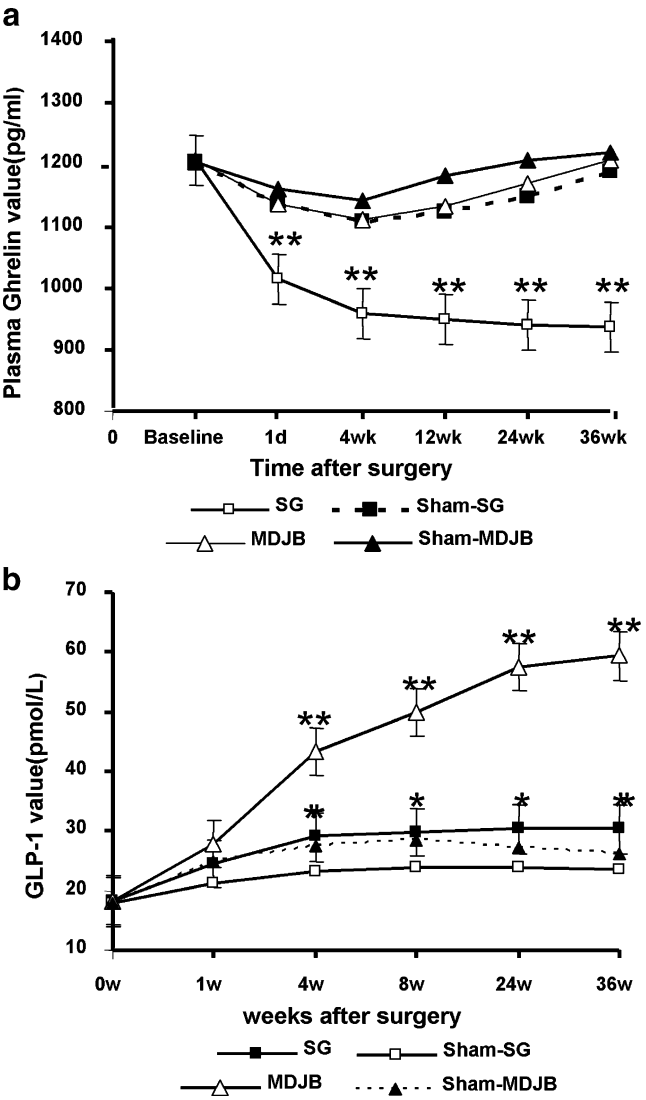


Figure 3 **A** Mean ± SD plasma fasting plasma Ghrelin. Mean fasting ghrelin levels for SG was significantly lower than that for MDJB or sham-operated rats ($P<0.001$) throughout the period (36 weeks). There were no significant differences between MDJB and sham-operated rats ($P>0.05$). **B** Mean ± SD plasma levels of GLP-1 after oral glucose administration. GLP-1 levels for MDJB was significantly higher than that for SG or sham-operated rats ($P<0.001$) ($^{*}P<0.01$ and $^{**}P<0.001$).

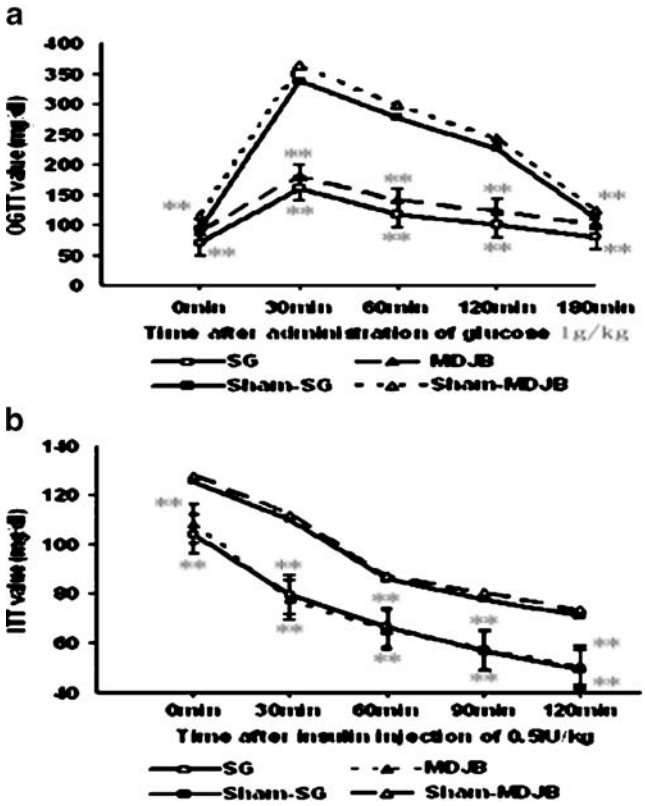


Figure 4 **A** OGTT was performed before and 10 weeks after operation. It showed an improvement of glucose tolerance in both SG and MDJB groups compared with the sham-operated rats ($P<0.001$). Meanwhile, SG group showed a better glucose tolerance than MDJB group ($P<0.001$). **B** ITT performed before and 10 weeks after operation displayed an improvement of insulin sensitivity. Both SG and MDJB showed effect on both fasting and feeding plasma insulin concentrations 10 weeks after operation ($P<0.001$). The glucose levels did not differ from SG to MDJB group ($P>0.05$) (**$P<0.001$).

Lipid For non-fasted rats, cholesterol levels for SG an MDJB groups were lower than that for sham groups ($P<0.001$), but SG did not differ from MDJB ($P>0.05$); free fatty acid levels for SG group were lower than that for MDJB or sham groups ($P<0.01$); triglyceride levels were similar among groups ($P>0.05$; Fig. 5a). For fasted cholesterol, triglyceride and free fatty acid levels for SG and MDJB were lower than that for sham groups ($P<0.001$), whereas SG did not differ from MDJB ($P>0.05$). It displays that free fatty acid levels for SG group were lower than that for MDJB groups ($P<0.05$; Fig. 5b).

Discussion

Currently, there is an exponential increase in the prevalence of Type 2 diabetes within the population. For this reason, to find a better way to treat patients with diabetes is needed. There is evidence that bariatric surgery is an effective form of therapy for Type 2 diabetes. However, determining the "best" surgical treatment for diabetes mellitus is an important task facing the bariatric surgical community. The optimal procedure should have acceptably low morbidity and mortality rates, resulting in significant and durable glycemic control. It should also lead to the improvement or resolution of diabetes-related comorbidities as well as increasing the quality of life.

The main focus of this report is the comparison of glycemic control outcomes following SG and MDJB. Both SG and MDJB showed sustained effect in the resolution of diabetes; however, we demonstrate that SG provides a significant advantage over MDJB when comparing Ghrelin. A similar effect with SG on OGTT, glycemia, plasma insulin, and plasma lipids was observed. Similar to previous observations, these surgeries achieved normal concentrations of fasting glycemia and fasting plasma insulin,[9,11,16,17] restored insulin sensitivity,[9,26–28] prevented progression in impaired glucose tolerance,[26,27] and potentially reduced mortality from diabetes mellitus.[29,30] Furthermore, our study gives strong evidence that the role of the Ghrelin in

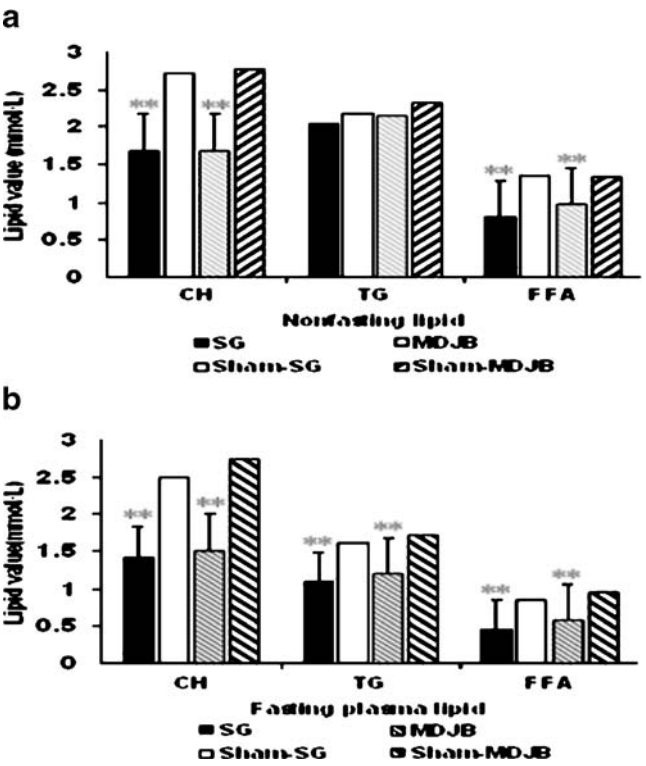


Figure 5 **A** For non-fasted rats 10 weeks after surgery, cholesterol levels for SG an MDJB groups were less than that for sham groups ($P<0.001$), but SG did not differ from MDJB ($P>0.05$); free fatty acid levels for SG group were less than that for MDJB and sham groups ($P<0.01$); triglyceride levels were similar among groups ($P>0.05$). **B** For fasted cholesterol, triglyceride and free fatty acid levels for SG and MDJB were less than that for sham groups ($P<0.001$), and free fatty acid levels for SG group were less than that for MDJB groups ($P<0.05$) (**$P<0.001$).

the resolution of diabetes is at least similar, if not more crucial than, with bypass of the proximal bowel. As we reported, SG shows better results in glycemic control and other values than MDJB in spite of the low level of GLP-1 compared with MDJB which has been demonstrated playing an important role in the control of diabetes.[31–33]

Thus, we speculate that because of the effect on Ghrelin by the SG procedure, SG surgery achieves superior control of diabetes compared with MDJB. In the present study, the fact that rats with SG surgery revealed high insulin sensitivity, glucose tolerance and low plasma glucose levels shows that Ghrelin results in the long-term remission of diabetes by improving insulin sensitivity through restoration of insulin signaling.[32] Increases in signaling pathways are considered among the most critical alterations underlying Type 2 diabetes, in which the incretin-like effect of Ghrelin is characteristically attenuated secondarily to decreased expression of Ghrelin receptors.[34–36]

Another issue we are trying to address is the comparison of postoperative recovery and complications between SG and MDJB. We herein demonstrate that postoperative recovery in rats with SG surgery is faster than that in the MDJB rats. Rats with SG have been previously shown to have no malabsorption problems and need little postoperative management.[37] As we all know, the easier the procedure is, the sooner the postoperative recovery is. The present data strongly supports this. Moreover, SG is associated with a shorter surgery time (47.6±7.5 vs. 67.8±8.7 min; $P<0.01$) and faster postoperative recovery (22.3±5.2 vs. 37.2±8.5 h; $P<0.01$). Additionally, the procedure appears to be reasonably safe with low mortality rates. These findings are in agreement with the observations by Schauer PR et al.[38] The issue mentioned above is a key point because it indicates that the SG is an alternative method of providing long-term control of glycemia and normal levels of insulin with better clinical advantages when compared with MDJB.

In addition to providing good glycemic control, the results of both operations presented herein corroborate and extend previous work in several ways. First, recently, it was demonstrated that the FFA levels might have played a role in glycemic control that high levels of FFA-induced insulin resistance and lowered FFA is associated with improved insulin sensitivity in hyperlipoidemic human subjects.[32,39] In our research, we also demonstrate that SG operations can effectively lower the FFA levels compared with MDJB or the sham-operated rats. Second, the control of diabetes induced by both operations is not dependent on the resolution of obesity-related abnormalities, for we used a non-obese model. The effect on glucose metabolism seems to be a direct consequence of the exclusion of the fundus of stomach rather than secondary to weight loss because the improvement of glycemia, glucose tolerance, insulin, and plasma lipid was observed prior to the weight loss. These findings are consistent with previous studies in humans that the control of plasma glucose and insulin has occurred before substantial weight loss after bariatric surgery.[40]

Conclusion

In summary, safely obtained and sustained glycemic control is the key goal of surgical treatment for diabetes. The study provides direct evidence that SG possesses better improvement of type 2 diabetes by reduction of Ghrelin which is independent of weight loss and other complications. Larger sample for further study and long-time follow-up should be needed to confirm and extend the present findings, including nutritional outcomes, resolution of comorbidities, and quality of life. However, SG has potentially satisfactory effect in the clinical scenario, it could be an alternative choice as a treatment for type 2 diabetic patients which providing long-time control of glycemia and with lower morbidity and mortality rate.

References

1. Papadopoulos AA, Kontodimopoulos N, Frydas A, Ikonomakis E, Niakas D. Predictors of health-related quality of life in type II diabetic patients in Greece. BMC Public Health 2007;7:186.
2. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. Diabetes Care 1998;21:1414–1431.
3. Chan BS, Tsang MW, Lee VW, Lee KK. Cost of type 2 diabetes mellitus in Hong Kong Chinese. Int J Clin Pharmacol Ther 2007;45:455–468.
4. Klein S, Fontana L, Young VL, Coggan AR, Kilo C, Patterson BW, Mohammed BS. Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. N Engl J Med 2004;350:2549–2557.
5. Kelley DE. Thermodynamics, liposuction, and metabolism. N Engl J Med 2004;350:2542–2544.
6. Kirchner H, Guijarro A, Meguid MM. Is a model useful in exploring the catabolic mechanisms of weight loss after gastric bypass in humans? Curr Opin Clin Nutr Metab Care 2007;10:463–474.
7. Pories WJ, Swanson MS, MacDonald KG, Long SB, Morris PG, Brown BM, Barakat HA, deRamon RA, Israel G, Dolezal JM. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. Ann Surg 1995;222:339–352.
8. Detournay B, Cros S, Charbonnel B, Grimaldi A, Liard F, Cogneau J, Fagnani F, Eschwège E. Managing type 2 diabetes in France: the ECODIA survey. Diabetes Metab 2000;26:363–369.
9. Scopinaro N, Adami GF, Marinari GM, Gianetta E, Traverso E, Friedman D, Camerini G, Baschieri G, Simonelli A. Biliopancreatic diversion. World J Surg 1998;22:936–946.
10. Pereferrer FS, Gonzàlez MH, Rovira AF, Blasco SB, Rivas AM, del Castillo Déjardin D. Influence of sleeve gastrectomy on several experimental models of obesity: metabolic and hormonal implications. Obes Surg 2008;18(1):97–108.
11. Vidal J, Ibarzabal A, Romero F, Delgado S, Momblán D, Flores L, Lacy A. Type 2 diabetes mellitus and the metabolic syndrome

following sleeve gastrectomy in severely obese subjects. Obes Surg 2008;18(9):1077–1082.
12. Rubino F, Marescaux J. Effect of duodenal-jejunal exclusion in a non-obese animal model of type 2 diabetes: a new perspective for an old disease. Ann Surg 2004;239:1–11.
13. Cohen RV, Schiavon CA, Pinheiro JS, Correa JL, Rubino F. Duodenal-jejunal bypass for the treatment of type 2 diabetes in patients with body mass index of 22–34 kg/m^2: a report of 2 cases. Surg Obes Relat Dis 2007;3:195–197.
14. Rubino F, Gagner M. Potential of surgery for curing type 2 diabetes mellitus. Ann Surg 2002;236:554–559.
15. Cowan GS Jr, Buffington CK. Significant changes in blood pressure, glucose, and lipids with gastric bypass surgery. World J Surg 1998;22:987–992.
16. Marceau P, Hould FS, Simard S, Lebel S, Bourque RA, Potvin M, Biron S. Biliopancreatic diversion with duodenal switch. World J Surg 1998;22:947–954.
17. Schauer PR, Ikramuddin S, Gourash W, Ramanathan R, Luketich J. Outcomes after laparoscopic Roux-en-Y gastric bypass for morbid obesity. Ann Surg 2000;232:515–529.
18. Wittgrove AC, Clark GW. Laparoscopic gastric bypass, Roux-en-Y-500 patients: technique and results, with 3–60 month follow-up. Obes Surg 2000;10:233–239.
19. Pontiroli AE, Pizzocri P, Librenti MC, Vedani P, Marchi M, Cucchi E, Orena C, Paganelli M, Giacomelli M, Ferla G, Folli F. Laparoscopic adjustable gastric banding for the treatment of morbid (grade 3) obesity and its metabolic complications: a three-year study. J Clin Endocrinol Metab 2002;87:3555–3561.
20. Scopinaro N, Gianetta E, Adami GF, Friedman D, Traverso E, Marinari GM, Cuneo S, Vitale B, Ballari F, Colombini M, Baschieri G, Bachi V. Biliopancreatic diversion for obesity at eighteen years. Surgery 1996;119:261–268.
21. Dixon JB, O'Brien PE. Health outcomes of severely obese type 2 diabetic subjects 1 year after laparoscopic adjustable gastric banding. Diabetes Care 2002;25:358–363.
22. Galli J, Li LS, Glaser A, Ostenson CG, Jiao H, Fakhrai-Rad H, Jacob HJ, Lander ES, Luthman H. Genetic analysis of non-insulin dependent diabetes mellitus in the GK rat. Nat Genet 1996;12:31–37.
23. Inabnet WB 3rd, Milone L, Korner J, Durak E, Ahmed L, Pomrantz J, Harris PE, Bessler M. A rodent model of metabolic surgery for study of type 2 diabetes and positron emission tomography scanning of beta cell mass. Surg Obes Relat Dis 2009;5(2):212–217.
24. National Research Council. Public Health Service Policy and Government Principles regarding the care and use of animals. Appendix D. Guide for the care and use of animals. Washington, DC: National Academy, 1996, pp 116–118.
25. de Bona Castelan J, Bettiol J, d'Acampora AJ, Castelan JV, de Souza JC, Bressiani V, Giroldi SB. Sleeve gastrectomy model in Wistar rats. Obes Surg 2007;17(7):957–961.
26. Pories WJ, MacDonald KG Jr, Morgan EJ, Sinha MK, Dohm GL, Swanson MS, Barakat HA, Khazanie PG, Leggett-Frazier N, Long SD. Surgical treatment of obesity and its effect on diabetes: 10-y follow-up. Am J Clin Nutr 1992;55:582S–585S.
27. Patriti A, Aisa MC, Annetti C, Sidoni A, Galli F, Ferri I, Gullà N, Donini A. How the hindgut can cure type 2 diabetes. Ileal transposition improves glucose metabolism and beta-cell function in Goto-kakizaki rats through an enhanced Proglucagon gene expression and L-cell number. Surgery 2007;142:74–85.
28. Castagneto M, De Gaetano A, Mingrone G, Tacchino R, Nanni G, Capristo E, Benedetti G, Tataranni PA, Greco AV. Normalization of insulin sensitivity in the obese patient after stable weight reduction with biliopancreatic diversion. Obes Surg 1994;4:161–168.
29. MacDonald KG Jr, Long SD, Swanson MS, Brown BM, Morris P, Dohm GL, Pories WJ. The gastric bypass operation reduces the progression and mortality of non-insulin-dependent diabetes mellitus. J Gastrointest Surg 1997;1:213–220. discussion 220.
30. Meneghini LF. Impact of bariatric surgery on type 2 diabetes. Cell Biochem Biophys 2007;48:97–102.
31. Frezza EE, Wachtel MS, Chiriva-Internati M. The multiple faces of glucagons-like peptide 1-obesity, appetite, and stress: what is next? A review. Dig Dis Sci 2007;52:643–649.
32. Langer FB, Reza Hoda MA, Bohdjalian A, Felberbauer FX, Zacherl J, Wenzl E, Schindler K, Luger A, Ludvik B, Prager G. Sleeve gastrectomy and gastric banding: effects on plasma Ghrelin levels. Obes Surg 2005;15:1024–1029.
33. Näslund E, Backman L, Holst JJ, Theodorsson E, Hellström PM. Importance of small bowel peptides for the improved glucose metabolism 20 years after jejunoileal bypass for obesity. Obes Surg 1998;8:253–260.
34. Brzozowski T, Konturek PC, Drozdowicz D, Konturek SJ, Pawlik M, Sliwowski Z, Pawlik WW, Hahn EG. Role of central and peripheral ghrelin in the mechanism of gastric mucosal defence. Inflammopharmacology 2005;13:45–62.
35. Kotidis EV, Koliakos GG, Baltzopoulos VG, Ioannidis KN, Yovos JG, Papavramidis ST. Serum ghrelin, leptin and adiponectin levels before and after weight loss: comparison of three methods of treatment–a prospective study. Obes Surg 2006;16:1425–1432.
36. Pusztai P, Sarman B, Ruzicska E, Toke J, Racz K, Somogyi A, Tulassay Z. Ghrelin: a new peptide regulating the neurohormonal system, energy homeostasis and glucose metabolism. Diabetes Metab Res Rev 2008;24:343–352.
37. Gentileschi P, Kini S, Catarci M, Gagner M. Evidence-based medicine: open and laparoscopic bariatric surgery. Surg Endosc 2002;16:736–744.
38. Schauer PR, Ikramuddin S. Laparoscopic surgery for morbid obesity. Surg Clin North Am 2001;81:1145–1179.
39. Lewis GF, Carpentier A, Adeli K, Giacca A. Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes. Endocr Rev 2002;23:201–229.
40. Strader AD, Vahl TP, Jandacek RJ, Woods SC, D'Alessio DA, Seeley RJ. Weight loss through ileal transposition is accompanied by increased ileal hormone secretion and synthesis in rats. Am J Physiol Endocrinol Metab 2005;288:E447–E453.

J Gastrointest Surg (2009) 13:2309–2313
DOI 10.1007/s11605-009-0953-0

CASE REPORT

Complete Response of an Initially Non-surgical Adenocarcinoma of the Duodenum to Chemotherapy with the Folfox 4 Regimen

Sylvain Manfredi · Thimote Thiebot · Sebastien Henno · Ludivine Falize · Jean François Bretagne · Bernard Meunier

Received: 28 April 2009 / Accepted: 12 June 2009 / Published online: 8 July 2009

Abstract
Introduction The incidence of adenocarcinoma of the small bowel is very low in comparison with that of colorectal cancer. Radical surgery is the only curative treatment, and results with chemotherapy and radiotherapy are disappointing. No standard chemotherapy is defined for non-surgical adenocarcinoma of the small bowel. In France, it is usually treated with the same chemotherapy regimens as used for colorectal cancer.
Case Report We report here the case of a young patient with an initially non-surgical adenocarcinoma of the duodenum treated in a palliative setting with the FOLFOX 4 chemotherapy regimen. After 4 months of treatment, CT scan showed no residual tumor and the patient was well. A multidisciplinary committee decided that a second surgical investigation was necessary, and a duodenal resection was performed, with no residual tumor in the final specimen. After 27 months of follow-up the patient was well and without recurrence.
Conclusion The FOLFOX 4 regimen seems to be efficacious for some small-bowel adenocarcinomas and can be expected to lead to downstaging. If the outcome of a few months of chemotherapy is favorable, it is appropriate for a multidisciplinary expert committee to consider further surgery. This case underscores the value of multidisciplinary expert committees in scrutinizing therapeutic decisions in rare and difficult cases.

Keywords Small bowel · Cancer · Chemotherapy · Second look · Multidisciplinary committee

S. Manfredi (✉) · L. Falize · J. F. Bretagne
Service des Maladies de l'Appareil Digestif (SMAD),
CHU Pontchaillou,
2 rue H le Guilloux,
35033 Rennes Cedex, France
e-mail: sylvain.manfredi@chu-rennes.fr

T. Thiebot · B. Meunier
Département de Chirurgie Viscérale, CHU Pontchaillou,
2 rue H le Guilloux,
35033 Rennes Cedex, France

S. Henno
Département d'anatomopathologie, CHU Pontchaillou,
2 rue H le Guilloux,
35033 Rennes Cedex, France

Introduction

The incidence of adenocarcinoma of the small bowel is very low in comparison with that of colorectal cancer. The duodenum is the most common location: accounting for 52% in a retrospective analysis of 217 patients with adenocarcinoma of the small bowel registered on the Tumor Registry of the M. D. Anderson Cancer Center between 1978 and 1998.[1] Radical surgery is the only curative treatment. Primary curative surgery is feasible for 40–65% of patients, with 5-year survival rates of 40–60% for resected tumors versus 15–30% for non-resected tumors.[2–5] Results with chemotherapy and radiotherapy are disappointing. Few studies have reported the outcomes of chemotherapy for adenocarcinoma of the small bowel, and, to our knowledge, no standard regimen has been defined for non-surgical cases. In France, they are usually treated with the same chemotherapy regimens as are used for colorectal cancer. We report here the case of a young

patient with an initially non-surgical adenocarcinoma of the duodenum treated in a palliative setting with a FOLFOX 4 chemotherapy regimen.

Case Report

A 26-year-old man was admitted to our unit in April 2006 with a history (since December 2005) of abdominal pain and a 15-kg weight loss. His personal medical history was marked by an appendicectomy, allergy to penicillin, and addiction to intravenous heroin. No familial history was noted. Colonoscopy and upper esogastroscopy carried out before admission were normal. Pain was localized in the left upper quadrant of the abdomen. Anemia (9.4 g/dl) and inflammation were noted on laboratory testing. Serology was negative for hepatitis B and C and HIV. Abdominal CT scan showed a 10-cm pathological mass on the third and fourth duodenum (Fig. 1). Endoscopy of the small bowel showed a tumoral stricture of the third duodenum (Fig. 2), and biopsy specimens confirmed adenocarcinoma (Fig. 3). The pathology report was confirmed by two experienced pathologists. Immunological investigation was positive for antibody against cytokeratin 20, and negative for antibody against cytokeratin 7, chromogranin A, and synaptophysin. Antibodies against lymphoma and endocrine tumors were negative. A laparotomy with curative intent was done, but when curative resection was found to be impossible due to complete invasion of the mesenteric artery, only a bypass was carried out.

Palliative chemotherapy with the FOLFOX 4 regimen was started in June 2006. After 2 months of treatment, the CT scan showed a partial response (Fig. 4a) and chemotherapy was continued for a further 2 months. After 4 months of chemotherapy the patient was well, asymptomatic, and had gained 11 kg. CT scan showed a complete response with no abdominal mass (Fig. 4b). A second surgical investigation in October 2006 showed a macroscopically complete involution of the tumor with sclerotic residue involving the mesenteric artery. A complete R0 duodeno-jejunal resection of the sclerotic mass with limited resection and re-construction of the mesenteric artery was done. The pathology report confirmed the complete response with no malignant cells and only sclerotic tissue; 13 lymph nodes were examined and found free of tumor. FOLFOX 4 chemotherapy was continued in an adjuvant setting for 3 months. The patient was followed up every 3 months, and underwent a CT scan every 6 months. After 27 months, no recurrence was detected (CT scan, colonoscopy, and upper gastroscopy were normal) and the patient was well and without symptoms.

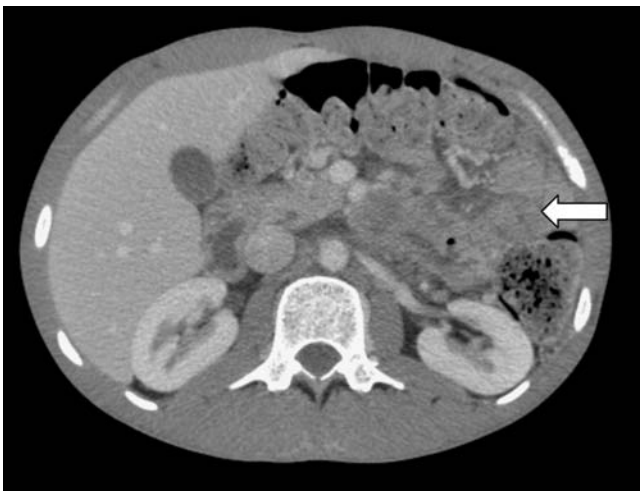


Figure 1 Abdominal CT scan: pathological mass of the third and fourth duodenum.

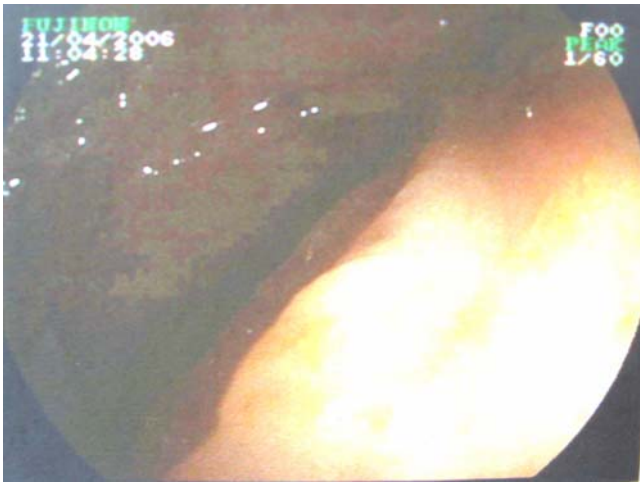


Figure 2 Endoscopic view of the tumoral stricture of the third duodenum.

Discussion

With an incidence of one to 1.4 per 100,000 people and a prevalence of 0.6%, small-bowel malignancies are very rare, representing only 1–2% of gastrointestinal malignancies.[1,6–12] Adenocarcinoma is the most common histologic subtype of carcinoma of the small bowel and is seen in 40–51% of all cases[1,10,12–14] and 73.8% of duodenal tumors.[12] The duodenum is the most likely location of adenocarcinoma of the small bowel, accounting for 48–63.2% patients.[1,10,13–15] On average, 30–34% of patients present with metastatic disease.[10,12,15] Mean age at diagnosis usually reported is 63.5–65.4 years.[12,15] The pathogenesis of adenocarcinoma of the small bowel is poorly understood, but the most significant known risk factor is previous Crohn's disease.[16–18] Neugut et al.[19] suggested that adenocarcinoma of the small bowel is associated with

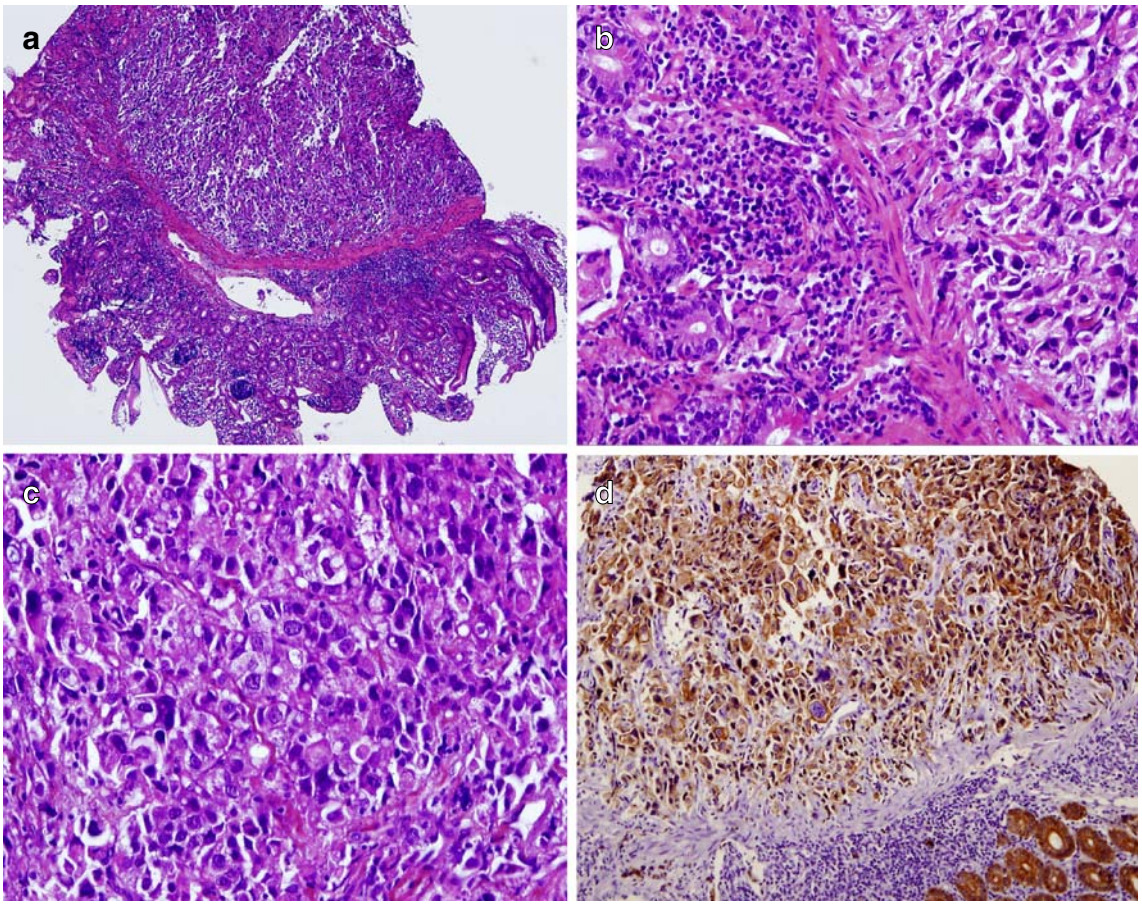


Figure 3 Endoscopic duodenal biopsy. **a** Lesion developed in duodenal wall (hematoxylin and eosin, ×25). **b** Infiltration of mucosa and sub-mucosa (hematoxylin and eosin, ×200). **c** Poorly differentiated adenocarcinoma with marked pleomorphism (hematoxylin and eosin, ×200). **d** Diffuse strong immunoreactivity with cytokeratin 20 in tumoral cells (×100).

familial adenomatous polyposis (FAP), celiac sprue, cystic fibrosis, and peptic ulcer disease. Our patient was very young compared to the median age at diagnosis reported by previous studies. No known or suggested risk factors were detected; notably, there was no Crohn's disease or FAP.

Prognosis of adenocarcinoma of the small bowel is very poor, with 5-year overall survival in the range of 20–38%.[3,15,22,23] The most important prognostic factors are resectability and distant metastatic disease.[12,20,21] Surgery with curative intent appears to be the only way to improve survival: 5-year survival when tumors are completely removed is 40–60% versus 10–30% for non-resected tumors.[1,3,5,15,20,22] The 5-year overall survival rate among patients with localized disease is 47.6–59.5% compared to 20.4–31.0% among those with regional disease and 3.9% when distant metastases are present.[1,12,15,22] All studies report a better prognosis for jejunal or ileal adenocarcinomas than for duodenal adenocarcinomas, with 5-year survivals of 26–37.6%, 25–37.8%, and 15–28.2%, respectively.[13,15] Only half of the duodenal tumors in the literature were treated with cancer-directed surgery, versus 90% of jejunal and ileal tumors. These differences in treatment are probably due to anatomic constraints.[13,15]

In a large population study, curative resection was feasible in 56.6% of cases.[12] Few data are available about chemotherapy in palliative or adjuvant settings. Treatment of adenocarcinoma of the small bowel is not well established because of the rarity of the tumor and the absence of prospective phase 3 studies. It is usually treated in the same way as colorectal cancer.[1,24] Adjuvant chemotherapy does not seem to improve survival.[1,22] In a large study covering 10 years, radiation therapy was given to 11.2% (6.1% as adjuvant therapy) of patients, and 25.8% had chemotherapy (17.5% as adjuvant therapy) with an increase of chemotherapy from 21.9% in 1985–1990 to 28.8% in 1991–1995. Increased chemotherapy use was particularly marked in patients with regional disease, rising from 28.4% to 40.6%.[15] Another large population study[12] covering 26 years reported that chemotherapy was performed in 27.2% of patients with primary malignant small-bowel cancers (14.8% adenocarcinoma), in an adjuvant setting for 24.5% of the cases and palliative setting for

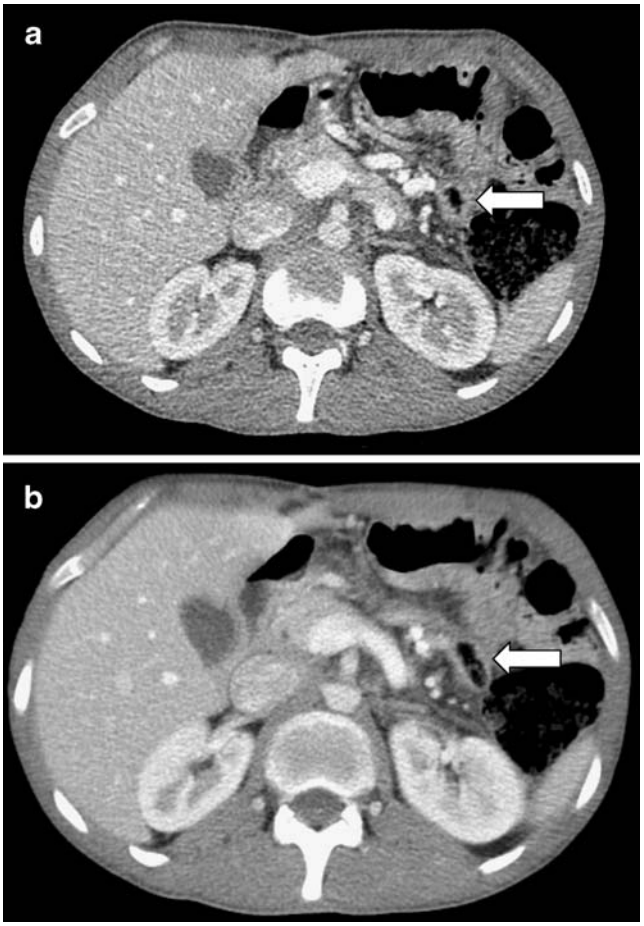


Figure 4 **a** Abdominal T scan: partial response after 2 months of chemotherapy. **b** Abdominal T scan: complete response after 4 months of chemotherapy.

60.4% (after palliative surgery in 38.3% of the cases, and among non-resected patients in 22.1%). The proportion of adenocarcinomas treated with chemotherapy increased significantly over time from 2.5% to 20.0% (p=0.009). Only one study, to our knowledge, reported a survival improvement in favor of palliative chemotherapy for patients who did not undergo surgery or who had Stage IV disease compared with patients who received no treatment (12 months vs. 2 months, p=0.02).[1]

In our case, chemotherapy in an initially palliative setting enabled us to achieve a surgically proven complete response and survival improvement without recurrence after 27 months of follow-up. That this good response is not usual underlines the importance of asking a multidisciplinary expert committee to evaluate the outcomes of such cases and to make agreed therapeutic decisions.

In conclusion, a FOLFOX 4 regimen seems to be efficacious in the treatment of some small-bowel adenocarcinomas. When the outcome remains favorable after a few months of chemotherapy, it is appropriate to ask a multidisciplinary expert committee to consider further surgery.

No gold standard adjuvant or palliative chemotherapy is validated for small-bowel adenocarcinoma. It is hoped that this report will stimulate the development of prospective trials to evaluate the efficacy of various chemotherapy regimens.

References

1. Dabaja BS, Suki D, Pro B, Bonnen M, Ajani J. Adenocarcinoma of the small bowel. Presentation, prognostic factors, and outcome of 217 patients. Cancer 2004;101:518–526.
2. Bauer RL, Palmer ML, Bauer AM, Nava HR, Douglass HO. Adenocarcinoma of the small intestine: 21-year review of diagnosis, treatment, and prognosis. Ann Surg Oncol 1994;1:183–188.
3. Ouriel K, Adams JT. Adenocarcinoma of the small intestine. Am J Surg 1984;147:66–71.
4. Barnes G, Romero L, Hess KR, Curley SA. Primary adenocarcinoma of the duodenum: management and survival in 67 patients. Ann Surg Oncol 1994;1:73–78.
5. Rose DM, Hochwald SN, Klimstra DS, Brennan MF. Primary duodenal adenocarcinoma: a ten-year experience with 79 patients. J Am Coll Surg 1996;183:89–96.
6. Treadwell TA, White RR. Primary tumors of the small bowel. Am J Surg 1975;130:749–755.
7. De Franchis R, Rondonotti E, Abbiati C, Beccari G, Signorelli C. Small bowel malignancy. Gastrointest Endosc Clin N Am 2004;14:139–148.
8. Gill SS, Heuman DM, Mihas AA. Small intestinal neoplasms. J Clin Gastroenterol 2001;33:267–282.
9. DiSario JA, Burt RW, Vargas H, McWhorter WP. Small bowel cancer: epidemiological and clinical characteristics from a population-based registry. Am J Gastroenterol 1994;89:699–701.
10. Chow JS, Chen CC, Ahsan H, Neugut AI. A population-based study of the incidence of malignant small bowel tumors: SEER, 1973–1990. Int J Epidemiol 1996;25:722–728.
11. Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1999. CA Cancer J Clin 1999;49:8–31.
12. Lepage C, Bouvier AM, Manfredi S, Dancourt V, Faivre J. Incidence and management of primary malignant small bowel cancers. A well-defined French population study. Am J Gastroenterol 2006;101:2826–2832.
13. Pashayan N, Lepage C, Rachet B, Woods LM, Coleman MP. Survival trends for small intestinal cancers in England and Wales, 1971–1990: national population-based study survival trends for small intestinal cancers. Br J Cancer 2006;95:1296–1300.
14. Severson RK, Schenk M, Gurney JG, Weiss LK, Demers RY. Increasing incidence of adenocarcinomas and carcinoid tumors of the small intestine in adults. Cancer Epidemiol Biomark Prev 1996;5:81–84.
15. Howe JR, Karnell LH, Menck HR, Scott-Conner C. Adenocarcinoma of the small bowel. Review of the National Cancer Data Base, 1985–1995. Cancer 1999;86:2693–2706.
16. Lashner BA. Risk factors for small bowel cancer in Crohn's disease. Dig Dis Sci 1992;37:1179–1184.
17. Munkholm P, Langholz E, Davidsen M, Binder V. Intestinal cancer risk and mortality in patients with Crohn's disease. Gastroenterology 1993;105:1716–1723.
18. Persson PG, Karlen P, Bernell O, Leijonmarck CE, Broström O, Ahlbom A et al. Crohn's disease and cancer: a population-based cohort study. Gastroenterology 1994;107:1675–1679.

19. Neugut AI, Jacobson JS, Suh S, Mukherjee R, Arber N. The epidemiology of cancer of the small bowel. Cancer Epidemiol Biomarkers Prev 1998;7:243–251.
20. Ito H, Perez A, Brooks DC, Osteen RT, Zinner MJ, Moore FD et al. Surgical treatment of small bowel cancer: a 20-year single institution experience. J Gastrointest Surg 2003;7:925–930.
21. Hutchins RR, Bani Hani A, Kojodjojo P, Ho R, Snooks SJ. Adenocarcinoma of the small bowel. ANZ J Surg 2001;71:428–437.
22. Talamonti MS, Goetz LH, Rao S, Joehl RJ. Primary cancers of the small bowel. Analysis of prognostic factors and results of surgical management. Arch Surg 2002;137:564–571.
23. Sant M, Aareleid T, Berrino F, Bielska Lasota M, Carli PM, Faivre J et al. EUROCARE-3: survival of cancer patients diagnosed 1990–94 results and commentary. Ann Oncol 2003;14 (Suppl 5):v61–v118.
24. Neugut AI, Marvin MR, Rella VA, Chabot JA. An overview of adenocarcinoma of the small intestine. Oncology 1997;11:529–536.

J Gastrointest Surg (2009) 13:2314–2320
DOI 10.1007/s11605-009-0952-1

HOW I DO IT

Total Proctocolectomy with Ileoanal J-Pouch Reconstruction Utilizing the Hand-Assisted Laparoscopic Approach

Liliana Bordeianou · Richard Hodin

Received: 2 March 2009 / Accepted: 12 June 2009 / Published online: 15 July 2009

Abstract This manuscript describes our technique for a minimally invasive ileoanal J- pouch procedure utilizing hand-assisted laparoscopy. We detail several important maneuvers that may be helpful to the surgeon faced with the challenge of a difficult laparoscopic pouch.

Keywords Laparoscopic surgery · Total proctocolectomy · Ileoanal J-pouch · Ulcerative colitis

Introduction

Ileal pouch-anal anastomosis (IPAA) is a surgical procedure that offers continence following extirpative proctocolectomy in patients with ulcerative colitis, familial adenomatous polyposis syndromes, and selected patients with small-bowel-sparing Crohn's disease. IPAA was first described by Parks in 1978, but since then, a variety of technical modifications have been made to the procedure.[1–3] These technical modifications have changed the original operative technique—an S-pouch configuration with mucosectomy and hand-sewn anastomosis—to a J-shaped reservoir made with intraluminal stapling devices and a double-stapled anastomosis without a mucosectomy. Although a steep learning curve for this operation appears to exist, the outcomes are generally considered to be excellent, with high volume centers reporting short-term pouch preservation rates of 96% and long-term preservation rates of 84%.[4–6] Patients undergoing this procedure can expect to have four to six bowel movements per day and one to two per night. Fecal incontinence has become less common with the recent technical improvements, though mild daily soiling can occur at first in 3–11% and nocturnal soiling can occur at first in 12–21%.[6,7] Without mucosectomy, the level of long-term continence in these patients ultimately improves until daytime accidents are nearly nil, and the overall anorectal function is not much different than the function seen in patients who are treated medically for their chronic ulcerative colitis.[7,8]

Recent technical advances have included minimally invasive approaches, such as total laparoscopic, laparoscopically assisted, and hand-assisted laparoscopy. While the safety of laparoscopy in IPAA is well documented, few authors provide a careful description of the key laparoscopic maneuvers, especially when the operation becomes technically challenging or when the pouch does not easily reach into the low pelvis.[9] We will describe our technique for a minimally invasive ileoanal J-pouch procedure utilizing hand-assisted laparoscopy, focusing on some of the important details of this operation. The indications for conversion to open surgery will be discussed, along with some important maneuvers that may be helpful to the surgeon faced with the challenge of a difficult laparoscopic pouch.

Indications for Surgery

Hand-assisted laparoscopic total proctocolectomy can be offered for a variety of indications, provided that the patient is clinically stable and is able to tolerate the somewhat longer operative procedure. In patients with ulcerative colitis, the indications for surgery include intractability despite maximum medical management, unrelenting or

L. Bordeianou (✉) · R. Hodin
Massachusetts General Hospital,
Boston, MA, USA
e-mail: lbordeianou@partners.org

significant hemorrhage, the finding of dysplasia, obstruction from stricture, systemic or extracolonic manifestations, and (in children) failure to thrive. In patients with documented colonic Crohn's, indications for a laparoscopic J-pouch include absence of small bowel and perianal disease and a clear understanding that the overall risk of pouch failure is increased.[10] Finally, laparoscopic J-pouch may be indicated for patients with a variety of polyposis syndromes.

Description of the Procedure

Positioning and Trocar Placement

The patient is positioned into lithotomy, with the hips straightened and the knees flexed so as to maintain a straight line between the abdomen and the thighs. This positioning maximizes the ability to maneuver the camera and laparoscopic instruments. The abdomen is entered via a small Phannensteil incision to allow for a handport. This incision is made transversely though the anterior rectus fascia. Flaps are raised superiorly and inferiorly so as to then allow a longitudinal incision between the rectus muscles to enter the peritoneal cavity. We then place a 10-mm umbilical port under direct vision, establish pneumoperitoneum to 15–18 mmHg, and insert two to four additional trocars: 5 mm right upper quadrant, 12 mm right lower quadrant, 10 mm left lower quadrant, and 5 mm left upper quadrant. The larger trocars are necessary to allow utilization of laparoscopic staplers or a 10-mm intracorporeal energy delivery device when taking vascular pedicles. In patients with a short torso, the right and left upper 5-mm trocars may not be needed. Before we proceed with the actual proctocolectomy in inflammatory bowel disease patients, the small intestine is examined from the ligament of Treitz to the cecum to rule out the presence of unsuspected small bowel Crohn's disease.

Total Colectomy

Using the medial to lateral approach, we first identify the ileocolic pedicle. The ileocolic pedicle is taken close to the right colon with a firing of the vascular 2.5-mm Endo GIA stapler (or laparoscopic intracorporeal energy delivery device). Preservation of a long ileocolic pedicle is unlike the procedure we use for the standard laparoscopic right colectomy for malignancy and serves to keep options open in case the mesentery of the small bowel needs further manipulation due to pouch non-reach. For those patients with dysplasia, a more radical mesenteric resection should be done, since up to 30% of such patients will be found to have cancer at the time of surgery. Control of the ileocolic pedicle is generally easiest without the assistance of the hand. We use our left lower quadrant port and a bowel grasper to pull the cecum superiorly and towards the right lower quadrant. This puts the ileocolic pedicle on stretch. The pedicle can now be safely dissected cirumferentially with a pointy dissector and then transected with a 2.5-mm stapler or an intracorporeal energy delivery device via the 12-mm LLQ port.

We then dissect the retroperitoneal plane to carefully identify and protect the duodenum and the ureter. This can be done by pulling the colonic mesentery towards the abdominal wall while a bowel grasper in the right hand pushes the flimsy attachments to the retroperitoneum down. The remaining mesentery to the right colon is usually thin and can be taken with an intracorporeal energy delivery device. In patients who have a short mesentery and are at risk for having difficulties with pouch reach, the goal is to stay as close as possible to the colon so as to preserve the marginal artery of the right colon and its communication with the right branch of the middle colic artery Finally, once the mesentery of the right colon is controlled, we take the lateral attachments of the right colon to the white line of Toldt and to the hepatic flexure using an intracorporeal energy delivery device.

We then turn to the transverse colon. The patient is positioned in reverse Trendelenburg. The omentum is carefully separated away from its colonic attachments with the Ligasure device. This can be accomplished by asking the assistant to hold the omentum up towards the abdominal wall from the patient's right side. This then allows the surgeon, who stands between the patient's legs, to pull the transverse colon down with their left hand (which can be either through the handport or straight laparoscopic) to expose the avascular attachments of the omentum to the transverse colon. Entry into the lesser sac allows us to subsequently mobilize the splenic flexure until it is fully separated from its retroperitoneal attachments. To see the splenic flexure, the patient needs to be rotated with the left side up.

The patient is then positioned in Trendelenburg and with the left side up to mobilize the left colon. We identify the left colic and superior rectal arteries in their medial positions and transect them with one firing of the vascular 2.5-mm Endo GIA stapler once the left ureter is clearly visualized. The left colon is then freed from the remainder of its avascular attachments along the white line of Toldt.

Finally, we turn our attention to the mesentery of the transverse colon. This is usually the toughest part of the laparoscopic procedure and the hand is very handy in speeding up the process. The patient is repositioned into reverse Trendeleburg. The surgeon moves to stand on the patient's left side. He inserts his left hand through the handport to expose the edge of the mesentery that was created following the takedown of the splenic flexure and

the superior rectal artery. This is done by pulling the colon towards the abdominal wall and to the patient's right. An intracorporeal energy delivery device can then be used to march across the remaining transverse colon mesentery until the entire colon is free. In cases when the patient is too tall to allow the reach of the hand to the transverse colon, this maneuver is done fully laparoscopically by having the assistant pull the transverse colon up and to the right through the right-sided ports.

Once the entire colon is mobilized, the handport is opened and the base of it is used as a wound protector. The colon is eviscerated through it. To allow for more room for the next steps of the procedure, which is mostly done open, we find it useful to transect the rectosigmoid and pass the colon off the field.

How to Assure the Reach of the J-Pouch

At this point, we perform several open maneuvers to ensure that the small bowel reaches into the pelvis to create an adequate IPAA without undue tension, a decision that must be made before one proceeds with proctectomy. To determine adequate reach, the terminal ileum is pulled out of the abdomen through the handport, folded onto itself at 15 cm, and pulled towards the pubis. In general, we consider the reach adequate if the ileum easily reaches at least a couple of centimeters beyond the pubis.

Fortunately, in the majority of cases, J-pouches reach to the anus easily. However, this is not always the case in the patients who are obese or very tall. In these situations, we routinely dissect the attachments of the small bowel mesentery to the third portion of the duodenum. Again, usually, this can be done open through the handport. However, if visualization is poor, it can also be done laparoscopically. In a laparoscopic setting, this maneuver is performed with the patient positioned into a steep reverse Trendelenburg, with the right side up. The assistant grasps the distal ileum with the hand and pulls it to the patient's left to expose its mesenteric attachments to the retroperitoneum. The operating surgeon approaches these while standing between the patient's legs and cuts with the Ligasure device. This is a delicate process, and it is extremely important to know the location of the duodenum and to see the mesentery of the small bowel clearly.

If any concerns about tension still exist following this maneuver, we use carefully placed transverse incisions of the anterior and posterior peritoneal layers of the ileal mesentery. Again, this can usually be done through the handport in an open fashion. However, if need be, it can also be done laparoscopically. In this case, this maneuver is performed as the assistant straightens the small bowel mesentery to expose the blood vessels. Only the peritoneum should be scored or cut. Trans-illumination with the camera can be helpful to visualize the blood vessels.

In some cases, especially in a patient that is particularly tall or obese and the mesentery is foreshortened, division of the distal ileocolic branches may be necessary (Fig. 1). We would advise doing this step through the open handport. It is prudent to test collateral circulation by placing a bulldog clamp across the vessel prior to division to assure that the bowel remains viable with the maneuver.

At this point, if the mesentery still does not reach, we would divide the ileocolic artery and the distal superior mesenteric artery (SMA) in the manner described by Goes et al.[11] We consider this maneuver only if the right branch of the middle colic artery has been preserved and the patency of the marginal artery has been verified (Fig. 2). We assess patency of the collaterals by clamping the ileocolic/distal SMA arteries with bulldogs while palpating for the remaining pulse in the apex of the pouch.

Finally, if there is not sufficient length of mesentery to achieve a tension-free anastomosis, we consider alternative pouch configurations, such as an S-shaped pouch.

Ultimately, if the surgeon lacks the experience to make a confident decision about proceeding with the J-pouch, we recommend intraoperative conversion to a subtotal colectomy with a Hartmann's pouch and end ileostomy. The patient could then be referred at a later time to a high volume center for a repeated attempt at pouch construction.

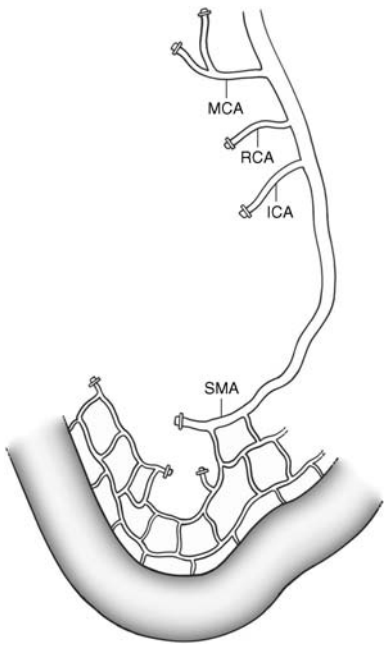


Figure 1 Division of distal ileocolic branches and distal SMA may be possible to provide pouch length as long as the collateral circulation through the small bowel arcades is adequate. *MCA* middle colic artery, *RCA* right colic artery, *ICA* ileocecal artery, *SMA* superior mesenteric artery.

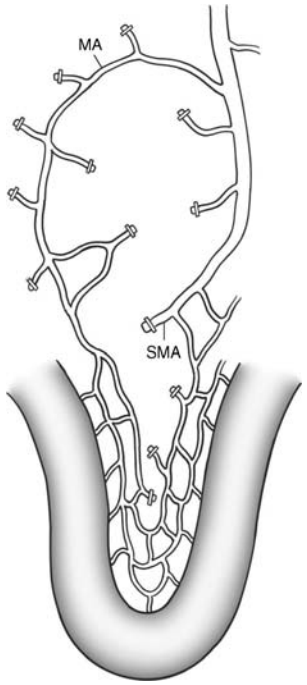


Figure 2 Division of distal SMA to provide length may be possible if marginal artery of right colon has been preserved in anticipation of difficulties with pouch reach. *MA* marginal artery of right colon, *SMA* superior mesenteric artery.

Proctectomy

Once we are confident that the pouch will reach without tension into the low pelvis, we proceed with the proctectomy. This can be done in a standard open fashion if the handport incision is large enough to allow adequate visualization to the levators. However, frequently, distal visualization is easier laparoscopically. To accomplish this, we position the patient into steep Trendelenburg. The surgeon stands on the patient's right side. He uses the left lower quadrant port to retract the proximal rectum anteriorly and to the left as he scores the peritoneum on the right side of the rectum into the pelvis. He then pulls the rectum anteriorly and begins the dissection through the Waldeyer's fascia. At this point, one can either stay in the mesorectal plane (LB) or makes his way toward the rectal wall itself (RH), staying as far away as possible from the hypogastric plexus as it divides into its two branches along the sides of the pelvis. Either way, the dissection is carried circumferentially all the way down to the levators.

If the surgeon intends to perform the eversion maneuver to remove the rectum (see below), the dissection down to the levators is performed along the rectal wall itself using an intracorporeal energy delivery device to assure meticulous hemostasis (Fig. 3a, b). In this case, the pelvic dissection is continued distally in the plane that is right on the muscular wall of the rectum, avoiding any possible injury to the pelvic autonomic nerves and allowing for utilization of the rectal eversion technique as originally described by Golligher et al.[12]

Alternatively, this dissection can be carried out in the standard avascular plane as done for a more standard total mesorectal excision. This is less bloody, but has the disadvantage of needing a bigger incision to fit the Controur stapler, as the rectal eversion cannot be performed due to the bulky rectal mesentery. Incision length considerations aside, standard total mesorectal excision is a must in all patients operated on for dysplasia.

As the dissection is carried distally to the levator ani musculature, we are meticulous in carefully separating the rectum from the posterior vaginal wall (or the prostate) anteriorly. If this dissection is done in a standard open fashion, lighted St. Marks retractors can be very helpful to ensure that the proper plane is maintained.

Rectal Eversion

A stapler is fired across the proximal rectum and then the operating surgeon goes below and passes a curved ring

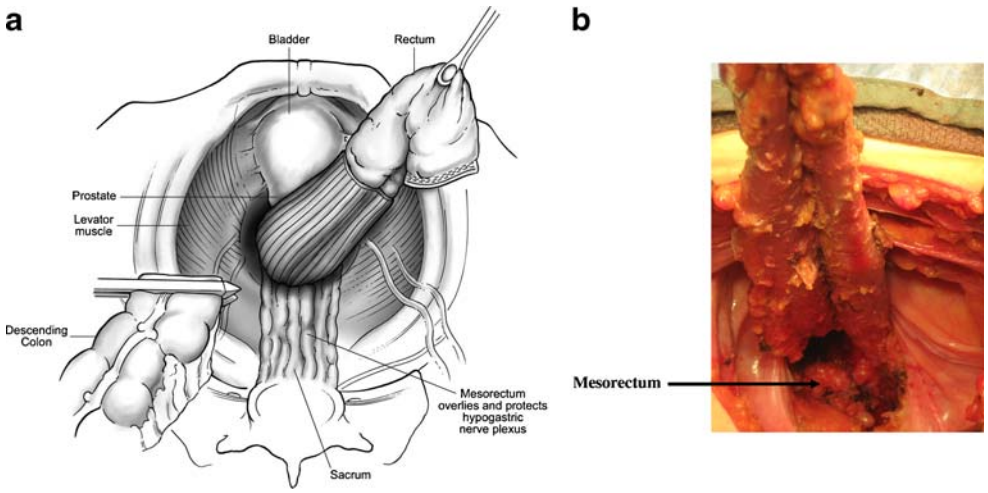


Figure 3 **a** Schematic representation of the rectum after it is completely dissected down to the levators. The dissection is carried close to the rectum, leaving the mesorectum behind. **b** Photograph of a dissected rectum. Note that the dissection is close to the rectum rather than in the mesorectal plane.

forceps through the anus and up to the rectal staple line. The assistant inserts the staple line into the forceps and the rectum is then everted outside of the patient. Assuming that the dissection has been carried sufficiently distal, the surgeon can clearly visualize the dentate line and choose the precise site for transection. The 55 4.8 Roticulator stapler is used to transect the distal rectum, preserving the anal transitional zone (Fig. 4a, b). Prior to staple firing in a woman, a finger is inserted into the vagina in order to be absolutely certain that the posterior vaginal wall is not included in the stapler. This critical maneuver will prevent the dreaded complication of a fistula to the vagina. Once the stapler is fired and the bowel transected, the rectal cuff is inverted back into the patient and assessed by digital exam to confirm its appropriate length. Note that the rectal staple line is inverted in relation to the peritoneal cavity, perhaps decreasing the risk of anastomotic leaks.

Fashioning of the J-Pouch

To fashion the J-pouch, we access the mobilized terminal ileum through the now open handport and fold it onto itself approximately 15 cm away from its transected margin. We then use electrocautery to create an enterotomy at the apex of the ileal loop and use the forks of a 100-mm intestinal stapler to perform a side-to-side anastomosis. The tips of the stapler are inspected carefully to assure that the mesentery is not included in the staple line (a laparoscopic Endo GIA can also be used for this purpose). We repeat this maneuver by telescoping the loops of the bowel onto the stapler so that the final anastomosis (pouch length) measures 15 cm. We then purse-string the exteriorized apical enterotomy with a 2–0 prolene stitch. The anvil of a no. 33 EEA stapler is tied down by the purse string, dropped into the peritoneal cavity, and the pneumoperitoneum is reestablished. The large no. 33 stapler can always be used and helps to prevent the problem of anastomotic stricture (Figs. 3 and 4).

Under direct vision, we penetrate the distal rectum by the pin of the EEA stapler. Cautery is used to cut the point of the stapler through so as to avoid any excess stretching or tearing of the rectal cuff. The anvil of the no. 33 EEA stapler is secured to the pin and the stapler is carefully closed. At this point, significant care must be taken to assure that the pouch is not rotated, that the anastomosis is not on tension, and that vagina/prostate are not incorporated into the stapler. Only after these criteria are met do we fire the stapler.

The pouch is then tested for any leaks via instillation of diluted Betadine (or water) via a Foley catheter positioned into the anal canal. The catheter balloon should be inflated outside of the patient and pushed up against the anus to prevent leakage around the catheter. The balloon should not be inflated inside the rectum since it will likely push against the anastomosis, thereby negating the utility of the leak test.

We do not leave drains.

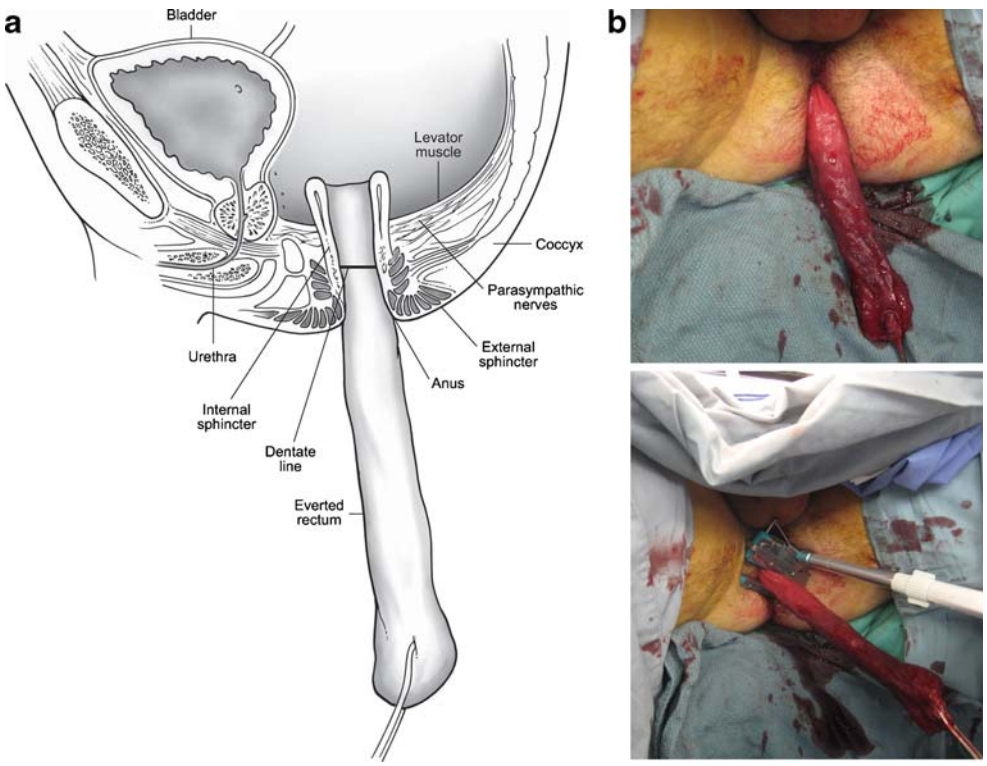


Figure 4 **a** Schematic representation of the everted rectum. A transection can then be performed 2–3 cm away from the dentate line. **b** Photographs of everted rectum. Note that transection can be easily accomplished with a TA stapler.

One Vs Two-Stage IPAA

The decision to do a one- vs two-stage operation is generally made preoperatively. In a selected group of patients who are off steroids and other immunosuppressants, we may consider performing a one-stage IPAA. The possibility of one-stage operation must be fully discussed with the patient, informing them of the 5–14% risk of leak, and that patients without a covering stoma may be at a higher risk of ultimate pouch failure should a leak occur, 15% vs 8%, based upon the data from St. Marks.[13–16]

In general, 80% of our patients are ultimately diverted. In this population, we create a loop ileostomy approximately 15 cm proximal to the pouch. In the patients who had a difficult pouch reach or who are obese and/or tall, we position the ileostomy site lower on the abdominal wall than normally, thus minimizing the tension on the mesentery of the pouch.

In the patients interested in avoiding a temporary ileostomy, the ultimate decision about its construction will be made intraoperatively. If the operation went smoothly, two complete anastomotic donuts are obtained, and the leak test is negative, the ileostomy is not performed. In these cases, we generally leave a Foley catheter though the anal anastomosis into the pouch and secured to the buttock with a stitch. This catheter is left in place for 2–3 days, preventing the pouch from becoming over-distended in the early post-op period.

Postoperative Care

Patients with a diverting ileostomy are generally given a liquid diet for the first couple of days post-op, and the diet advanced to soft solids once the stoma begins to function. We try to ensure that the patient is able to keep up with the ileostomy output before considering discharge in order to prevent dehydration at home. Occasionally, in situations of high stoma output, we use a carefully titrated regimen of Immodium and/or DTO to prevent postoperative dehydration. We perform a gastrografin enema in about 6 to 8 weeks to document a patent J-pouch without leak prior to ileostomy reversal. Ileostomy reversal can almost always be accomplished directly through the stoma site itself using the side-to-side stapling technique.

Patients without a diverting ileostomy are kept nil per orally until they are passing gas and/or stool. For the first 3 days following surgery, their pouch is gently irrigated daily via the catheter in order to ensure catheter patency and promote pouch drainage. In this group of patients, we start clear liquids only after the pouch begins to function and the diets are advanced with caution.

Conclusion

The decision to perform a hand-assisted laparoscopic total proctocolectomy with J-pouch reconstruction is dictated by the patient's prior surgical history, body habitus, clinical status, as well as surgeon's preference and expertise. This approach is safe and technically feasible in an appropriate patient population. However, the procedure is more technically challenging and more time-consuming than open surgery. It should be noted that even when we perform the IPAA through a standard open approach, the operation is almost always able to be done through a low, infra-umbilical midline incision, thus avoiding the increased pain and relatively worse cosmesis of the upper midline scar.

The advantages of laparoscopy, especially the hand-assisted approach, for this particular operation remain a matter of debate. There is a cosmetic advantage, but the importance of this factor differs from patient to patient. Another potential advantage may be a decrease in adhesions and adhesion-related complications, most notably small bowel obstructions and infertility.[16] From this standpoint, the extra time spent in the operating room during the index surgery may provide an improvement to the rates of readmissions and reoperations for small bowel obstructions and to the cumulative incidence of pregnancy in this young group of patients.

Acknowledgements We would like to thank our medical illustrator, Peggy Firth, for her beautiful drawings.

References

1. Parks AG, Nicholls RJ. Proctocolectomy without ileostomy for ulcerative colitis. British Medical Journal 1978;2:85–88.
2. Heald RJ, Allen DR. Stapled ileo-anal anastomosis: a technique to avoid mucosal proctectomy in the ileal pouch operation. Br J Surg 1986;73(7):571–572.
3. Choen S, Tsunoda A, Nicholls RJ. Prospective randomized trial comparing anal function after hand sewn ileoanal anastomosis with mucosectomy versus stapled ileoanal anastomosis without mucosectomy in restorative proctocolectomy. Br J Surg 1991;78 (4):430–434.
4. Tekkis PP, Fazio VW, Lavery IC et al. Evaluation of the learning curve in ileal pouch-anal anastomosis surgery. Ann Surg 2005;241 (2):262–268.
5. Raval MJ, Schnitzler M, O'Connor BI, Cohen Z, McLeod RS. Improved outcome due to increased experience and individualized management of leaks after ileal pouch-anal anastomosis. Ann Surg 2007;246(5):763–770.
6. Hahnloser D, Pemberton JH, Wolff BG, Larson DR, Crownhart BS, Dozois RR. Results at up to 20 years after ileal pouch-anal anastomosis for chronic ulcerative colitis. Br J Surg 2007;94 (3):333–340.

7. Michelassi F, Lee J, Rubin M et al. Long-term functional results after ileal pouch anal restorative proctocolectomy for ulcerative colitis: a prospective observational study. Ann Surg 2003;238 (3):433–441. discussion 442–435.
8. Gawad KA, Wenske S, von Schrenck T, Izbicki JR. Ileoanal-pouch reconstruction does not impair sphincter function or quality of life. Hepatogastroenterology 2007;54(77):1477–1482.
9. Tan JJ, Tjandra JJ. Laparoscopic surgery for ulcerative colitis—a meta-analysis. Colorectal Dis 2006;8(8):626–636.
10. Reese GE, Lovegrove RE, Tilney HS et al. The effect of Crohn's disease on outcomes after restorative proctocolectomy. Dis Colon Rectum 2007;50(2):239–250.
11. Goes RN, Nguyen P, Huang D, Beart RW Jr. Lengthening of the mesentery using the marginal vascular arcade of the right colon as the blood supply to the ileal pouch. Dis Colon Rectum 1995;38 (8):893–895.
12. Golligher JC. Eversion technique for distal mucosal proctectomy in ulcerative colitis: a preliminary report. Br J Surg 1983;71 (1):26–28.
13. Tjandra JJ, Fazio VW, Milsom JW, Lavery IC, Oakley JR, Fabre JM. Omission of temporary diversion in restorative proctocolectomy—is it safe? Dis Colon Rectum 1993;36(11):1007–1014.
14. Galandiuk S, Wolff BG, Dozois RR, Beart RW Jr. Ileal pouch-anal anastomosis without ileostomy. Dis Colon Rectum 1991;34 (10):870–873.
15. Tulchinsky H, Hawley PR, Nicholls J. Long-term failure after restorative proctocolectomy for ulcerative colitis. Ann Surg 2003;238(2):229–234.
16. Ording Olsen K, Juul S, Berndtsson I, Oresland T, Laurberg S. Ulcerative colitis: female fecundity before diagnosis, during disease, and after surgery compared with a population sample. Gastroenterology 2002;122(1):15–19.

J Gastrointest Surg (2009) 13:2321–2329
DOI 10.1007/s11605-009-0927-2

REVIEW ARTICLE

Enhanced Recovery after Surgery (ERAS) Programs for Patients Having Colorectal Surgery: A Meta-analysis of Randomized Trials

Cagla Eskicioglu · Shawn S. Forbes · Mary-Anne Aarts · Allan Okrainec · Robin S. McLeod

Received: 22 April 2009 / Accepted: 28 April 2009 / Published online: 21 May 2009

Abstract
Background Enhanced recovery after surgery programs have been introduced with aims of improving patient care, reducing complication rates, and shortening hospital stay following colorectal surgery. The aim of this meta-analysis was to determine whether enhanced recovery after surgery programs, when compared to traditional perioperative care, are associated with reduced primary hospital length of stay in adult patients undergoing elective colorectal surgery.
Methods MEDLINE, EMBASE, the Cochrane Central Registry of Controlled Trials, and the reference lists were searched for relevant articles. Only randomized controlled trials comparing an enhanced recovery program with traditional postoperative care were included.
Results Three of four included studies showed significantly shorter primary lengths of stay for patients enrolled in enhanced recovery programs. There was no significant difference in postoperative mortality when the two groups were compared [relative risk (RR)=0.53; 95% CI=0.12–2.38; test for heterogeneity, p=0.40 and I_2=0], and patients in enhanced recovery programs were less likely to develop postoperative complications (RR=0.61, 95% CI=0.42–0.88; test for heterogeneity, p=0.95 and I_2=0).
Authors' Conclusions There is some evidence to suggest that enhanced recovery after surgery programs are better than traditional perioperative care, but evidence from a larger, better quality randomized controlled trial is necessary.

Keywords Enhanced recovery after surgery · Colorectal surgery · Meta-analysis · Postoperative complications

No funding was sought for the conduct of this study; it is not based on a previous communication to a society or meeting.

C. Eskicioglu · S. S. Forbes · M.-A. Aarts · A. Okrainec · R. S. McLeod
Department of Surgery, University of Toronto, Toronto, Canada

C. Eskicioglu · S. S. Forbes · R. S. McLeod
Department of Health Policy, Management, and Evaluation, University of Toronto, Toronto, Canada

C. Eskicioglu · S. S. Forbes · R. S. McLeod
Zane Cohen Digestive Diseases Research Center, Mount Sinai Hospital, Toronto, Ontario, Canada

R. S. McLeod (✉)
Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, Ontario, Canada
e-mail: rmcleod@mtsinai.on.ca

M.-A. Aarts
Toronto East General Hospital, Toronto, Ontario, Canada

A. Okrainec
Toronto Western Hospital, University Health Network, Toronto, Ontario, Canada

Introduction

Colorectal surgery has been associated with complication rates ranging from 10% to 20% and mean postoperative hospital stays from 6 to 10 days.[1] In an effort to improve postoperative outcomes in patients undergoing colorectal surgery, enhanced recovery after surgery (ERAS) programs have been designed and evaluated.[2,3] ERAS programs, also known as fast-track surgery, are multimodal perioperative programs that aim to accelerate recovery, shorten hospital

stay, and reduce complication rates following colorectal surgery. These programs address many factors thought to prolong hospital stay, including prolonged parenteral analgesia use, overuse of intravenous hydration, and delayed mobilization.[4]

ERAS programs described in the literature are incredibly diverse and include recommendations for a variety of interventions.[4,5] These can be classified as preoperative, intraoperative, or postoperative interventions. The preoperative interventions include extensive preoperative counseling, avoidance of mechanical bowel preparation (MBP), avoidance of fasting, avoidance of premedication, administration of pre- and probiotics, and preoperative carbohydrate loading until 2 h prior to surgery. Intraoperative interventions are strict fluid management to avoid fluid overload, normothermia, hyperoxia, and tailored optimal analgesia. Finally, postoperative components include epidural anesthesia, early routine mobilization, early enteral nutrition, avoidance of nasogastric (NG) tubes, avoidance of peritoneal drains, and early removal of catheters.[4,5] Many studies have shown that the avoidance of individual components, such as NG tubes or MBP, have not led to increased complications.[4,6,7] Experience with other components, such as type of surgical incision or methods to address postoperative nausea and vomiting, has been limited, but these factors are still included in the comprehensive programs based mostly on consensus.[4,5]

ERAS programs are designed to minimize the stress response that is associated with surgery.[4] Clinically, ERAS regimens result in better physical performance, measured by treadmill exercise, pulmonary function, and body composition as measured by lean body mass.[8] It appears that the combination of many of these factors has a synergistic positive effect on postoperative outcomes following colorectal surgery as compared to each individual parameter alone.[5]

Designing a multimodal ERAS program and organizing a devoted surgical team to implement this program may be costly. Before embarking on an extensive intervention, it is important to clearly delineate the benefits of such programs. The individual studies evaluating ERAS programs have revealed both advantages and disadvantages of these programs. The purpose of this meta-analysis is to synthesize the evidence and determine the utility of ERAS programs for patients undergoing elective colorectal surgery.

The primary goal of this review was to determine whether ERAS programs, when compared to traditional perioperative care, are associated with reduced primary and total postoperative hospital stay in adult patients undergoing elective colorectal surgery. The impact of ERAS programs on other outcomes such as major and minor postoperative complications, mortality, rates of readmission, and reoperation is also reviewed.

Methods

Systematic Review

A systematic review of the medical literature was performed with the assistance of a medical librarian to identify all potential abstracts regardless of publication status or language that compared ERAS programs to traditional perioperative care in patients undergoing elective colorectal surgery. MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials were searched between 1950 and May 2008 using the following strategy: Explode "intestinal diseases," "colectomy," "laparotomy," "laparoscopy," "video-assisted surgery," "cecal neoplasms," or "colorectal neoplasms" combined with "multimodal," "optimization," "enhanced recovery," or "fast track." The associated text and title words were similarly searched. Standard limiters were used to identify randomized trials and review articles. Reference lists of randomized controlled trials (RCTs), meta-analyses, and systematic reviews were hand-searched for studies that were not captured by the initial electronic search. Content experts (MA, AO) were consulted to ensure no published or unpublished work had been missed. Two authors (CE, SSF) independently reviewed all citations generated by the literature search to

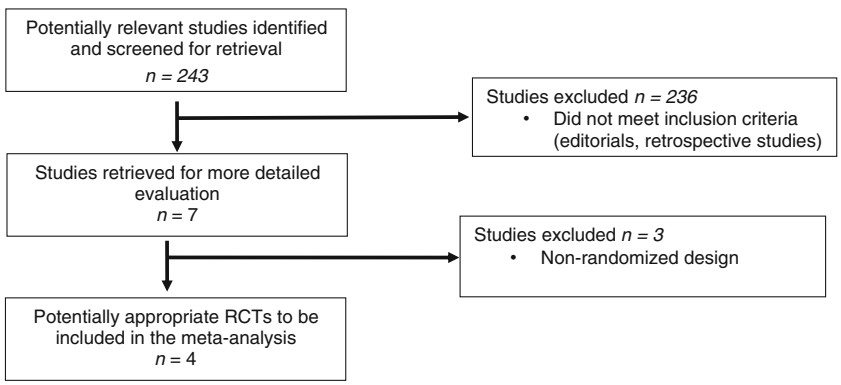


Figure 1 Summary of literature search and study selection.

Table 1 Components of ERAS Interventions Used in the Four Included Studies

	Delaney et al.[12]	Anderson et al.[13]	Gatt et al.[14]	Khoo et al.[15]
Preoperative	Preoperative counselling and written information	Verbal/written preoperative information	Verbal/written preoperative information	MBP—Fleet phospho-soda (2 bottles)
		Pre-assessment by anesthesia/surgery	Pre-assessment by anesthesia/surgery	Oral fluids until 3 h prior to surgery
		Synbiotics	Synbiotics	No intravenous (IV) fluids overnight
		Omission of MBP	Omission of MBP	
		Oral carbohydrate loading	Oral carbohydrate loading	
		Preoperative fast 3 h prior to surgery	Preoperative fast 3 h prior to surgery	
Intraoperative	NG tubes removed before extubation	80% FiO_2	80% FiO_2	Intra-op fluid restriction—1,500 cc unless blood loss >500 cc occurred
		Transverse incision	Transverse incision	
Postoperative	Offer clear fluids on the evening of surgery	No drains	No drains	Free oral fluids immediately postoperatively
	Encouraged to ambulate on the evening of surgery	No NG tubes	No NG tubes	IV fluids discontinued once tolerating 200 cc of water over 30 min
	Solid food POD#1 at dinner	Early fluid and diet reintroduction	Early fluid and diet reintroduction	NG tube removed in recovery room
	Oral analgesia started on POD#2	Aggressive structured mobilization plan by physiotherapists	Aggressive structured mobilization plan by physiotherapists	Diet commenced immediately postoperatively
	Wall chart to emphasize ambulation	Epidural analgesia with standing acetaminophen and ibuprofen, PRN morphine	Epidural analgesia until 24–36 h postoperatively	Regular domperidone, magnesium hydroxide 8% and liquid protein/calorie supplements from admission
	PCA analgesia + ketorolac q6hr PRN			Thoracic epidural—infusion rate not adjusted unless there were features of narcotization
				Epidurals discontinued at 48 h postoperatively
				Standing paracetamol and ibuprofen starting immediately postoperatively
				Urinary catheters removed 24 h post-colonic surgery and 72 h post-TME
				Mobilization encouraged from night of OR and patients were encouraged to meet predefined mobility targets

include relevant studies. A consensus meeting was used to resolve any disagreements on selection.

Study Selection

All RCTs comparing ERAS programs to traditional perioperative care in patients undergoing elective colorectal surgery were included in this review. Studies evaluating adult patients (>18 years of age) undergoing elective, open or laparoscopic, colon or rectal resections regardless of indication for surgery (i.e., colon cancer, inflammatory bowel disease, diverticulosis, etc.) were included. Quasi-randomized trials, non-randomized trials, and uncontrolled studies were excluded. Trials investigating patients who had a colon resection for bowel obstruction, bowel perforation, or any emergent cause were excluded.

Data Extraction, Outcomes, and Study Quality

Two reviewers independently abstracted data and rated the methodological quality of all included studies, resolving discrepancies by consensus (CE, SSF). Methodological quality criteria were adapted from the US Preventative Task Force Criteria.[9] The following criteria were assessed: concealment of the randomization allocation, description of the randomization method, blinding of the outcome assessor, similarity of baseline patient characteristics between the two study arms, definition of study outcomes, minimum of 80% patient follow-up, and use of intention-to-treat analysis.

One important study characteristic, which was abstracted in order to comment on clinical heterogeneity, was the nature of the ERAS intervention. This included the number and details of the parameters involved in each ERAS intervention. The primary outcomes were primary and total postoperative hospital stay. Primary hospital length of stay was defined as the number of days in hospital after surgery until discharge. Total hospital length of stay included primary hospital stay and any additional days during hospital readmission within 30 days of surgery. Secondary outcomes included postoperative mortality, postoperative complications (major and minor), and rate of readmission. Major complications included intra-abdominal infections, anastomotic leaks, cardiac complications, respiratory complications, venous thromboembolic disease. Minor complications included superficial surgical site infections, pneumonia, and urinary tract infections. For binary outcomes, the number of outcomes in the intervention and control groups were recorded. For continuous outcomes, the mean and standard deviation (SD) were recorded when available.

Statistical Analysis

Calculations of effect sizes for dichotomous variables are presented as relative risk (RR) with 95% confidence intervals (CI) and for continuous outcomes as weighted mean differences. Pooled analyses were performed using both the random effects and fixed effects models with the Mantel–Haenszel method when appropriate. Clinical heterogeneity was explored by examining study characteristics, specifically ERAS intervention modalities and the reported outcomes. Statistical heterogeneity was assessed using the Cochran's Q test ($p<0.10$) and the I^2 statistic. Funnel plots were used to assess for publication bias. These analyses were performed using RevMan 5.0 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark).

Results

Two hundred forty-three abstracts were retrieved from the search, of which 236 did not fulfill the inclusion criteria (Fig. 1). Of the seven identified for further review, three were excluded due to a non-randomized design.[2,10,11] The four RCTs included in the review were published between 2003 and 2007 and enrolled a total of 198 patients.[12–15] There were no studies comparing one ERAS program to another. The number of ERAS interventions, which were addressed by the four studies, ranged from 8 to 14 (Table 1). Some of the components included in the ERAS intervention of the four studies were similar. However, there was some clinical heterogeneity regarding number of included interventions and some of the other intervention components. For example, one trial[15] included the use of mechanical bowel preparation as part of the ERAS intervention, whereas two other trials included the omission of mechanical bowel preparation as part of the intervention.[13,14]

All four studies reported randomized allocation to each study arm as well as concealment of allocation. Three studies[12–14] used sealed envelopes to allocate patients and one study[15] used a central randomization system with a

Table 2 Primary Hospital Length of Stay

Study	ERAS	Traditional perioperative care	p value
Delaney et al.[12]			
Mean±SD (days)	5.2±2.5	5.8±3	0.12
Anderson et al.[13]			
Median (range, days)	3 (2–7)	7 (4–10)	0.002
Mean±SD (hours)	95.1±42.5	167.8±49.6	0.002
Gatt et al.[14]			
Median (range, days)	5 (4–9)	7.5 (6–10)	0.027
Khoo et al.[15]			
Median (range, days)	5 (3–37)	7 (4–63)	<0.001

Table 3 Overall Hospital Length of Stay

Study	ERAS	Traditional perioperative care	*p* value
Delaney [12]			
Mean±SD (days)	5.4±2.5	7.1±4.8	0.022
Khoo [15]			
Median (range)	5 (3–37)	7 (4–63)	<0.001

random number generator. None of the four studies reported the use of blinding of the surgeon, patient, or outcome assessors. Complete patient data (100% follow-up) were reported in all four studies. There was no evidence or reporting of protocol violations in three of the studies; as such, intention-to-treat (ITT) analysis was not necessary.[13–15] One study reported protocol violations and the subsequent use of ITT analysis Table 2.[12]

Hospital Stay

Pooling of the primary and overall hospital length of stay was not possible. One study[12] reported the results as a mean±SD. Two studies reported length of stay as a median and range.[14,15] The fourth study[13] reported both mean±SD and median with range. Although it is possible to estimate mean and standard deviation from median and interquartile range, this was felt to be statistically inappropriate. In summary, three of these four studies showed significantly shorter primary length of stays for patients enrolled in ERAS programs (Table 2).[13–15] In the one study[12] that did not find a statistically significant shorter primary hospital stay, the patients enrolled in the ERAS program were significantly older than those patients receiving traditional perioperative care despite randomization. Only two studies reported overall hospital stay and these results were also not pooled.[12,15] Both studies,[12,15] however, reported significantly shorter overall hospital length of stay in patients enrolled in ERAS programs (Table 3).

Postoperative Mortality and Complications

Three studies reported on postoperative mortality. Compared to patients receiving traditional perioperative care, there was no significant difference in postoperative mortality for patients enrolled in ERAS programs (RR=0.53; 95% CI=0.12–2.38; test for heterogeneity, p=0.40 and I^2=0; Fig. 2). All four studies reported on major and minor postoperative complications. Patients who were treated using ERAS programs were significantly less likely to develop postoperative complications than those patients receiving traditional perioperative care (RR=0.61; 95% CI=0.42–0.88; test for heterogeneity, p=0.95 and I^2=0; Fig. 3). There were no significant differences in the rates of major (RR=0.40; 95% CI=0.06–2.59; test for heterogeneity, p=0.04 and I^2=63%; Fig. 4) and minor complications (RR=0.67; 95% CI=0.37–1.23; test for heterogeneity, p=0.17 and I^2=41%; Fig. 5) in patients receiving ERAS care as compared to those patients receiving traditional perioperative care. Since significant statistical heterogeneity was observed for major complications, the random effect model was used to pool the data. Furthermore, there was no significant difference in readmission to hospital in ERAS patients compared to traditional perioperative care patients (RR=0.67; 95% CI=0.20–2.19; test for heterogeneity, p=0.27 and I^2=24%; Fig. 6). Only one trial reported on reoperation as an outcome, and this study showed a non-significant trend toward a reduced risk of reoperation in ERAS patients compared to traditional perioperative care patients (RR=0.35; 95% CI=0.04–3.23).[12]

Discussion

This meta-analysis evaluates postoperative outcomes which are relevant in the care of surgical patients by using data from four randomized controlled trials comparing ERAS with traditional perioperative care. The results for primary and total hospital length of stay could not be pooled; however, three of the four studies revealed a significantly

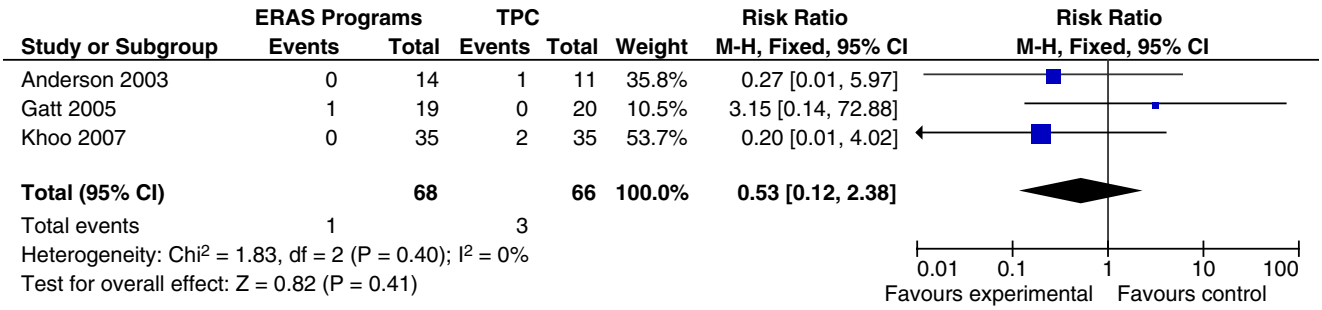


Figure 2 Pooled analysis of postoperative mortality, ERAS vs. traditional perioperative care (*TPC*).

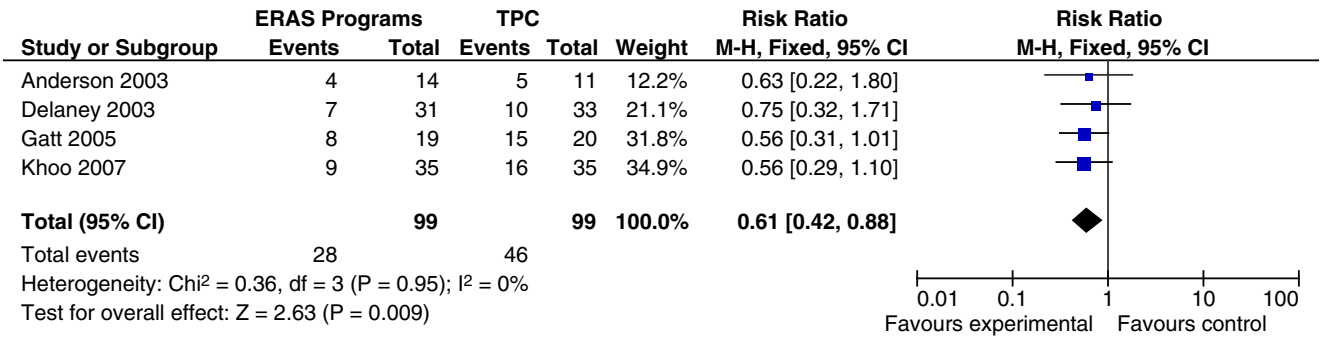


Figure 3 Pooled analysis of total complications (major and minor), ERAS vs. traditional perioperative care (*TPC*).

shorter primary length of hospital stay in patients enrolled in ERAS programs as compared to traditional perioperative care. Furthermore, this meta-analysis revealed a significant decreased rate of overall complications with a trend towards decreased mortality and reoperation rate for patients enrolled in ERAS programs. However, there were only four deaths and 18 readmissions in total observed in the four trials, and this likely accounts for the failure to observe a statistically significant difference.

In addition to statistical heterogeneity, there was also some clinical heterogeneity that is important to note. In addition to differences in the particular components that were included in each ERAS program, the number of components also varied. For example, the trial by Delaney et al.[12] included eight components in the ERAS intervention. Interestingly, this trial was the only one of the four not to detect a statistically significant difference in primary hospital length of stay between the control and intervention groups. The other three trials included 13 or 14 components, and these trials all showed a 2-day reduction of primary hospital length of stay in the ERAS intervention arm.[13–15] Also of note is that two of these three trials included very similar ERAS intervention components.[13,14]

This review includes evidence from randomized controlled trials only and therefore assesses the best available evidence. It is, however, limited by the small number of included studies and the low number of patients (total of 198) included in these trials. Furthermore, it is also limited by the methodological quality of the included studies. All four studies were found to have a high risk of bias. Blinding of outcome assessment was either not performed or not reported. Given the nature of the interventions being compared, blinding of the patient and surgeon is not feasible; however, outcome assessors could be blinded to reduce measurement bias. Since none of the studies reported or performed this aspect of methodological quality, studies were not excluded based on the lack of blinding. All four studies, however, did describe predefined discharge criteria used to determine patients' readiness for discharge. This may somewhat reduce possible bias of surgeons deciding when to discharge patients.

Further affecting the quality of the evidence was the lack of well-defined outcomes[15] and the lack of comparable groups at entry into the trial.[12] All four trials reported length of stay as a primary outcome. Since there are often social barriers delaying discharge, length of stay (LOS) may not be the most objective outcome. For example, even if a patient has met the predefined discharge criteria, hospital discharge may be delayed for social reasons. In two of the studies included in this review, only patients who were living independently prior to surgery were included.[13,14] This, therefore, limits the generalizability of the

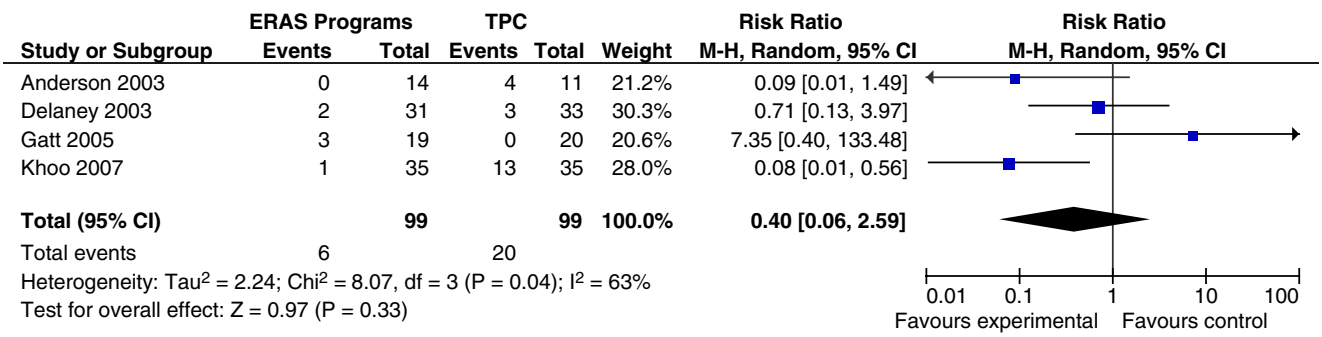


Figure 4 Pooled analysis of major complications, ERAS vs. traditional perioperative care (*TPC*).

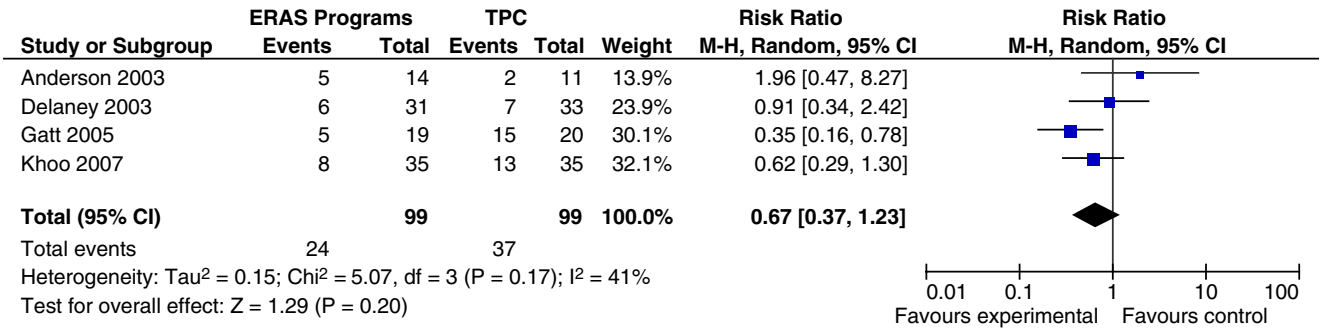


Figure 5 Pooled analysis of minor complications, ERAS vs. traditional perioperative care (*TPC*).

results and the ERAS programs. Furthermore, although LOS is an important outcome for cost-effectiveness and allocation of resources, it may not be the most important outcome for delivering quality care to patients. These studies were not powered to primarily assess more clinically relevant outcomes such as complications or even mortality. As well, patient satisfaction was not assessed. Further research in this field designed to evaluate these outcomes would be beneficial.

The review process was performed to minimize bias. The literature strategy used in this review was designed to be broad and capture evidence on any type of ERAS programs. However, there is a possibility that this review missed non-published studies. As well, meeting abstracts were not reviewed. Selection of articles for inclusion as well as data extraction and quality assessment were performed by two independent reviewers. Finally, the inclusion criteria for studies, quality criteria, outcomes, and analysis techniques were all designated a priori.

There is currently only one other review which compares ERAS to traditional perioperative care in patients undergoing elective colorectal surgery. Wind et al.[4] performed a meta-analysis of six trials including 512 patients: three randomized trials which are included in our review and three non-randomized trials. One RCT[15] included in this meta-analysis was not included in the meta-analysis by Wind et al.[4] The meta-analysis revealed a shorter hospital stay when comparing patients enrolled in ERAS programs to traditional perioperative care. This review also reported no increase in mortality, morbidity, or readmission to hospital in patients enrolled in ERAS programs.[4] In comparison, this review includes only randomized controlled trials and includes the most recently published trial by Khoo et al.[15] The results of this meta-analysis are similar to those of the previously published meta-analysis. However, inclusion of only randomized controlled trials adds to the methodological rigor of this meta-analysis.

Larger randomized trials with improved methodological quality could add to the current literature in this field. In particular, trials must report on allocation concealment, blinding of outcome assessors, and include well-defined objective endpoints. Trials evaluating ERAS programs must set predefined discharge criteria for patients in both the ERAS arm and traditional perioperative care arm in order to further reduce bias. These predefined discharge criteria will ensure that only those patients who are clinically ready for discharge will be discharged from hospital regardless of the clinical pathway.

On the other hand, these trials are difficult to perform. Many of the individual components have already been adopted into standard care despite variable evidence of their effectiveness. So, performing a trial without contamination

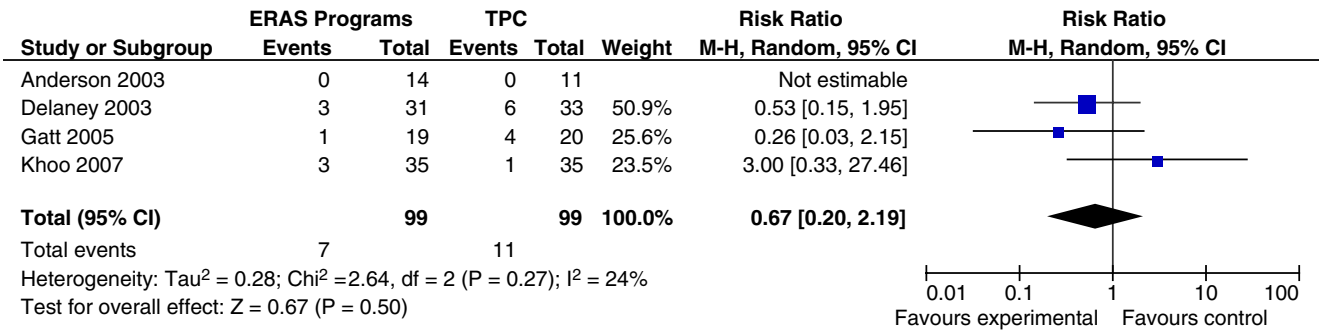


Figure 6 Pooled analysis of readmission to hospital, ERAS vs. traditional perioperative care (*TPC*).

in the control group might be difficult. In all future studies, besides clinical outcomes, patient satisfaction must be considered. As well, feasibility and hospital resources and costs must be included. Finally, identifying which individual strategies are effective and should be included in the ERAS package should be an important consideration since many are resource intense.

Randomized controlled trials have shown that length of stay is reduced with laparoscopic colorectal surgery.[16–18] However, there has been no evaluation of ERAS versus traditional perioperative care in patients having laparoscopic surgery. Two randomized controlled trials have compared open to laparoscopic surgery in the setting of an ERAS program.[19,20] In one trial which included 62 patients, Basse et al.[19] reported rapid postoperative recovery and discharge with a median of length of stay of 2 days; however, there was no difference in this outcome when comparing the laparoscopic and open groups. In another similar trial also evaluating 62 patients, length of stay was 2.2 days shorter (p=0.018) in patients undergoing laparoscopic surgery. Furthermore, patients undergoing laparoscopic surgery were also less likely to be readmitted with an odds ratio (OR) of 0.13 (95% CI=0.02–0.79, p=0.027).[20] Currently, with evidence only from these two small trials, it is difficult to draw conclusions regarding the potential benefits of ERAS programs for patients undergoing laparoscopic colorectal surgery. A large randomized controlled trial on this topic would be beneficial.

Conclusions

Although the individual studies showed that ERAS programs were associated with shorter primary and total hospital length of stay, we chose not to pool these data for statistical reasons and thus cannot provide further evidence for these outcomes. Our review does indicate, however, that ERAS programs are associated with reduced total complications. Furthermore, it is also difficult to draw conclusions regarding reductions in mortality and readmission, as the pooling of these outcomes was still underpowered. There is some evidence to suggest that ERAS programs are better than traditional perioperative care, but a larger randomized controlled trial is necessary. This study, with more rigorous methodology, is required to more clearly define components for ERAS programs as well as assess more clinically relevant endpoints.

Acknowledgments The authors would like to thank Dr. Prakesh Shah, Department of Pediatrics, University of Toronto, for his input during the conduct of the systematic review and preparation of the manuscript and Dr. Joseph Beyene, Department of Medicine, University of Toronto and Population Health Sciences Research Institute, Hospital for Sick Children for his input during the statistical analysis.

References

1. Bokey EL, Chapuis PH, Fung C, Hughes WJ, Koorey CG, Brewer D et al. Postoperative morbidity and mortality following resection of the colon and rectum for cancer. Dis Colon Rectum 1995;38 (5):480–487. doi:10.1007/BF02148847.
2. Bradshaw BGG, Liu SS, Thirlby RC. Standardized perioperative care protocols and reduced length of stay after colon surgery. J Am Coll Surg 1998;186(5):501–506. doi:10.1016/S1072-7515 (98)00078-7.
3. Moiniche S, Bulow S, Hesselfeldt P, Hestbaek A, Kehlet H. Convalescence and hospital stay with balanced analgesia, early oral feeding and enforced mobilisation. Eur J Surg 1995;161:283–288.
4. Wind J, Polle SW, Fung Kon Jin PHP, Dejong CHC, von Meyenfeldt MF, Ubbink DT et al. Systemic review of enhanced recovery programmes in colonic surgery. Br J Surg 2006;93:800–9. doi:10.1002/bjs.5384.
5. Fearon KCH, Ljungqvist O, von Meyenfeldt M, Revhaug A, Dejong CHC, Lassen K et al. Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. Clin Nutr 2005;24:466–477. doi:10.1016/j.clnu.2005.02.002.
6. Nelson R, Edwards S, Tse B. Prophylactic nasogastric decompression after abdominal surgery. Cochrane Database Syst Rev, July 2007, issue 3:CD004929.
7. Guenaga KF, Matos D, Castro AA, Atallah AN, Wille-Jorgensen P. Mechanical bowel preparation for elective colorectal surgery. Cochrane Database Syst Rev, January 2005, issue 1:CD001544.
8. Basse L, Raskov HH, Hjort Jakobsen D, Sonne E, Billesbolle P, Hendel HW et al. Accelerated postoperative recovery programme after colonic resection improves physical performance, pulmonary function and body composition. Br J Surg 2002;89:446–453. doi:10.1046/j.0007-1323.2001.02044.x.
9. Harris PH, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, Methods Work Group, Third US Preventive Services Task Force et al. Current methods of the U.S. Preventive Services Task Force: a review of the process. Am J Prev Med 2001;20(3S):21–35. doi:10.1016/S0749-3797(01)00261-6.
10. Basse L, Thorbol JE, Lossl K, Kehlet H. Colonic surgery with accelerated rehabilitation or conventional care. Dis Colon Rectum 2004;47(3):271–278. doi:10.1007/s10350-003-0055-0.
11. Raue W, Haase O, Junghans T, Scharfenberg Muller JM, Schwenk W. "Fast-track" multimodal rehabilitation program improves outcome after laparoscopic sigmoidectomy. Surg Endosc 2004;18:1463–1468. doi:10.1007/s00464-003-9238-y.
12. Delaney CP, Zutshi M, Senagore AJ, Remzi FH, Hammel J, Fazio VW. Prospective, randomised, controlled trial between a pathway of controlled rehabilitation with early ambulation and diet and traditional postoperative care after laparotomy and intestinal resection. Dis Colon Rectum 2003;46(7):851–859. doi:10.1007/s10350-004-6672-4.
13. Anderson ADG, McNaught CE, MacFie J, Tring I, Barker P, Mitchell CJ. Randomized clinical trial of multimodal optimisation and standard perioperative surgical care. Br J Surg 2003;90:1497–1504. doi:10.1002/bjs.4371.
14. Gatt M, Anderson ADG, Reddy BS, Hayward-Sampson P, Tring IC, MacFie J. Randomized clinical trial of multimodal optimisation of surgical care in patients undergoing major colonic resection. Br J Surg 2005;92:1354–1362. doi:10.1002/bjs.5187.
15. Khoo CK, Vickery CJ, Forsyth N, Vinall NS, Eyre-Brook IA. A prospective randomised controlled trial of multimodal perioperative management protocol in patients undergoing elective colorectal resection for cancer. Ann Surg 2007;245(6):867–872. doi:10.1097/01.sla.0000259219.08209.36.

16. Chapman AE, Levitt MD, Hewett P, Woods R, Sheiner H, Maddern GJ. Laparoscopic-assisted resection of colorectal malignancies: a systematic review. Ann Surg 2001;234(5):590–606. doi:10.1097/00000658-200111000-00003.
17. Braga M, Vignali A, Gianotti L, Zuliani W, Radaelli G, Gruarin P et al. Laparoscopic versus open colorectal surgery: a randomized trial on short-term outcome. Ann Surg 2002;236(6):759–766. doi:10.1097/00000658-200212000-00008.
18. Lacy AM, Garcia-Valdecasas JC, Delgado S, Castells A, Taura P, Pique JM et al. Laparoscopy-assisted colectomy versus open colectomy for treatment of nonmetastatic colon cancer: a randomised trial. Lancet 2002;359(9325):2224–2229. doi:10.1016/S0140-6736(02)09290-5.
19. Basse L, Jakobsen DH, Bardram L, Billesbolle P, Lund C, Mogensen T et al. Functional recovery after open versus laparoscopic colonic resection: a randomized, blinded study. Ann Surg 2005;241(3):416–423. doi:10.1097/01.sla.0000154149.85506.36.
20. King PM, Blazeby JM, Ewings P, Franks PJ, Longman RJ, Kendrick AH et al. Randomized clinical trial comparing laparoscopic and open surgery for colorectal cancer within an enhanced recovery programme. Br J Surg 2006;93(3):300–308. doi:10.1002/bjs.5216.

J Gastrointest Surg (2009) 13:2330–2332
DOI 10.1007/s11605-009-0879-6

GI IMAGE

Gallbladder Carcinoma as a Long-Term Complication of Cholecystojejunostomy

Charles H. C. Pilgrim · Laveniya Satgunaseelan · Salena M. Ward · Peter M. Evans

Received: 8 March 2009 / Accepted: 24 March 2009 / Published online: 16 April 2009

Abstract
Introduction Development of gallbladder cancer following cholecystojejunostomy has not previously been described.
Methods A case of a patient who developed gallbladder cancer 22 years following cholecystojejunostomy is presented, and a literature review of known complications of cholecysto-enteric anastomosis was performed.
Discussion Cholangitis is the commonest reported complication, known to predispose the biliary epithelium to malignant change, but has not been described until now as being carcinogenic for the gallbladder. Gallbladder carcinoma may be a rare long-term complication of cholecystojejunostomy.

Keywords Gallbladder cancer · Bilio-enteric bypass · Postoperative risk factor · Cholecystojejunostomy

Introduction

Gallbladder cancer as a complication of cholecystojejunostomy has not been described previously in the English literature. We describe a case of a man who developed gallbladder cancer 22 years following bilio-enteric bypass with a cholecystojejunostomy for what at the time was thought to be pancreatic carcinoma. A literature review of the recognized complications of cholecystojejunostomy, and of the association of cholangiocarcinoma with bilio-enteric bypass, is presented.

Case Report

An 81-year-old man presented with a 3-week history of a painful right upper quadrant mass, with a past history of cholecystojejunostomy 22 years prior for suspected pancreatic cancer which had no further treatment. On examination, the patient was febrile with a temperature of 38°C, and a tender firm 4-cm mass was palpable in the right upper quadrant. Tumor markers were markedly increased (carbohydrate antigen 19.9 (CA19.9) of 2,895 kU/L (normal 0–37 kU/L) and carcino-embryonic antigen (CEA) of 495 μg/L (normal 0–3 μg/L)). Bilirubin level was initially normal (6 mmol/L (normal <23 mmol/L)). An initial computed tomography (CT) scan demonstrated irregular thickening of the gallbladder extending to the biliary tree and dilated right lobe intrahepatic ducts, with lymphadenopathy noted adjacent to the superior mesenteric artery and celiac axis. Assessment of biliary anatomy and flow was attempted with a hepatobiliary iminodiacetic acid (HIDA) scan which was difficult to interpret but showed at least some flow through the common bile duct to the small bowel. A subsequent CT intravenous cholangiogram (CTIVC) demonstrated extrinsic compression of the right hepatic and common hepatic ducts, with porta hepatis lymphadenopathy and a thickened proximal gallbladder suspicious of malignancy. Contrast was seen in the common bile duct and duodenum but none was seen in the gallbladder fundus (Fig. 1).

The patient underwent an exploratory laparotomy which showed an inflamed gallbladder fundus consistent with cholecystitis, with an adjacent loop of jejunum forming the cholecystojejunostomy, but also a hard irregular mass at the body of the gallbladder confluent with large porta hepatis

C. H. C. Pilgrim · L. Satgunaseelan · S. M. Ward · P. M. Evans
Upper Gastrointestinal Surgery Unit, Alfred Hospital,
Commercial Road,
Prahran, Victoria, Australia 3181

C. H. C. Pilgrim (✉)
13A Percy Street,
Prahran, VIC 3181, Australia
e-mail: charlespilgrim@hotmail.com

lymphadenopathy consistent with locally advanced malignancy. A subtotal cholecystectomy and small bowel resection was performed, with transection of the gallbladder through the malignant body of gallbladder. At no stage was any bile found to drain from the transected surface of gallbladder, suggesting complete obstruction of the proximal gallbladder and cystic duct with malignancy. Fig. 2 shows the macroscopic resected specimen. Histopathology showed poorly differentiated adenocarcinoma arising in gallbladder with extensive local spread and secondary involvement of lymph nodes, and on examining the rest of the gallbladder the fundus epithelium showed chronic inflammation and metaplasia.

Post-operatively, the patient recovered well from the laparotomy but his bilirubin level slowly increased to 62 mmol/L 1 week later and was associated with increasing inflammatory markers with white cell count (WCC) of 13.8×10^9/L (normal $4.6–10.5\times10^9$/L). Repeat CT scan showed more prominent biliary dilatation now including the left hepatic ducts. The patient underwent a percutaneous transhepatic cholangiogram (PTC) via the left hepatic duct and insertion of an expanding metal stent across the strictured common hepatic duct (Fig. 3), with subsequent reduction of his serum bilirubin. A sample of bile cultured *Enterococcus faecalis*, and he was treated with a course of intravenous antibiotics. He was subsequently discharged home with palliative care support.

Discussion

The long-term complications of cholecystojejunostomy are difficult to characterize. This is partly due to the fact that it is usually performed for bypass in malignant disease, and these patients rarely live long enough to develop late complications related to surgery.[1,2]

One of the largest published series reviewed 34 patients having undergone cholecystojejunostomy for benign disease, with long-term follow-up to a mean of 8 years. In this series, five complications of recurrent cholangitis or biliary obstruction were directly attributable to the cholecystoen-

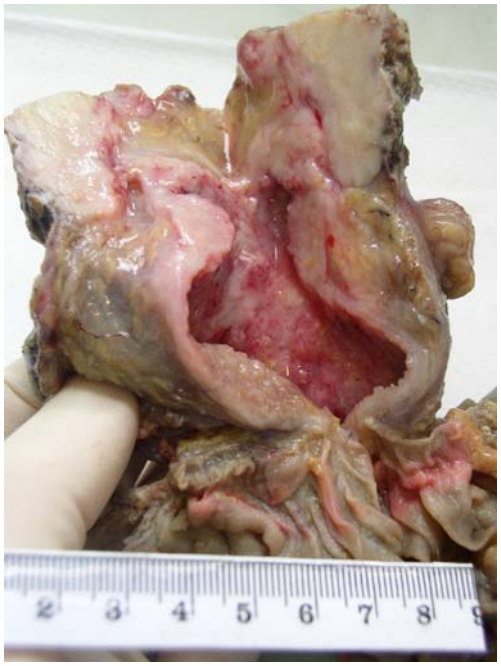


Figure 2 Macroscopic picture of resected specimen, showing the cholecystojejunostomy at the bottom of the picture, inflamed thickened gallbladder fundus consistent with cholecystitis in the middle of the picture, and cancer in the body of the gallbladder at the top.

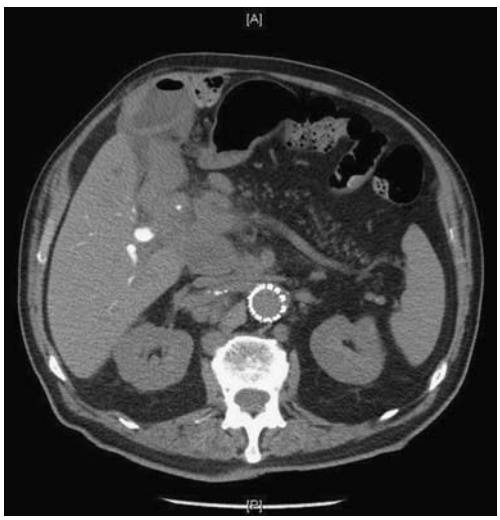


Figure 1 CTIVC showing porta hepatis lymphadenopathy and biliary obstruction with dilated intrahepatic ducts, and the anteriorly placed gallbladder fundus containing gas but no contrast with the adjacent loop of jejunum forming the cholecystojejunostomy.

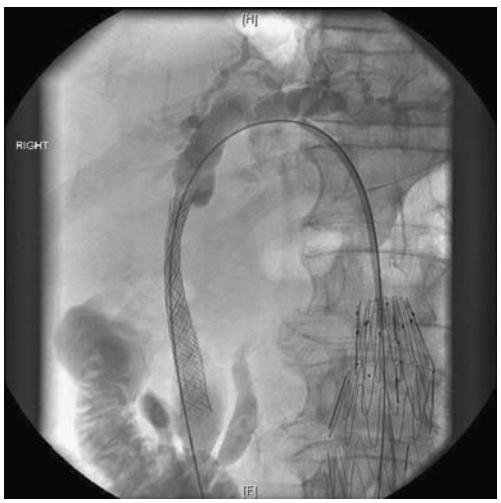


Figure 3 Percutaneous transhepatic cholangiography, access from left hepatic duct and stent insertion across bile duct stricture with flow achieved into duodenum. Also note past abdominal aortic aneurysm stent.

terostomy, but no patient developed malignancy.[3] Another reported case series of five patients developed recurrent cholangitis between 2 and 9 years following cholecystoenteric bypass and three required operation. All three demonstrated chronic inflammation at the site of the anastomosis at operation and pathologically, with transmural inflammation seen not only in the gallbladder but extending to involve the anastomosis.[1]

There are case reports of gastrointestinal bleeding, presenting either as hemocholecyst[4] or as recurrent bleeding from varices at the anastomosis[2], and also rarities such as intussusception of the jejunum into gallbladder[5], but no references in the English literature to gallbladder carcinoma as a complication of cholecystojejunostomy. There is only one article in Spanish that reports one gallbladder carcinoma following bilio-enteric anastomosis.[6]

Much more established in the literature is the development of cholangiocarcinoma following bilio-enteric anastomosis[7] and there is experimental, clinical, and epidemiological data available to support this link.[8] The rate was determined to be 5.5% among 1,003 patients collected over 30 years in Italy as reported by Tocchi et al. This was higher in patients with choledochoduodenostomy compared with hepaticojejunostomy or transduodenal sphincteroplasty (7.6% vs. 1.9% vs. 4.8%, respectively). A pattern was found that only patients who developed recurrent cholangitis developed cholangiocarcinoma. The recommendation from these authors was that chronic inflammatory changes consequent to biliary-enteric drainage should be closely monitored for the late development of biliary tract malignancies.[9]

In the case of cholecystojejunostomy, cholelithiasis and cholangitis may take several years to develop, but have been suggested to be inevitable.[1] The passage of food into the gallbladder via the cholecystojejunostomy and then back into duodenum via the common bile duct has been demonstrated[10] and food particles have even been visualized in the gallbladder on ultrasound when a patient was scanned in a non-fasting state[11], and this clearly predisposes to cholangitis and cholelithiasis. In the development of cholangiocarcinoma, this backflow of unwanted substances into the biliary tract is felt to be important pathologically[9], and it stands to reason that the same chronic irritation also predisposes the gallbladder to carcinomatous change in anastomoses involving this organ.

Some authors feel the presence of this abnormal circulation is indication enough for cholecystectomy in patients with cholecystojejunostomies.[10]

The role of cholecystojejunostomy may be maintained in emergency situations not amenable to percutaneous or endoscopic decompression[10], as it remains a simple and quick method for relief of biliary obstruction[3], but in the long term, it is not recommended for definitive treatment of benign disease.[1,2] The longer survival afforded these patients will likely lead to problems with cholangitis and probably risk of malignancy. Consideration should be given to revisional surgery in the setting of cholecystojejunostomy if a benign diagnosis becomes apparent, including cholecystectomy, or at least close monitoring to detect early biliary obstruction or cholangitis.

Conclusion

Gallbladder carcinoma is a potential late complication of cholecystojejunostomy and should be remembered when considering performing this operation or when dealing with patients previous having had this operation, particularly in the setting of benign biliary disease.

Acknowledgements 1. Dr Catriona McLean, Pathologist, Anatomical Pathology Department, Alfred Hospital.
2. Radiology Department, Alfred Hospital.

References

1. Thomson SR. Sequelae of cholecystojejunostomy for benign intrapancreatic biliary strictures. S Afr J Surg 1998;36(1):26–29.
2. Carpenter S, Brown KA. Chronic complications after cholecystojejunostomy. Am J Gastroenterol 1994;89(11):2073–2075.
3. Oishi AJ, Sarr MG, Nagorney DM, Traynor MD, Mucha P Jr. Long-term outcome of cholecystoenterostomy as a definitive biliary drainage procedure for benign disease. World J Surg 1995;19(4):616–619. discussion 620.
4. Winters DA, Smith DC. Cholecystojejunostomy complicated by massive hemocholecyst. Radiology 1982;144(2):265–266.
5. Porter DH, Kim D, Austin RM. Cholecystojejunostomy intussusception. Gastrointest Radiol 1988;13(3):227–229.
6. Perez Ruiz L, Gabarrell Oto A, Vinas Salas J, Torres Romana S, Gomez Quiles L. [Biliary tract cancer following bilioenteric anastomosis]. Rev Esp Enferm Dig 1994;86(5):853–855.
7. Strong RW. Late bile duct cancer complicating biliary-enteric anastomosis for benign disease. Am J Surg 1999;177(6):472–474.
8. Bettschart V, Clayton RA, Parks RW, Garden OJ, Bellamy CO. Cholangiocarcinoma arising after biliary-enteric drainage procedures for benign disease. Gut 2002;51(1):128–129.
9. Tocchi A, Mazzoni G, Liotta G, Lepre L, Cassini D, Miccini M. Late development of bile duct cancer in patients who had biliary-enteric drainage for benign disease: a follow-up study of more than 1,000 patients. Ann Surg 2001;234(2):210–214.
10. Lontoft E, Rasmussen L, Pedersen SA. Deleterious circulation of intestinal contents through the biliary tract after cholecystojejunostomy. Endoscopy 1991;23(5):309–310.
11. Gooding GA. Food particles in the gallbladder mimic cholelithiasis in a patient with a cholecystojejunostomy. J Clin Ultrasound 1981;9(6):346–347.