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The Preoperative Manometric Pattern Predicts the Outcome of Surgical Treatment for Esophageal Achalasia

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Abstract
Background A new manometric classification of esophageal achalasia has recently been proposed that also suggests a correlation with the final outcome of treatment. The aim of this study was to investigate this hypothesis in a large group of achalasia patients undergoing laparoscopic Heller–Dor myotomy.
Methods We evaluated 246 consecutive achalasia patients who underwent surgery as their first treatment from 2001 to 2009. Patients with sigmoid-shaped esophagus were excluded. Symptoms were scored and barium swallow X-ray, endoscopy, and esophageal manometry were performed before and again at 6 months after surgery. Patients were divided into three groups: (I) no distal esophageal pressurization (contraction wave amplitude <30 mmHg); (II) rapidly propagating compartmentalized pressurization (panesophageal pressurization >30 mmHg); and (III) rapidly propagating pressurization attributable to spastic contractions. Treatment failure was defined as a postoperative symptom score greater than the 10th percentile of the preoperative score (i.e., >7).
Results Type III achalasia coincided with a longer overall lower esophageal sphincter (LES) length, a lower symptom score, and a smaller esophageal diameter. Treatment failure rates differed significantly in the three groups: I=14.6% (14/96), II=4.7% (6/127), and III=30.4% (7/23; p=0.0007). At univariate analysis, the manometric pattern, a low LES resting pressure, and a high chest pain score were the only factors predicting treatment failure. At multivariate analysis, the manometric pattern and a LES resting pressure <30 mmHg predicted a negative outcome.
Conclusion This is the first study by a surgical group to assess the outcome of surgery in 3 manometric achalasia subtypes: patients with panesophageal pressurization have the best outcome after laparoscopic Heller–Dor myotomy.

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Keywords Achalasia · Manometric pattern · Heller–Dor · Conventional manometry · High resolution · Manometry

Background

Achalasia is a relatively rare esophageal motility disorder characterized by an impaired lower esophageal sphincter (LES) relaxation and the absence of esophageal peristalsis, resulting in a functional outflow obstruction at the gastroesophageal junction.[1,2] The pathogenesis of esophageal achalasia is still unknown, and the available therapies (surgical cardiomyotomy, endoscopic pneumatic disruption or chemical paralysis of the cardia muscle fibers with botulinum toxin injection) are considered only palliative measures.[3,4]

In the last decade of the past century, laparoscopic cardiomyotomy (Heller's procedure) progressively gained popularity and, being perceived as less invasive and more effective, in most Western countries it became the procedure of choice in the new millennium. In a minority of patients (estimated between 5% and 15%), however, symptoms persist or recur after surgery.[5–10] It is hard to say why the treatment sometimes fails: a technical defect (incomplete myotomy) may be the culprit in some cases (especially if the failure occurs soon after surgery or symptoms persist) but, in most cases, the reason for the failure remains obscure.[11,12]

A new esophageal achalasia classification—obtained using high-resolution manometry (HRM), which records the pressure readings from 36 sensors placed 1 cm apart and enables pressure topography plotting—has recently been proposed, which considers three different manometric patterns: type I, achalasia with minimal esophageal pressurization; type II, achalasia with esophageal compression; type III, achalasia with spasm. Most importantly, the authors also suggested a correlation between the manometric subtype and the final outcome of treatment.[1]

The aim of our study was to investigate this hypothesis in a large group of achalasia patients who underwent laparoscopic Heller–Dor myotomy, by re-analyzing and re-grouping their manometry tracings according to the new classification.

Material and Methods

The study population consisted of 246 consecutive patients (134 men, 112 women, median age 44 years, IQR 31–55) with a definitive diagnosis of achalasia, who underwent laparoscopic Heller myotomy and Dor anterior partial hemifundoplication from January 2001 to December 2009. Only patients operated at our center were considered. Patients who had already been treated for achalasia (with Heller myotomies, endoscopic dilations or botulinum toxin injections) and patients with sigmoid-shaped megaesophagus (stage 4 achalasia) were ruled out.

Preoperative Evaluation

The diagnosis of primary achalasia was established by (conventional or high-resolution) esophageal manometry on the basis of accepted esophageal motility characteristics (i.e., absence of peristalsis in the esophageal body and impaired relaxation of the LES on swallowing).[2,3] Demographic and clinical data were collected prospectively on each patient using a questionnaire and the patient's symptoms were scored according to their severity and frequency. The scores for dysphagia, regurgitation and chest pain were calculated by combining the severity of each symptom (0=none, 2=mild, 4=moderate, 6=severe) with its frequency (0=never, 1=occasionally, 2=once a month, 3=every week, 4=twice a week, 5=daily). The symptom score was defined as the sum of the dysphagia and regurgitation scores, while the chest pain score was considered separately. Barium swallow X-rays were used to assess esophageal diameter and shape. The maximum esophageal diameter was measured at the barium-air interface in the standard anteroposterior image obtained during a barium swallow. Endoscopy was always performed to rule out any malignancies.

Conventional Manometry

Esophageal manometry was performed using a pneumohydraulic perfusion system. The LES pressure was calculated by averaging the pressures recorded by four side-holes positioned on the same level, 90° apart, withdrawing the catheter twice using a motorized pull-through technique at a constant speed of 1 mm/s from the stomach to the esophageal body, passing through the high-pressure zone (so the LES pressure was the average of eight pressure recordings). The LES pressure was calculated as the mid-expiratory pressure at the respiratory inversion point. Abdominal and overall LES lengths were calculated as the average distance from the point where the pressure trace rises steadily by at least 2–3 mmHg in relation to the intragastric baseline pressure, the respiratory inversion point (abdominal part), and the point where the pressure trace falls below the esophageal baseline pressure (overall length). LES relaxation, residual LES pressure, esophageal body contraction amplitude and duration were assessed on ten consecutive swallows consisting of 5 ml of water at 20 s interval, with the catheter side-holes positioned in the LES and then 5, 10, 15, and 20 cm higher up, using the method described elsewhere.[13] The normal values obtained in our Center on 20 healthy controls served as reference.[14]

High-Resolution Manometry

HRM was performed using a catheter 4.2 mm in diameter with 36 solid-state circumferential sensors spaced at 1 cm intervals and spanning the whole esophagus (Sierra Scientific Instruments; Los Angeles, CA). Each of the 36 pressure-sensing elements is circumferentially sensitive with the extended frequency response characteristic of solid-state manometric systems. Before the beginning of the procedure, the transducers were calibrated at 0 and 100 mmHg using an externally applied pressure. The HRM catheter was inserted transnasally with approximately five intragastric sensors. Manometry was performed in a supine position after a fast of at least 6 h. The protocol included a

5-min period for assessing the basal LES pressure, after which the manometric procedure was completed according to the protocol for conventional manometry, with ten saline swallows containing a standardized concentration of electrolytes to ensure proper catheter function (e.g., 10×5 ml) separated by an interval of at least 20 s.[15,16]

The manometric data were analyzed using the Mano-View™ software (Sierra Scientific Instruments; Los Angeles, CA). The pressure readings were converted into topographic (color contour) plots to provide a continuous picture of the pressure throughout the segment considered. This enables a thorough spatial and temporal analysis of a patient's esophageal motor events.

The normal values considered in defining abnormal topographic, timing and pressure features were those established by the University of Rochester, New York, within the 5th and 95th percentiles of 50 healthy volunteers.[16]

Manometric Patterns in Achalasia

Achalasia patients were further characterized according to their dominant distal esophageal pressurization features, as proposed by Pandolfino et al.[1] If HRM was used, the analysis was performed with the Manoview software and the isobaric contour tool was set at 30 mmHg to measure the pressurization front velocity (i.e., the slope of the line connecting the distal temporal margin of the transition zone to the superior proximal margin of the LES, expressed in cm/s). Each swallow was defined as: (1) normal (intact isobaric contour and pressurization front velocity PFV <8 cm s; (2) failing (complete contraction failure); (3) hypotensive (>2 cm break in the 30 mmHg isobaric contour between the distal segment and the LES); (4) spastic contractions or panesophageal pressurization with simultaneous esophageal pressurization extending from the UES to the LES. Type I achalasia described cases with no distal esophageal pressurization to >30 mmHg in at least eight of ten swallows; in type II achalasia, at least two test swallows were associated with panesophageal pressurization >30 mmHg; in type III achalasia, patients had two or more spastic contractions (PFV >8 cm/s). When patients had a mixed pattern (contractions of types II and III) they were classified as type III.[1] (Figs. 1, 2, and 3a).

All conventional manometric traces were reviewed by one of the Authors (RS) using the Dynosystem software (Memphis, Bologna, Italy), which enables the complete esophageal manometry sequence to be reviewed on the screen and the amplitude, duration and propagation velocity of the contraction waves to be calculated automatically. The contraction waves recorded 5 and 10 cm above the upper margin of the LES were considered. Patients were classified as having type I achalasia when 8/10 swallows elicited contractions with an amplitude <30 mmHg; when two or more contractions had an amplitude >30 mmHg, they were classified as having type II achalasia and, when at least two spastic waves were detected (i.e., amplitude >70 mmHg and duration >6.0 s)[17], patients were classified as type III (Figs. 1, 2, and 3b). To confirm the congruity of this classification, the analogical HRM traces were reviewed and the amplitude and duration of the contractions recorded by the sensors 5 and 10 cm above the LES were measured. The traces were attributed to one of the achalasia types, based on the above-mentioned amplitude and duration of the contractions, by operators unaware of the classification obtained using the Manoview software. The two classifications coincided in all patients.

Surgical Technique

The surgical technique has been described in detail elsewhere[18]. Briefly, only the anterior part of the esophagus was dissected and a myotomy 6–8 cm long was performed, extending it 1.5–2 cm on the gastric side. A 30 mm Rigiflex balloon was placed inside the esophageal lumen at cardia level during the myotomy, using an endoscopically positioned guide wire; during the myotomy, the balloon was gently inflated and deflated with 40–60 cm^3 of air using a syringe. This maneuver exposed the circular fibers, which were stretched and then easily cut or torn apart; the edges of the myotomy were separated and peeled away from the submucosal plane: minimal bleeding from submucosal vessels was easily controlled by inflating the balloon, thus reducing the use of the cautery. A Dor anterior partial hemifundoplication completed the operation.

All patients underwent water-soluble contrast swallows (with Gastrografin®, Bracco, Milan, Italy) on the first postoperative day and the nasogastric tube was removed and a liquid diet was allowed if this procedure identified no leaking from the myotomy. Patients started eating soft foods on the second postoperative day.[5]

Follow-up

The follow-up procedures are listed briefly in Table 1. The clinical outcome was assessed by repeating the questionnaire used preoperatively 1, 6, and 12 months after surgery, and every 2 years thereafter. Treatment failure was defined as a postoperative symptom score>the 10th percentile of the preoperative score (i.e., >7).[5]

Barium swallows were obtained 1 month and then 2 years after the myotomy.

Endoscopy was repeated 12 months after surgery and then every 2 years to rule out any neoplastic degeneration. Any esophagitis was graded according the Los Angeles classification.

Esophageal manometry was performed as for the preoperative test (CM or HRM) 6 months after the

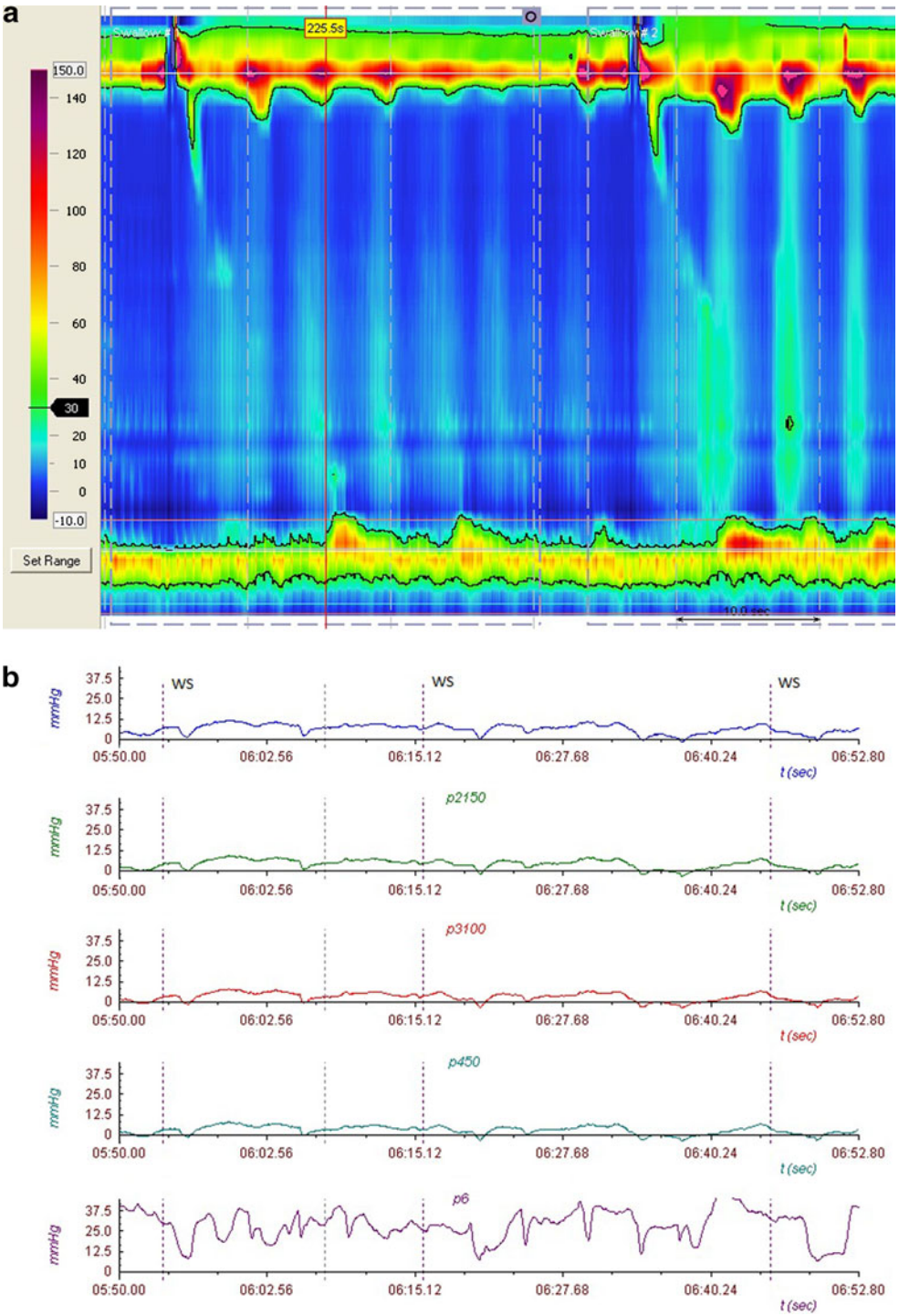

Fig. 1 Achalasia Type I: **a** High-resolution manometric picture with no distal esophageal pressurization. As the isobaric contour tool shows, the esophageal body area has no component above the nadir pressure of 30 mmHg. Impaired LES relaxation is also easy to see as a continuous high-pressure band across the lower portion of the image. **b** Conventional manometry trace showing esophageal body contraction with maximal pressure below 30 mmHg. The scale of pressure values (*y*-axis) is from 0 to 37.5 mmHg

Heller–Dor procedure, when 24-h pH monitoring was also performed to assess any abnormal gastroesophageal reflux: a glass electrode was positioned 5 cm above the upper border of the LES, according to the standard procedure adopted at our laboratory and described elsewhere.[19] Traces from patients with abnormal reflux on computer analysis were carefully reviewed to distinguish true gastroesophageal reflux episodes from false reflux due to stasis.[20]

Statistical Analysis

Continuous data were expressed as median and interquartile range, categorical data as number and percentage. Demographic and clinical findings were compared between patients grouped by type of achalasia using the Kruskal-Wallis test followed by the Wilcoxon–Mann–Whitney test, with Bonferroni's adjustment for multiple comparisons, and using Fisher's

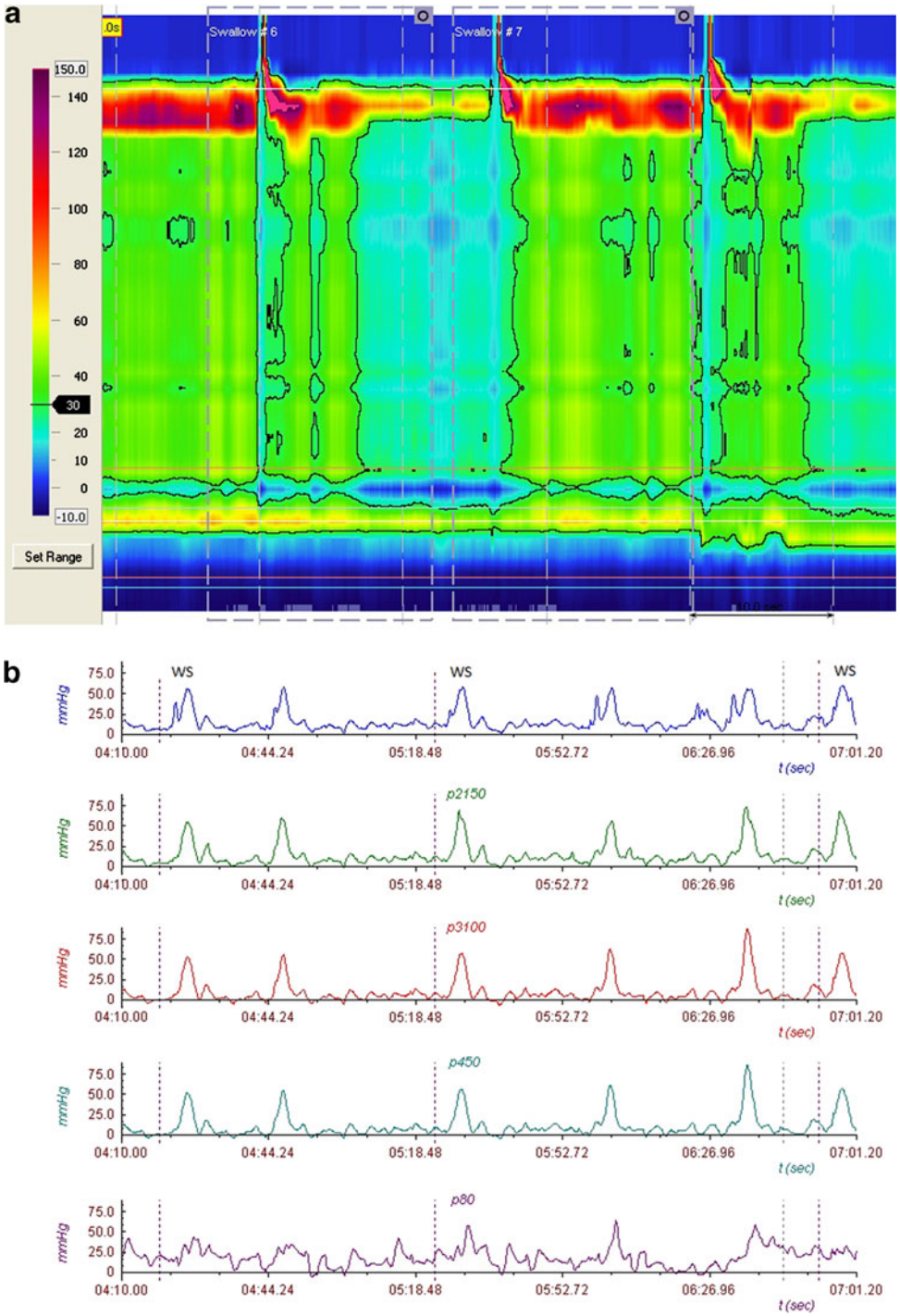

Fig. 2 Achalasia Type II: **a** High-resolution manometric picture of panesophageal pressurization, showing the simultaneous isobaric esophageal pressurization ≥30 mmHg. **b** Conventional manometry trace of type II achalasia, showing esophageal body waves with pressure above 30 mmHg but of normal duration. The scale of pressure values (*y*-axis) is from 0 to 75 mmHg

test followed by Fisher's test with Bonferroni's adjustment for multiple comparisons (for continuous data and categorical data, respectively). Pre- to postoperative variations in continuous variables, calculated as a percentage decrease in each subject, were evaluated using Wilcoxon's test for paired data.

A logistic regression model was used to identify independent predictors of treatment failure. A p value of less than 0.05 was considered significant. Statistical analyses were performed using the SAS 9.1 software.

Results

The demographic, clinical and manometric data for the 246 patients are summarized in Table 2. The vast majority of the patients (230) had conventional manometry, while HRM was performed in the last 16 cases. According to the manometric classification, 96 (39%) patients were classified as having achalasia type I, 127 (51.6%) as type II, and 23 (9.4%) as type III. Patients with type I achalasia were

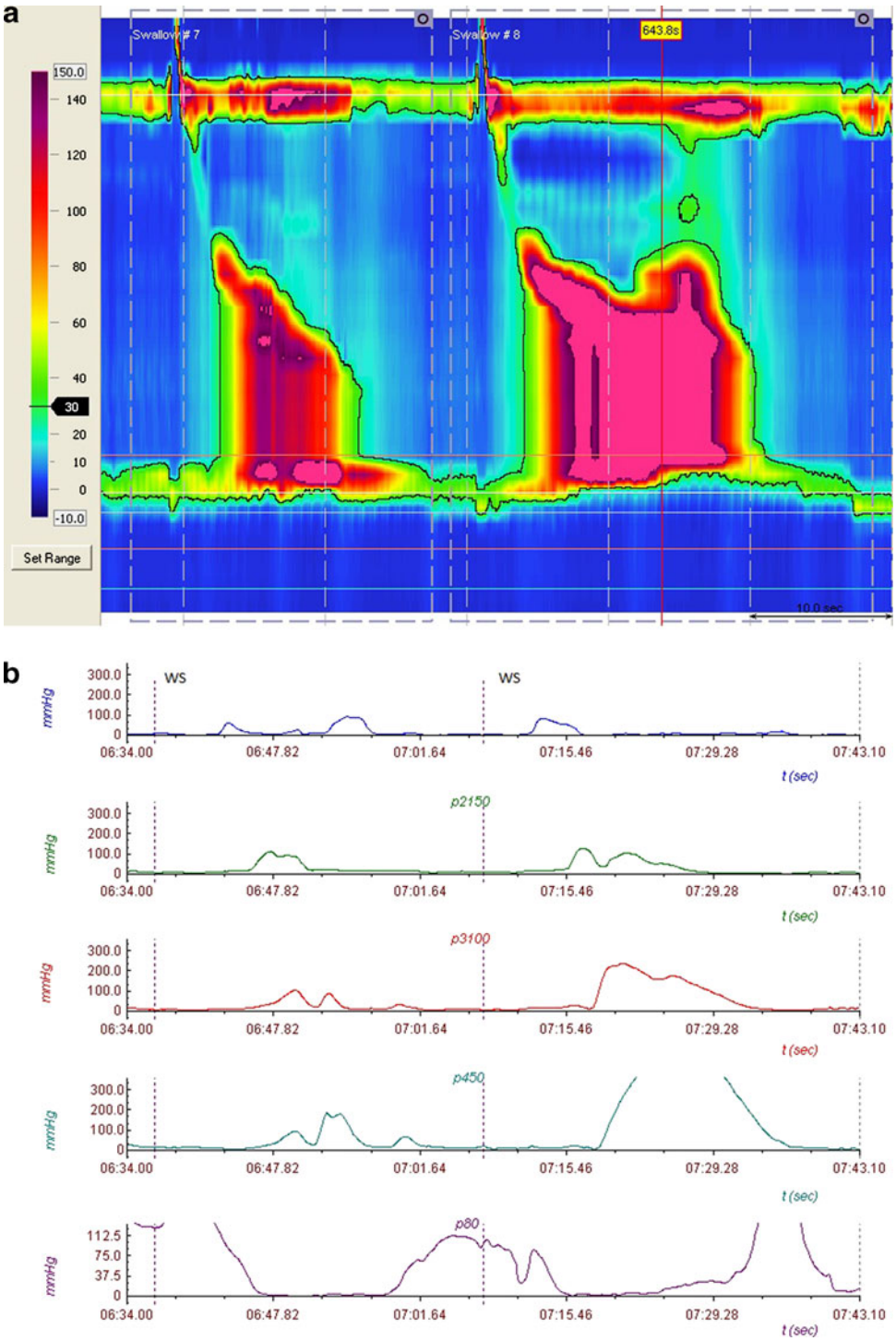

Fig. 3 Achalasia Type III: **a** High-resolution manometric picture of rapidly propagating pressurization with spastic contractions. The high amplitude contractions of the distal esophageal body is represented by the red high-pressure area of the esophageal body contraction. **b** Conventional manometry of long-lasting, high-pressure spastic esophageal contraction. The scale of pressure values (*y*-axis) is from 0 to 300 mmHg

younger and had a larger esophageal diameter than those in the other two groups; patients with type III achalasia had a longer overall LES length (Fig. 4) and lower symptom scores than those in the other groups (Table 2). Chest pain was more common and tended to be scored higher among type III achalasia patients than in the other two groups. Type III patients also had shorter-lived symptoms than the other two groups. These differences failed to reach statistical significance, however. Furthermore the percent of patients with abnormal LES parameters (resting and residual pressure, overall and abdominal lengths) were not different in the three groups (Table 3) but for the overall length that was abnormal in a higher percent of subjects of group III.

The surgical procedure was completed laparoscopically in all but one patient. Mortality due to the surgical treatment was nil. Intraoperative perforations of the esophageal mucosa

Table 1 Follow-up procedures and timing

Procedure	1 month	6 months	12 months	Every 2years
Symptom questionnaire	X	X	X	X
Barium swallows	X			X
EGDS			X	X
Esophageal manometry		X		
24-hour pH monitoring		X		

occurred in six patients, repaired intraoperatively in all cases (one of these patients complained of persistent dysphagia and required postoperative pneumatic dilations). Three additional mucosal tears were revealed by the Gastrografin swallows performed on the first postoperative day, none of which caused persistent or recurrent symptoms.

Follow-up data were available for 241 patients (98%), while five were lost to follow-up.

After a median 31 months (IQR 14–54), there were significant decreases in symptom score (median preoperatively, 18.5 (IQR 13–20) vs median postoperatively, 0 (IQR 0–4); $p<0.0001$), resting LES pressure (median preoperatively, 28 (IQR 9–39.3) vs median postoperatively, 11 (IQR 14–9); $p<0.0001$), and residual LES pressure (median preoperatively, 9 (IQR 4.3–14.4) vs median postoperatively, 2 (IQR: 1–4); $p<0.0001$).

Eleven patients (of the 121 who agreed to undergo postoperative pH monitoring) were positive for acid exposure of the distal esophagus (9.1%).

Twenty-seven patients had a postoperative symptom score >7 and were considered as treatment failures; in 16 of them (59%), symptoms persisted or recurred within a year of the operation. All the patients whose surgical treatment failed had one or more pneumatic dilations (median, 2; range, 1–5) using Rigiflex balloons (30, 35, or 40 mm). One patient developed a distal esophageal cancer 8 years after the Heller–Dor procedure.

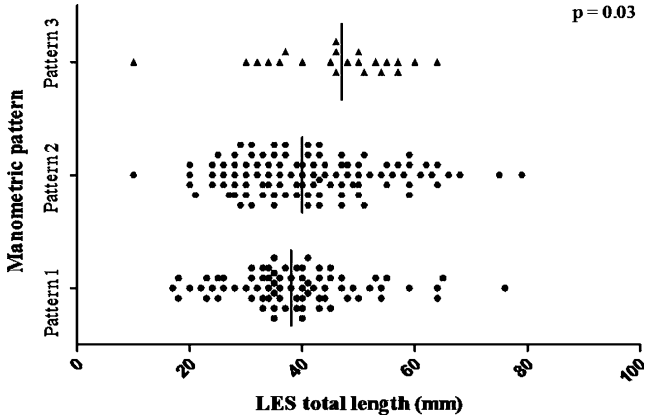

Fig. 4 Scatter plot of preoperative LES total length in the three groups of patients ($p=0.03$)

At univariate analysis, a higher chest pain score, a lower resting LES pressure (Fig. 5) and a type III achalasia pattern correlated with treatment failure (Table 4).

When the outcome was stratified by type of achalasia, patients with type II achalasia had the lowest incidence of failures (4.7%, 6/127), type I had a 14.6% failure rate (14/96), and type III a 30.4% failure rate (7/23), $p<0.0007$. Recurrences occurred earlier in type I (7 months, IQR 4–25) than in the other two types of achalasia (type II: 21 months, IQR 7–38; type III: 22 months, IQR 4–25), but this difference was not statistically significant.

At multivariate analysis, type II (vs type III, $p=0.004$) and a LES resting pressure >30 mmHg ($p=0.004$) were identified as independent predictors of a positive outcome. Details of multivariate analysis are shown in Table 5.

Discussion

The aim of this study was to determine whether surgical outcome could be correlated with esophageal manometry patterns, as hypothesized by Pandolfino et al., who recently

Table 2 Demographic and clinical findings of achalasia types

	Pattern 1 $n=96$ (39%)	Pattern 2 $n=127$ (51.6%)	Pattern 3 $n=23$ (9.4%)	p value
Age	40 (28–50)	46 (32–58)	46 (30–53)	0.04
Sex (m/f)	53/43	70/57	11/12	n.s.
Duration of symptoms (months)	24 (12–42)	18 (10–48)	12 (6–30)	0.10
Symptom score	18.5 (14–20)	19 (14–21)	16 (9–19)	0.02
Chest pain score	7 (0–8)	5 (0–9)	7 (3–11)	n.s
N° of pts with chest pain	54 (62.1%)	73 (60.3%)	18 (78.3%)	n.s.
LES resting pressure (mmHg)[a]	25.5 (18–34.5)	30 (19–43)	24 (18–43)	n.s.
LES residual pressure (mmHg)[a]	10 (5.1–14.5)	8.7 (4–14.6)	7 (2.4–15)	n.s.
LES overall length (mm)[a]	37 (31.5–43.5)	40.5 (31–50)	46 (36–54)	0.03
LES abdominal length (mm)[a]	25 (20–33)	26 (17.5–33)	34 (24–37)	n.s.
Esophageal diameter (mm)	40 (35–50)	35 (30–45)	35 (30–40)	0.05

Data are shown as median and IQR (in brackets)

[a] Only CM procedures were considered

Table 3 Percent of patients with abnormal LES findings in the three subgroups of achalasia patients

	Pattern 1	Pattern 2	Pattern 3	*p* value
PSEI >30 mmHg	27 (28.1%)	47 (37%)	7 (30.4%)	n.s.
Total LES length >50 mm	10 (10.4%)	24 (18.9%)	8 (34.8%)	0.02
Abdominal LES length >35 mm	13 (13.5%)	22 (17.3%)	8 (34.8%)	n.s.
LES residual pressure >7 mmHg	50 (52.1%)	61 (48%)	10 (43.5%)	n.s.

Data are shown as the number of patients with abnormal LES parameters and the percent of abnormal values (in brackets)

proposed a new achalasia classification based on manometric findings obtained by HRM (a new tool enabling pressures to be recorded at 1 cm intervals along the esophagus, using a catheter with 36 solid-state sensors, and submitted to sophisticated software analysis). Using this tool, they classified achalasia in 3 types according to the pressurization conditions in the esophageal body (no pressurization, compartmentalized pressurization, or rapidly propagating pressurization attributable to spastic contractions). Judging from the results of the present study, the outcome of surgery correlated strongly with the type of achalasia, type III (compartmentalized pressurization due to spastic contractions) having a strong negative impact on outcome.[1] On conventional manometry, type 1 was easily identified as coinciding with low-amplitude aperistaltic contractions. The other two types of achalasia (with "high"-amplitude contractions)—once classified on conventional manometry as "vigorous achalasia"—were further separated based on the duration of the contractions, i.e., when lengthy, high-amplitude contractions were identified, patients were classified as having type III "spastic" achalasia. All other patients (those with high-amplitude, but short-lived contractions) formed the type II group. Although this grouping was probably less precise than the sophisticated HRM-based classification, the three patient groups were similar to those reported by Pandolfino, in terms of both clinical features and outcome after therapy: type I patients had a slightly larger diameter of the esophagus than the other two groups, and chest pain was prevalent in type III achalasia patients, who also fared worse after surgery.[1]

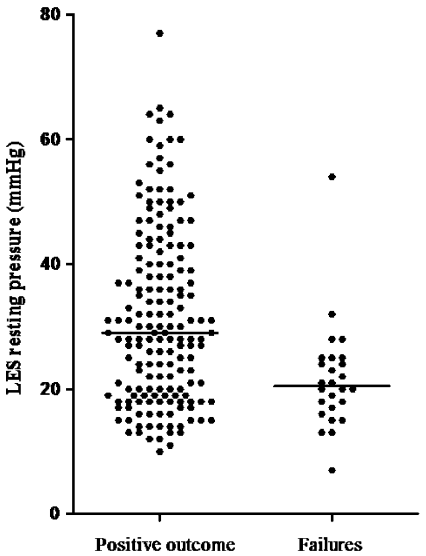

Fig. 5 Scatter plot of preoperative LES resting pressure in patients with positive outcome versus treatment failures (p=0.0006)

Table 4 Univariate analysis of failure predictors

	Positive outcome n=219	Failure n=27	*p* value
Age	41 (31–55)	44 (31–55)	n.s.
Sex (m/f)	120/99	14/13	n.s.
Symptom score	18 (12–20)	20 (17–21)	n.s.
Chest pain score	5 (0–8)	8 (3–10)	0.01
LES resting pressure (mmHg)[a]	29 (19–41)	21 (17–25)	0.0006
LES residual pressure (mmHg)[a]	9 (4.3–15)	8 (3–14)	n.s
Total LES length (mm)[a]	39 (31–48)	45 (35–50)	n.s
Abdominal LES length (mm)[a]	25 (19–33)	31 (22–35)	n.s
Esophageal diameter (mm)	40 (30–45)	40 (30–50)	n.s
Intraoperative mucosal lesions	8	1	n.s
Pattern			0.0007
I	82 (85.4%)	14 (14.6%)	
II	121 (95.3%)	6 (4.7%)	
III	16 (69.6%)	7 (30.4%)	

Data are shown as median and IQR (in brackets)

[a] Only CM procedures were considered

In the surgical literature, the results of laparoscopic achalasia treatment are generally consistent: a good outcome is reported after 5 years in between 95% and 85% of patients[5–10] and the few studies that analyzed outcome after a longer follow-up report good results in nearly 80% of patients.[21,22] Why surgery sometimes fails is hard to say. Patients with decompensated, stage IV achalasia have an advanced form

Table 5 Multivariate analysis of failure predictors

	p value	OR (95% C.I.)
Pattern		
I vs III	0.68	–
II vs III	0.004	0.13 (0.04–0.50)
LES resting pressure (>30 mmHg vs≤30 mmHg)	0.004	0.11 (0.03–0.49)
Chest pain score (>8 vs≤8)	0.08	–

of the disease and are considered the most difficult to treat, with a success rate that drops to 50%–70%. When a "megaesophagus" has developed as a consequence of long-standing achalasia, the gullet's dilation and the tortuosity of the cardia interfere with the progress of the bolus under the effect of gravity alone and food retention is a normal event in such patients—even in those reporting an improvement in symptoms after myotomy.[5,23,24]

A second negative prognostic factor (for some authors, at least) is prior endoscopic treatment. The potential negative impact of prior therapy probably relates to the repeated trauma to the LES and to the scar tissue formation or fibrosis, which might hamper the efficacy of myotomy[25]. The failure of prior endoscopic treatments may also earmark patients more refractory to any kind of treatment, however. To avoid such biases, patients with stage IV achalasia and those who with a history of endoscopic treatments were not considered in this study.

A third important possibility when surgery fails lies in a defective surgical technique that leaves some of the LES fibers uncut. Generally speaking, the uncut fibers are on the gastric side of the LES, where the submucosal plane is more difficult to separate from the muscle layer and bleeding from small submucosal vessels is more frequent. Part of the muscle clasp and gastric sling fibers (essential components of the LES) may be left untouched if the myotomy is too short, and this can lead to symptoms persisting or recurring soon after surgery[7]. Such an explanation for treatment failures cannot apply to recurrences occurring later in the follow-up, however.

Several authors recently focused on the impact of LES pressure on the outcome of cardiomyotomy: a high pressure (>30 mmHg) consistently emerged as a factor positively associated with a good outcome, suggesting that certain intrinsic features of achalasia might influence the outcome of treatments.[5,26,27] The data reported by Pandolfino et al. take us a step further in this direction by identifying a group of patients whose obstruction encompassed not only the esophagogastric junction, but also the distal smooth muscle segment, in much the same way as in patients with distal esophageal spasm.[1]

Our findings confirm their data (even though they were obtained mainly using CM), showing that patients with spastic contractions in the esophagus have a worse outcome. Our study also confirms the role of high chest pain scores in predicting a negative outcome after surgery: these two factors are probably related (chest pain was reported by 80% of type III achalasia patients), though exactly how this is so remains to be seen.

At conventional manometry, type III achalasia patients also had a longer LES: maybe these patients require a longer myotomy (extending both downwards and upwards) than type I and II patients to deal with the excessive spastic contractions in the distal portion of the esophagus, which may contribute to the outflow obstruction. It is also worth noting that the majority of type I achalasia patients had recurrent symptoms soon after their operation (within 12 months in ten of 14 cases, 71.4%): the matter of surgical technique emerged as the main cause of recurrences in these patients, who would otherwise have been expected to fare well.

In conclusion, detailed conventional manometric analysis can help to identify patients at high risk of recurrence after surgery. Further studies with HRM might pinpoint these patients better and help the surgeon to tailor the length of the myotomy according to each patient's type of achalasia.

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Discussant

Dr. John E. Pandolfino (Chicago, IL): I would like to thank Dr. Salvador for a wonderful study. He spent some time with us in our lab, and he obviously extended this to a very nice piece of work. I think that when you look at achalasia, it's still, even though it's the most well-defined esophageal motor disorder, there's still significant heterogeneity when we look at this. When you evaluate high-resolution manometry, you're struck by the variability in the peristaltic contractions and the intrabolus pressure patterns.

So when we originally saw this, we theorized that there should be some predictive value of this. And subsequently, we validated this work, but it was difficult. And really, we were very happy to see Dr. Salvador's work because this was a much-needed confirmation that there was something we can glean from high-resolution manometry.

I think the strengths of this particular study are: 1) the large numbers, 2) the fact that the patients underwent one particular type of therapy, surgery, and 3) also the novel concept of applying these patterns back to conventional manometry for other investigators and clinicians to utilize.

Once again, it's logical that type 2 patients would do better. They have intact esophageal mechanics. They also have intact longitudinal muscle function. It's also logical that the type 3 patients that we have identified with spastic features are going to do poorly.

So with that, I have a few questions:

And once again, congratulations on a very detailed and wonderful study. What do you actually do for the type 3 patients? I think that's an important thing now that we have defined them.

The other issue was, how hard is it—and you are an experienced manometric evaluator—but how hard is it to take these concepts and apply them back to conventional tracing manometry?

Closing Discussant

Dr. Renato Salvador: The answer is: a longer myotomy, maybe. Before starting this study, especially after reading your own paper, we thought that maybe a myotomy extended into the chest could be the answer for the spastic type. However, when we analised our own data, we noticed that the spastic type had a longer lower esophageal sphincter, so maybe also a longer myotomy on the gastric side could be indicated in these patients. The answer is then probably a longer myotomy on both sides.

On the other hand, we do not know much about pneumatic dilations in these patients. In this very moment, the results at 2-year follow-up of the European trial (comparing dilations and laparoscopic myotomy) are presented in another room of this building. We actively participated in this trial. It could be interesting to go back to the manometric tracings of these patients and compare the results of myotomy and dilations in this particular group of patients (spastic type), and in the other two groups. It is important to underline that all the patients in the trial, as in this study, were patients with primary achalasia, without previous endoscopic treatment.

What about conventional manometry? In our study, the vast majority of patients had conventional manometry. As you know from the paper, we applied the concepts of high resolution manometry to the conventional tracings. It was quite easy for Group 1 and 2, a little more difficult for the 3rd Group (that also resulted to be the most intriguing group). By applying the parameters of other well known authors, we are confident that we have categorized the three groups of patients even with the old conventional manometry well. We agree with you, from the experience I personally had in Rochester, NY, with Dr. Peters, and now in Italy where we have lately acquired the system, that high resolution manometry provides us with a lot more details than conventional manometry, allowing a better characterisation of the motility of the esophagus before and after myotomy.

Discussant

Dr. Jeffrey Peters (Rochester, NY): I agree with John's comments. First, I have a question about the classification. You have classified achalasia into three subsets, Group 1 was characterized by a cutoff of 30-millimeter mercury pressurization in the esophagus. That seems to be awful high. I wonder how the data would change if you change the 30-millimeter threshold and reanalyze the data at to 10 or 15. Second, as I've had the opportunity to see the manuscript, I wonder if there weren't some patients in group 3 that have a normal residual pressure of their sphincter?

Closing Discussant

Dr. Renato Salvador: We chose a cut-off of 30 mmHg following Dr. Pandolfino et al. paper with the proposed new classification of achalasia based on high resolution manometry. Again, we applied those concepts to conventional manometry. We do not know if lowering the threshold to 15 or 10 mmHg could change the classification of patients in Group 1 or 2. That is something that we have to look at.

As far as the second question is concerned, we agree that in some patients of group 3 (but also in other groups) residual pressure may fall in the normal range. Unfortunately our protocol did not include a sleeve sensor to carefully evaluate the LES relaxation with conventional manometry and the patients studied with HRM are only a few. However, if we look at the percentage of patients with abnormal parameters of the LES (i.e.: resting and residual pressure, overall and abdominal lengths) we found no differences among the three groups of patients in all the parameters but in the overall length, that is longer in a significant percentage of pattern 3 patients.

Discussant

Dr. Michael S. Nussbaum (Jacksonville, FL): As a follow-up to what Dr. Peters was asking. How can you be certain that some of these failures or differences aren't due to an incomplete myotomy? Have you considered performing intraoperative manometry in order to tailor the myotomy; particularly in the type 3 patients?

Closing Discussant

Dr. Renato Salvador: This is a good question. This is also exactly what we were discussing when we saw the final results of our study. Intraoperative manometry, that usually is not performed during myotomy, may play an important role in group 3 patients, and could represent the answer also to Dr. Pandolfino and Dr. Peters' questions. Intraoperative manometry may be conclusive in objectively verifying the completeness of the myotomy in this particular group of patients that, as said before, also appeared to have a longer lower esophageal sphincter.

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2010 SSAT PLENARY PRESENTATION

Comparing Complications of Esophagectomy and Pancreaticoduodenectomy and Potential Impact on Hospital Systems Utilizing the Accordion Severity Grading System

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Keywords Esophagectomy · Pancreaticoduodenectomy · Complication severity · Complication reporting · Morbidity comparison

Introduction

The formalized assessment of surgical outcomes can be a straightforward process when assessing certain parameters such as operative time, length of hospital stay, and mortality. Although complications are typically reported, the opportunity to specifically compare morbidity between centers and individual operations is impaired by the lack of standardized criteria defining complications associated with surgical procedures.[1–3] Various assessments have demonstrated that surgical complications will have measureable impact on mortality,[4] length of stay (LOS),[4,5] survival,[4,6] and costs.[7] However, the lack of a standardized system or "gold standard" for assessing the incidence and impact of complications[1–3] remains a significant problem in interpreting the surgical literature.[8,9]

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Esophagectomy (EG) and pancreaticoduodenectomy (PD) have been historically identified as more complex procedures associated with higher rates of morbidity and mortality.[10,11] This issue has resulted in increased scrutiny of these procedures by independent agencies such as the Leapfrog group (www.leapfroggroup.org).

In spite of the fact that there is no general consensus regarding the specific definition of surgical complications, the Accordion Severity Grading System (ASGS) provides a framework for complication assessment which is based on grading the complexity of therapy for the complication rather than just the occurrence of complications associated with a surgical procedure.[1,12] In 1992, Clavien et al. presented such a system (T92).[13] The system has evolved and has seen increasing acceptance and application over time.[8] The ASGS grades the complexity of treatment required for a complication providing a system which minimizes subjective interpretation and grades complications due to standardized criteria.[14]

The current study analyzed two large, single-institution, surgical experiences with EG and PD and applied the ASGS retrospectively to assess the impact on hospital resources by the complications associated with these two operations. Could ASGS be used retrospectively? ASGS scores were also compared to more standardized outcome measures such as length of stay, overall morbidity, and mortality.

Methods

The study population involved patients undergoing EG or PD between February 1991 and December 2008 that were recorded in two single surgeon, IRB-approved, prospective

databases. Basic demographic and specific clinical information had been collected prospectively including operative time, intraoperative blood loss, transfusion requirements, length of ICU, and in-hospital stay as well as recording overall morbidity and 30-day or in-hospital mortality for both procedures.

The databases were audited by surgeons (MK and YH) not involved in the operations and who had validated experience with the current Accordion Severity Grading System. All complications were reviewed to document the complexity of the treatments required, and were given an Accordion score (Table 1).[8] If there were multiple complications in one patient, final scoring of each individual procedure was the highest score in the case of each patient.

It should be noted that ASGS criteria require documentation of 100-day mortality. This review has accurate information on 30-day and in-hospital mortality, which was utilized in this report.

Statistical Methods

Chi-square, Fisher exact, and Student *t* tests were used to compare ASGS scores (1–6) for EG and PD where appropriate. If the sample was not normally distributed, the non-parametric Mann—Whitney *U* test was utilized. All statistical calculations were done using PASW Statistics 18 (SPSS Inc., an IBM Company, Chicago, Illinois) and $p \leq 0.05$ was considered significant.

Results

Between 1991 and 2008, there were 463 consecutive EG and 493 consecutive PD cases recorded in preexisting IRB-approved databases. The specific demographics of the two populations are outlined in Table 2. The EG group had a higher percentage of males (81% vs. 52%), a higher percentage of patients with ASA≥3 (60% vs. 42%), and a higher percentage of patients presenting with malignant disease (96% vs. 52%).

Postoperative outcomes are demonstrated in Table 3. Operative mortality was low in both series. The majority of PD patients underwent pylorus-preserving pancreaticoduodenectomy while the esophagectomy patients underwent a variety of operative procedures modified according to their presentation. Reoperations were more common following esophagectomy (3.5% vs. 0.4%). Readmissions were more commonly seen following PD (8% vs. 3%). There were very similar rates documented of overall morbidity, incidences of surgical and medical complications and postoperative median ICU and hospital length of stay. Figures 1 and 2 demonstrate that in both operative series, length of hospital stay improved over the duration of study. This outcome was seen in association with a progressive increase in the volume of procedures over time.

Complications were seen in 46% of EG patients and 44% of PD patients. These complications were retrospectively assigned ASGS grades according to Table 1. The distribution of ASGS grades between the two patient populations are listed in the top part of Table 4 and also depicted in Fig. 3 as a bar graph. There was a remarkable similarity between lower grades 1 and 2 and the higher grades 5 and 6. Although there was no statistically significant differences noted between any of the severity grades, EG versus PD had less "% in grade" in grade 3 (4.9% vs. 10%) yet had more percentage in grade for grade 4 (4.1% vs. 0.4%).

A typical grade 3 intervention without general anesthesia would be percutaneous drainage by interventional radiology, a

Table 1 Accordion severity classification of postoperative complications: expanded classification

Severity Grade	
1. Mild complication	Requires only minor invasive procedures that can be done at the bedside such as insertion of intravenous lines, urinary catheters and nasogastric tubes, and drainage of wound infections. Physiotherapy and the following drugs are allowed—antiemetic, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy.
2. Moderate complication	Requires pharmacologic treatment with drugs other than such allowed for minor complications, for instance antibiotics. Blood transfusions and total parenteral nutrition are also included.
3. Severe: invasive procedure without general anesthesia	Requires management by an endoscopic, interventional procedure or reoperation[a] without general anesthesia.
4. Severe: operation under general anesthesia	Requires management by an operation under general anesthesia.
5. Severe: organ system failure[b]	
6. Death	Postoperative death.

[a] An example would be a wound re-exploration under conscious sedation and/or local anesthetic

[b] Such complications would normally be managed in an increased acuity setting but in some cases patients with complications of lower severity might also be admitted to an ICU

Table 2 Demographics

Demographics	Esophagectomy (n=463)		Pancreatoduodenectomy (n=492)	
Median age (years) (range)	64 (15–90)		62 (41–86)	
Age≥75	77 (17%)		84 (17%)	
Male	373 (81%)		255 (52%)*	
Patients with ASA≥3	278 (60%)		205 (42%)*	
BMI≥30	124 (27%)		121 (25%)*	
Type of procedure	Left thoracoabdominal Ivor Lewis	281 137	Pylorus-preserving PD	462 (94%)
	Transhiatal	27	Standard PD	30 (6%)
	Right thoracoabdominal	13		
	Others	5		
Pathologic diagnosis malignant disease	445 (96%)		258 (52%)*	

Values are median (range) or number of patients (%)

PD pancreatoduodenectomy

*p<0.05, chi-square test

procedure common with PD. There were a total of 72 grade 3 cases in both groups (EG=23 and PD=49) making comparison meaningful. The incidence of grade 3 in the PD group was twice that seen in EG patients yet it was not reflected by a significant increase of LOS due to its minimally invasive nature.

A typical grade 4 complication would be reoperation under general anesthesia for anastomotic leak, a procedure more common to EG. There were a total of 21 cases with this ASGS score (EG=19, PD=2) making comparison less meaningful. However, the incidence of reoperations requiring general anesthesia was ten times higher with EG which was also not reflected with a change in LOS due to the timely and minimally impacting procedure of opening the cervical incision or endoscopic stenting of an anastomosis leak under general anesthesia.

In general, Table 4 demonstrates that postoperative length of stay increases as Accordion Severity Grade rises. However, exceptions are twofold. Patients in grade 6 (death) died early accounting for a low LOS and cases in Grades 4 and 5 contain only 3% of the patients providing less meaningful LOS information.

Discussion

Many surgical outcomes such as length of stay, operative mortality, and even quality of life, can be monitored and reported easily due to the fact that they are defined parameters or there are generally accepted specific measurement tools currently available. The assessment of surgical morbidity has historically been more difficult due to the absence of a recognized and accepted classification system.[1–3] A general review by Martin, demonstrated that only one third of surgical reports provided a framework for defining complications[2] and that there is no consistency between reports of morbidity within the surgical literature making accurate comparisons impossible.[8] There is an

Table 3 Postoperative outcomes in patients after esophagectomy and pancreatoduodenectomy

Outcomes	Esophagectomy (n=463)	Pancreatoduodenectomy (n=492)
Perioperative mortality	2 (0.4%)	5 (1%)
Overall morbidity	211 (46%)	216 (44%)
Re-operation	16 (3.5%)	2 (0.4%)*
Median length of postoperative hospital stay (days)	10 (6–49)	9 (6–79)*
ICU stay	1 (1–30)	1 (1–11)
Re-admission	13 (3%)	42 (8%)*
Patients with operation-specific complications (bleeding, leak, etc.)	121 (26%)	130 (26%)
Patients with complications not specific to operation (pneumonia, DVT etc.)	90 (19%)	87 (17%)

*p<0.05, chi-square test

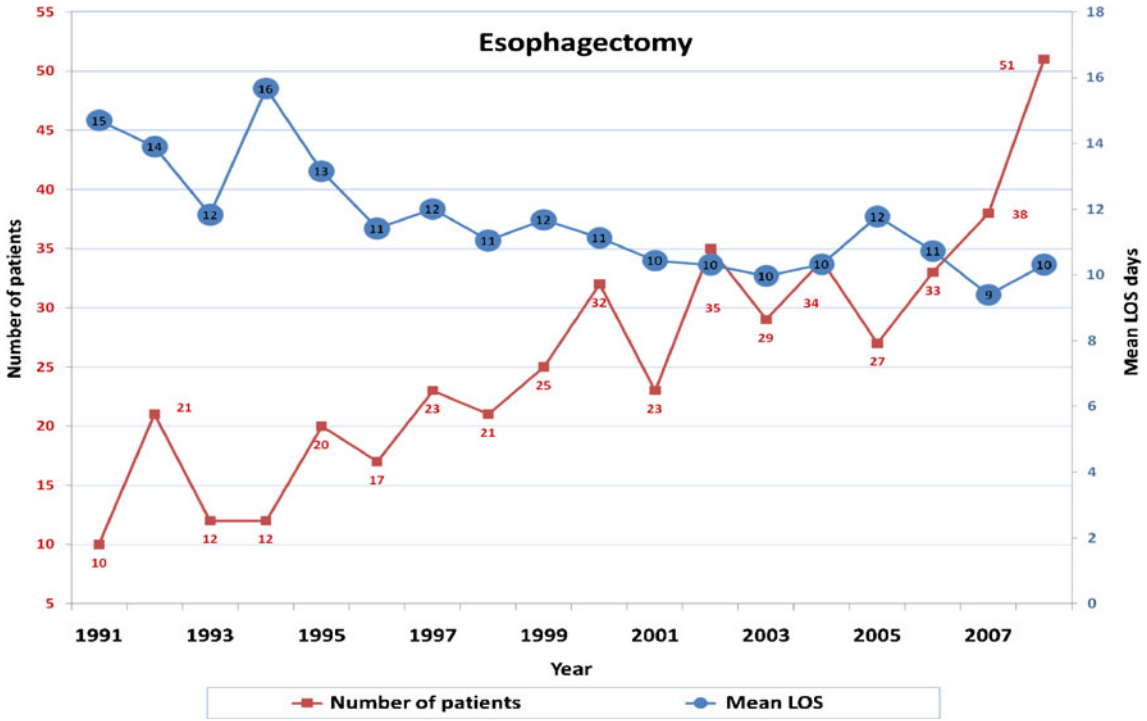

Fig. 1 Evolution in length of stays and case volumes overtime for esophagectomy

increasing awareness that postoperative morbidity is the major factor affecting outcome parameters such as length of stay, operative mortality, survival in cancer surgery, costs, and quality of life.[4–7,15] The need for a simple, reproducible, objective but comprehensive tool of assessing postoperative complications is clear not only for comparing outcomes between surgical reports but also to define an accurate and meaningful system to assess impact on our health systems.

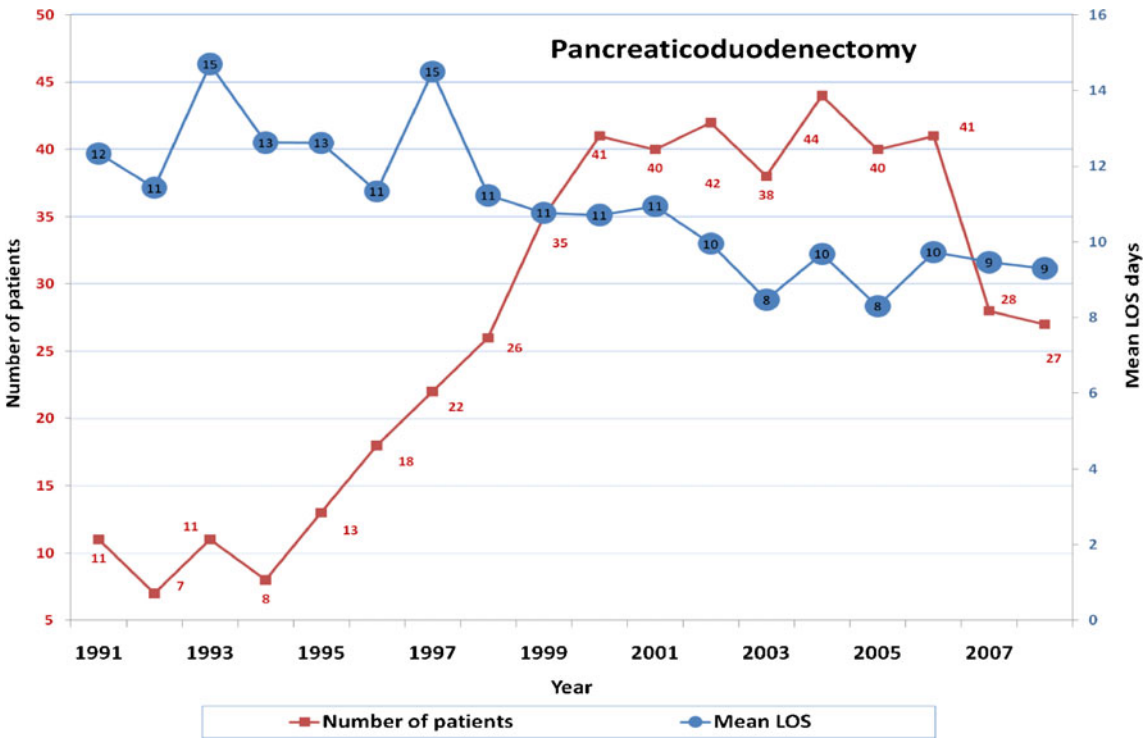

Fig. 2 Evolution in length of stays and case volumes overtime for pancreaticoduodenectomy

Table 4 Comparison of complication grades between procedures and effect on hospital length of stay

Operation		No of complications *n* (%)	Highest Accordion grade for any type of complication *n* (%)					
			1	2	3	4	5	6
Percentage in grade	EG (*N*=463)	252 (54%)	57 (12.5%)	102 (22%)	23 (4.9%)	19 (4.1%)	8 (1.5%)	2 (0.4%)
	PD (*N*=492)	276 (56%)	59 (12%)	97 (20%)	49 (10%)	2 (0.4%)	4 (1%)	5 (1%)
Mean LOS (days)	EG (*N*=463)	9 (range 6–24)	11	12	18	18	29	8
	PD (*N*=492)	9 (range 6–15)	9	12	14	29	34	12

The Accordion Severity Grading System provides a validated framework for reporting postoperative complications by grading the complexity of the therapeutic process required rather than the incidence of individual complications. The system has evolved over time to make the individual scoring levels more clinically relevant.[12–14]

The current ASGS system provides simple criteria and standardized definitions, which minimizes subjective interpretation. It can be applied in a study of any size and results should not vary according to the experience of the data entry personnel. Although it is validated for use prospectively,[12] as is the case with the current series, it is applicable for retrospective analysis because of the general availability of information regarding therapeutic interventions in the standard clinical record. Importantly, the system is based on not just the incidence of complications, but on the amount of therapy which ultimately can be used to assess health care resource consumption and potential costs of medical service delivery.

The current study applies the ASGS retrospectively in two large single-institution series of esophagectomy and pancreaticoduodenectomy which had been previously highlighted as outliers with respect to morbidity but particularly mortality.[10,11] Table 3 demonstrates that a high-volume center's 30-day mortality associated with EG and PD can be reduced to levels of 1% or less. However, overall morbidity figures, although consistent with the surgical literature are significant, ranging in the current series between 40% and 50%. The interpretation of these figures is problematic because, typically, the recognition of an event as a complication is based on the interpretation of the recording physician, or even more concerning the data manager. As a result, the types of complications reported are not standardized but more importantly, there is a lack of standardized definitions for specific complications.[2]

There are specific exceptions including the International Study Group of Pancreatic Surgery Clinical Grading System which provides defined criteria for pancreatic anastomotic failure and delayed gastric emptying.[16,17] That system was utilized for PD anastomotic leaks in this study, but there is no currently similar system for investigating or classifying esophageal anastomotic failure.[1,18,19] In addition, there is no consensus or consistency in the documenting of major subgroups such as cardiac and pulmonary complications. This variability precludes accurate comparison of morbidity outcomes between studies and institutions.

We document a surprising degree of consistency between the two procedures when comparing 30-day mortality, standard morbidity (including operation-specific complications), and length of stay. Due to preexisting prospective databases, we benefited from an accurate record of the incidence of complications in all patients. This made it a

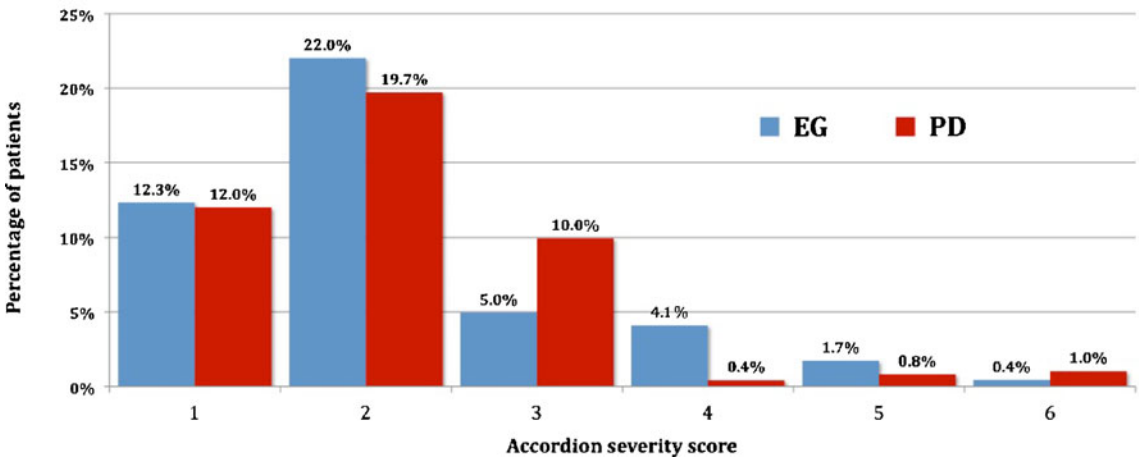

Fig. 3 Distribution of Accordion Severity Grades in patients with complications for *EG* and *PD* procedures

rather straightforward process of reviewing the medical records to document the therapeutic complexity required and apply an ASGS score for each complication. This produced an overall assessment of complication severity, which should reflect resource expenditure with respect to complications. The ASGS can clearly provide a meaningful comparison of morbidity between different or similar procedures.

However it is appropriate to acknowledge two pertinent issues with the ASGS as applied in this study. The first is the fact that each patient is assigned only one score. Therefore in patients with multiple complications the score will reflect only the highest level of therapy required. This has the potential to understate the impact on resource utilization in certain patients. This issue is being assessed in ongoing iterations of the ASGS to provide a quantitative weighting of complications in individual patients.[12] The second issue involves the recognition that the severity grades can be impacted on the basis of the availability of professional skills and technical expertise in different institutions. Examples would include the differing responses to anastomotic leak in both EG and PD operations. In institutions with aggressive interventional radiology and endoscopic services, most leaks can be managed with stenting and without general anesthesia (grade 3); whereas in the absence of these services, many will require operative management (grade 4). This was not a relevant factor in present study because professional and technical resources were identical.

Table 4 demonstrates that the incidence of complication severity grade 1 (patients requiring minor invasive procedures or simple drug therapy) or grade 2 (patients requiring more sophisticated drug therapy, transfusion, or TPN) is remarkably similar between the two operations at our institution. The same degree of similarity is documented in severity grade 5 (severe organ failure) or grade 6 (postoperative mortality) although the number of cases in these grades were small. However, there are differences noted in grade 3, where twice as many patients following PD required endoscopic, interventional radiology, or surgical procedure without general anesthesia and in grade 4 where ten times as many patients having esophagectomy required reoperation with general anesthesia. These comparisons are easy to understand and meaningful. They take into account the impact of complications on hospital systems by emphasizing risk and invasiveness of the therapy required to correct the complication. They may suggest where improvements in surgical delivery systems are required. The system also limits subjective interpretation because grading is based on easy-to-interpret therapeutic interventions. As a result, the system can be used to compare outcomes between different procedures or potentially, more to the point, similar operations in different institutions, health systems, or countries.

As expected, length of stay rises with increasing severity grade. Although comparisons of length of stay internationally is difficult due to cultural differences, with this study taking place in the same institution, it would appear that the effect of length of stay with increasing severity grade may be more marked in PD patients than EG patients.

The availability of consistent, easy to apply, and reliable mechanisms for assessing complications not only allows comparison between institutions, it also facilitates designing performance targets with respect to individual surgical procedures. These targets need not be putative but could be utilized as quality initiatives by centers looking to improve outcomes and lower costs of the delivery of surgical services.

In the current environment of healthcare reform, and with increasing concerns regarding the economic impact of healthcare, the cost of delivering surgical services will come under increasing scrutiny. Dindo has previously indicated that cost comparisons among centers is not a valid tool because detailed systems that permit comparative, uniform cost accounting for complications are not fully developed.[14] However, the ASGS utilizes resource allocation as an inherent component of severity grading. Economic impact of various procedures can be assessed because previous work has clearly linked resource utilization and costs.[20]

This study highlights that the ASGS can provide a simple, but comprehensive assessment of postoperative complications. In the current study, it was used to document similarities between the outcomes of EG and PD. However, differences in outcome and resource utilization between the two procedures have become evident. It could be effective in comparisons of the impact on health systems of different surgical procedures and provide a standardized format for comparing similar operations regionally and internationally. The ASGS should be considered for testing in institutional and national databases to facilitate meaningful comparison of morbidity and designing surgical outcome goals. It should not replace efforts to specifically classify standard complications such as anastomotic leak as demonstrated by the International Study Group of Pancreatic Surgery.[16,17]

A particularly interesting opportunity for the utilization of the Accordion Severity Grading System would be the comparison of outcomes between open and minimally invasive esophageal and pancreatic resections in the future.

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Discussant

Dr. Juan M. Sarmiento (Atlanta, GA): I want to congratulate the authors for this presentation of a fine paper and thank you for sending me the manuscript in advance. The study evaluates the availability of the Accordion system to find the usefulness of this grading procedure and to set the standard for longitudinal evaluation and compression with all institutions. It is very important in this current era of cost containment.

Basically, I have just one simple question.

Now that you have such a great result because you know the mortality and morbidity is just outstanding, do you think we should get a different format, a different table to evaluate the complications for a certain procedure, like esophagectomy, liver transplantation, pancreaticoduodenectomy, or we should put everybody on the main bag, and then start a comparison from there?

Closing Discussant

Dr. Donald Edward Low: I believe your question is aimed as to whether we should have a different approach for assessing complications in different operations. The goal of this particular study was to test the applicability of the Accordion Classification retrospectively in two very different procedures.

This study is of particular interest to our managers, who are already very happy with the results of pancreaticoduodenectomy and esophageal resection in our institution. Dr. Traverso and I had no idea how these operations compare with respect to outcomes and resource utilization.

The Accordion system provided a process that enabled us to take two very different procedures and compare them with respect to outcomes and complications, but also resource utilization and costs at our institution. We believe it will be easy to use this system in series done regionally, nationally, and internationally to provide better definition and consistency regarding the incidence and impact of complications in complex operations, which has not been possible in the past.

There are some current flaws within the Accordion system. I mentioned the fact that people with multiple complications will be understated because they are only given a single severity grade. I do believe this classification system provides us with something we have not had before. It provides us with an opportunity to reproducibly compare complications and ultimately resource utilization in a meaningful way.

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2010 SSAT PLENARY PRESENTATION

Loss of Alkalization in Proximal Esophagus: a New Diagnostic Paradigm for Patients with Laryngopharyngeal Reflux

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Abstract
Introduction Cervical esophageal pH monitoring using a pH threshold of <4 in the diagnosis of laryngopharyngeal reflux (LPR) is disappointing. We hypothesized that failure to maintain adequate alkalization instead of acidification of the cervical esophagus may be a better indicator of cervical esophageal exposure to gastric juice. The aim of this study was to define normal values for the percent time the cervical esophagus is exposed to a pH ≥7 and to use the inability to maintain this as an indicator for diagnosis of LPR.
Material and Methods Fifty-nine asymptomatic volunteers had a complete foregut evaluation including pH monitoring of the cervical esophagus. Cervical esophageal exposure to a pH <4 was calculated, and the records were reanalyzed using the threshold pH ≥7. The sensitivity of these two pH thresholds was compared in a group of 51 patients with LPR symptoms that were completely relieved after an antireflux operation.
Results Compared to normal subjects, patients with LPR were less able to maintain an alkaline pH in the cervical esophagus, as expressed by a lower median percent time pH≥7 (10.4 vs. 38.2, $p<0.0001$). In normal subjects, the fifth percentile value for percent time pH≥7 in the cervical esophagus was 19.6%. In 84% of the LPR patients (43/51), the percent time pH≥7 were below the threshold of 19.6%. In contrast, 69% (35/51) had an abnormal test when the pH records were analyzed using the percent time pH<4. Of the 16 patients with a false negative test using pH<4, 11 (69%) were identified as having an abnormal study when the threshold of pH≥7 was used.
Conclusion Normal subjects should have a pH ≥7 in cervical esophagus for at least 19.6% of the monitored period. Failure to maintain this alkaline environment is a more sensitive indicator in the diagnosis of the LPR and identifies two thirds of the patients with a false negative test using pH <4.

Keywords Laryngopharyngeal reflux (LPR) · Gastroesophageal reflux disease (GERD) · Esophageal pH monitoring · Diagnosis · Sensitivity · pH Monitoring · Esophagus · Pharynx · Diagnostic test

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Introduction

Laryngopharyngeal reflux (LPR) is a proposed diagnostic term that refers to a variety of respiratory and laryngeal symptoms suspected to be due to reflux of gastric contents into the cervical esophagus and pharynx. Establishing the diagnosis of the LPR is difficult, owing to the variety of other disease states that can cause similar symptoms. It has been proposed that use of a validated symptom scoring system or findings at laryngoscopy or an empirical trial of proton pump inhibitors (PPIs) may aid the clinician in establishing reflux as the cause of these symptoms, but each has been shown to lack specificity.

Although the measurement of cervical esophageal acid exposure may represent a more objective way to diagnose LPR, there is controversy regarding the clinical usefulness

of this approach. While some studies have shown increased acid exposure in the cervical esophagus in patients with LPR symptoms,[1,2] others have failed to show such a relationship.[3–5] Further, it has been shown that patients with LPR symptoms and increased cervical esophageal acid exposure have a variable and unpredictable response to acid suppression therapy and antireflux surgery.[5–8] Until recently, limited data were available regarding normal levels of acid exposure in the cervical esophagus,[9] which may in part explain the disagreement in previously published studies.

Despite these inconsistencies, the majority of the experts in the field have accepted cervical esophageal pH monitoring as the most objective method for diagnosing LPR, but all emphasize the need to improve its accuracy. In particular, there is a need for improved sensitivity,[10] based on the common observation that patients with symptoms strongly suggestive of LPR often have normal levels of cervical esophageal acid exposure.

One way to improve the sensitivity of cervical esophageal pH monitoring may be to change the pH threshold to one that is more appropriate for the upper aerodigestive tract. The threshold pH<4, that is currently used, is a carryover from distal esophageal pH monitoring where exposure to gastric contents with a pH below this level has been shown to cause mucosal damage and result in typical symptoms of reflux. In the upper aerodigestive tract, a weaker acid exposure may be more important in the pathogenesis of LPR in which case a different pH threshold would be required. In support of this concept is the observation that the upper airway epithelium is more susceptible to injury by gastric juice than the esophageal epithelium.[11,12] Further, pepsin has been identified as a major injurious agent in the pathogenesis of LPR, and this enzyme retains some of its activity up to a pH of 6.5.[13,14]

Since the average pH of saliva is 7 and saliva has a considerable buffering capacity, it is reasonable to hypothesize that failure to maintain a pH at or above 7 in the cervical esophagus may be a better indicator of a pathologic pH environment than measuring a drop below a pH of 4. The aim of this study was to define normal values for the percent total time the cervical esophagus is exposed to a pH ≥7 and to use the inability to maintain this pH as an indicator for diagnosis of laryngopharyngeal reflux.

Material and Methods

Study Populations

1. Normal Subjects: To define the normal values for the percent total time the cervical esophagus was exposed to a pH ≥7, we analyzed the pH tracings from 59 normal subjects who underwent dual probe pH monitoring in a previously published study to define normal cervical esophageal exposure to pH<4.[9] These subjects were selected from a group of 81 healthy volunteers with no gastroesophageal reflux (GER) or LPR symptoms. All underwent a complete foregut investigation including a videoesophagram, esophageal manometry, and dual probe pH testing to ensure they had normal foregut physiology and anatomy. Those with a normal composite pH score in the distal esophagus and no hiatal hernia on their videoesophagram were entered into this study as normal subjects.
2. LPR Patient Group: To evaluate sensitivity, we performed a retrospective review of the records of patients with LPR symptoms who underwent antireflux surgery and had complete relief of their LPR symptoms. In this way, we identified a group of patients that can be reasonably considered to have reflux as the cause of their laryngopharyngeal symptoms (i.e., a positive control group). We identified 51 patients who had complete relief of their symptoms with an intact fundoplication on a postoperative videoesophagram performed a minimum of 3 months after surgery. All of these patients had preoperative esophageal manometry and dual probe pH monitoring of the distal and cervical esophagus performed off of acid suppression medication. In addition, none of these patients were taking medications or had a systemic disorder that affects salivary flow, and none had previous foregut surgery.

Esophageal Manometry

Esophageal manometry was performed using a previously described technique in both the normal subjects and LPR patients.[15] In brief, a 12-French 8-channel water-perfused motility catheter (Arndorfer Medical Specialties, Greendale, WI, USA) was passed through the anesthetized nostril after an overnight fast, and the position of the lower esophageal sphincter (LES) and upper esophageal sphincter (UES) in centimeter from the nostril was recorded using a commercially available software program (Polygram® Net, Medtronic Inc., Minneapolis, MN, USA). All drugs interfering with foregut function were discontinued for at least 48 h before the study.

Ambulatory pH Monitoring Using Dual Sensor pH Catheter

Ambulatory esophageal pH monitoring was performed using one of three dual sensor pH catheters (Alpine Biomed Corp., Fountain Valley, CA, USA) designed with a distance between pH sensors of 10, 15, or 18 cm. The appropriate catheter was selected for each subject based on esophageal length measured by manometry so that when the distal pH

sensor was positioned 5 cm above the upper border of the LES, the proximal sensor would be located in the cervical esophagus as close as possible but below the lower border of the UES. In all patients, the proximal pH sensor was located between <1 and ≤4 cm below the lower border of the UES. The pH study was performed according to a previously described protocol.[16] Subjects and patients were instructed to follow a controlled diet, remain in an upright or sitting position until retiring to bed in the evening, avoiding eating or drinking between meals, refraining from chewing gum or smoking, perform normal activities at home or at work, and lie flat at night. All acid-suppressing medications were discontinued 3 (H2-blocking agents) or 14 days (PPIs) before the study. No medications effecting gastrointestinal function were allowed during the monitored period. Subjects and patients maintained a diary to identify meal periods, contents of the meals, and the times when they retired to bed in the evening and when they arose in the morning.

Analysis of the pH Tracings

The pH data from normal subjects and LPR patients were analyzed using a commercially available software program (Polygram® Net, Medtronic Inc., Minneapolis, MN, USA). The percent time pH<4 for the total monitoring period was calculated for the proximal and distal pH sensors. The cervical pH records of the normal subjects and LPR patients were also analyzed to determine the exposure time to pH≥7. To do so, the setting of the software program was adjusted so that a reflux event was defined as pH drops below 7. The values obtained were subtracted from 100 to calculate the percent time the pH was ≥7 for the 24-h monitored period.

Data Analysis

We have previously reported the upper limit of normal for the percent time the pH was <4 in the cervical esophagus using the 95th percentile value in the normal subject group.[9] This normal value was applied to the LPR patient group to determine the sensitivity of the threshold pH<4 in the diagnosis of LPR.

We then calculated the percent time the pH≥7 in the 59 normal subjects to define the lower limit of normal for exposure to pH≥7 using the fifth percentile value. The sensitivity of percent time pH≥7 as a diagnostic criterion for LPR was compared to exposure to pH<4 in the LPR patient group.

Statistical Methods

Values are reported as median and interquartile range (IQR). The Mann–Whitney *U* test was used for comparison of continuous variables between the groups. A *p* value of less than 0.05 was considered statistically significant. The analysis was performed using Prism 4 statistical software (Graphpad, San Diego, CA, USA).

The study was approved by the institutional review board of the University Of Southern California, Keck School of Medicine.

Results

The normal subjects consisted of 59 volunteers (29 males and 30 females) with a median age of 27 (23–36) years. The LPR patient group consisted of 51 patients (26 males and 25 females, median age 54 (48–66) years) who had complete elimination of their extraesophageal reflux symptoms after antireflux surgery. Of these 51 patients, 43 had typical GERD symptoms in addition to their LPR symptoms and eight patients had only LPR symptoms.

In the normal subjects, the median percent time the cervical esophagus was exposed to a pH <4 was 0.10 (0.0–0.30). The upper limit normal (95th percentile value) for exposure to pH<4 was 0.9% (Fig. 1). The median percent time the cervical esophagus was exposed to a pH ≥7 was 38.2 (IQR 27–56), and the lower limit of normal (fifth percentile value) for exposure to pH≥7 was 19.7% (Fig. 2).

Patients with LPR had significantly greater reflux in the cervical esophagus, expressed as increased exposure to pH<4, and failed to maintain a neutral pH in the cervical esophagus, as expressed by a lower exposure to pH≥7 compared to normal subjects (Table 1). Based on conventional analysis of their pH tracings, 35 of 51 patients with LPR were considered abnormal using percent time pH<4, yielding a sensitivity of 69%. Using the inability to maintain cervical esophageal pH≥7, 43 of 51 patients were defined as abnormal, yielding a sensitivity of 84%. There were 16 patients with LPR symptoms relieved by antireflux surgery who had normal acid exposure based on percent time pH<4 in the proximal sensor, and of these, 11 (69%) were abnormal based on the percent time pH≥7. If either or both the percent time pH<4 and percent time pH≥7 were abnormal, 45 of 51 patients would be considered abnormal,

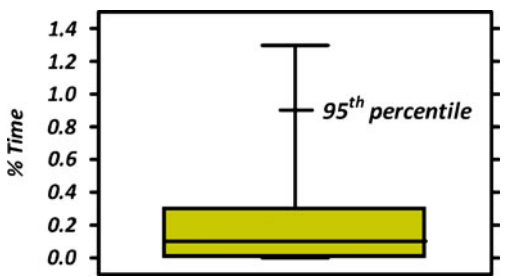

Fig. 1 Cervical esophageal exposure to pH<4 in normal subjects (*n*=59)

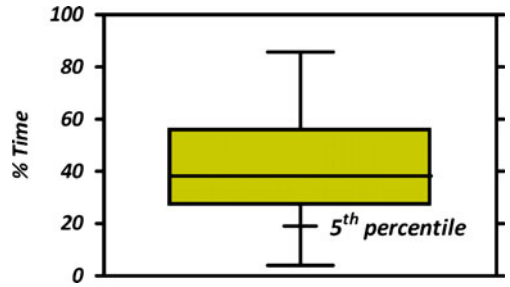

Fig. 2 Cervical esophageal exposure to pH≥7 in normal subjects (n=59)

yielding a sensitivity for detecting reflux as the cause of laryngopharyngeal symptoms of 90%.

Discussion

The relationship between gastroesophageal reflux and respiratory and laryngeal symptoms has been recognized since Bray proposed a relationship between the upper gastrointestinal symptoms and airway disease in 1934[17] and Cherry et al. described acid induced laryngeal ulcerations and granulomas in 1968.[18] Since then, reflux of gastric juice into upper aerodigestive tracts has been implicated as a cause for a variety of extraesophageal symptoms such as cough, asthma, hoarseness, and globus sensation collectively referred to as LPR symptoms. Confirming the diagnosis of LPR is challenging. Similar symptoms can be caused by a variety of non-reflux etiologies, and even when reflux is documented, there is a variable and unpredictable response to acid suppression therapy and antireflux surgery.[5–8] In fact, a recent meta-analysis of randomized clinical trials shows that therapy with high-dose proton pump inhibitors is no more effective than placebo in resolving or improving LPR symptoms.[19] Similarly, antireflux surgery does not reliably eliminate LPR symptoms.[20] One likely explanation for this variability in treatment response is the inability to correctly identify individuals whose laryngopharyngeal symptoms are caused by abnormal reflux.

A number of approaches have been tried unsuccessfully to establish reflux as the cause of LPR symptoms. It has been shown that the use of symptoms alone is inaccurate.[21,22] ENT physicians often rely on symptoms and the findings at laryngoscopy including erythema, edema, laryngeal granulomas, and interarytenoid hypertrophy to confirm the diagnosis. Studies have shown, however, that similar findings may be present in as many as 80% of the general population,[23] indicating a lack of specificity of these findings. Gastroenterologists have advocated a trial of PPI therapy in patients suspected to have LPR. Meta-analysis of studies on the response of patients with LPR symptoms to PPI therapy show that only 50% have improvement of their LPR symptoms,[19] suggesting a lack of sensitivity of this approach.

Table 1 Comparison of normal subjects and patients with LPR

	Normal subjects (N=59)	LPR patients (N=51)	p value
% Time pH<4	0.10 (0.0–0.30)	1.6 (0.7–4.5)	<0.0001
% Time pH≥7	38.20 (27.0–56.0)	14.7 (3.1–29.40)	<0.0001

Values reported as median (IQR)

Measurement of esophageal exposure to acid using dual probe pH monitoring has been proposed as an alternative way to establish the relationship between LPR symptoms and gastroesophageal reflux. By convention, the threshold used to define a reflux event in the cervical esophagus has been pH<4, consistent with the approach used in distal esophageal pH monitoring for GERD. Clinical experience with this approach has been mixed.[1–5] Despite the inconsistencies reported in the literature, dual probe pH monitoring is accepted as the most objective method for diagnosing LPR. It is considered to be highly specific, with errors limited to patients in whom the probe is placed incorrectly where artifacts may yield a false positive result. This error can be avoided by choosing a dual probe catheter with sensors properly spaced based on the patient's esophageal length measured at manometry as we have done.

From the perspective of the surgeon who is contemplating performing an antireflux procedure in patients with LPR symptoms, a highly specific test is of great importance. False positive tests would result in procedures performed on patients not likely to realize any benefit. From the perspective of the patient dealing with LPR symptoms, a highly sensitive test is important so that reflux is not inappropriately excluded as a potential cause of the patient's symptom. In this study, we have explored a new method of analysis of the cervical pH tracings in normal subjects and applied these results to a group of patients that can reasonably be assumed to truly have reflux as the cause of their LPR symptoms based on the elimination of symptoms after effective antireflux surgery. Our results suggest that the sensitivity for detecting abnormal reflux as the cause of LPR symptoms is maximized by the use of both the percent time pH<4 and percent time pH≥7.

One potential limitation of our study relates to the age range of normal subjects. They were significantly younger than the LPR patient group. This difference is potentially important when one considers the fact that previous studies have shown a lower salivary flow in older subjects. However, this is largely the result of systemic diseases that affect the production of saliva and the use of multiple medications in the elderly population and not the result of the aging process itself.[24,25] Patients with these systemic diseases and those taking medications known to affect

saliva production were specifically excluded in this study, which should minimize the impact of the age disparity on our conclusions.

Using failure to maintain a pH at or above 7 in the cervical esophagus as an indicator of a pathologic pH environment switches the focus of pH monitoring in the cervical esophagus to measuring the capacity to protect rather than the ability to damage. This approach, using a higher pH threshold, makes sense from a physiologic perspective for several reasons. First, it has been shown that pepsin, an important factor in the pathogenesis of LPR, retains enzymatic activity up to a pH 6.5 and that even up to pH 7 it remains stable for 24 h, capable of return of enzymatic activity on re-acidification.[26] Second, the sheer volume of saliva produced under basal conditions (0.5 ml/min) represents a large buffering capacity which may make reflux events of significance difficult to detect when lower pH thresholds are used. Using failure to maintain alkalinization in the cervical esophagus in the diagnosis of LPR is also consistent with recent studies that show a reduction in salivary pH in LPR patients when compared to normal individuals without LPR, and a positive correlation has been shown between the presence of the laryngopharyngeal symptoms and a reduction in salivary volume.[27,28]

Although we have shown that sensitivity can be improved by adding the assessment of percent time pH≥7 to dual probe monitoring, further studies will be needed to determine whether the overall accuracy is affected. In clinical practice, enhanced sensitivity often comes at the expense of reduced specificity. Unfortunately, the design of this study does not allow calculation of specificity, which should be addressed in future studies that include patients with LPR symptoms in whom it is determined that reflux is not the cause of the LPR symptoms. This would allow determination of all of the reference statistics including the false negative rate. This may prove to be challenging. The best approach may be to conduct a prospective study of patients presenting with symptoms suggestive of LPR, with a complete evaluation of all potential causes including dual probe pH monitoring using the normal data we have provided. The outcome in such patients could be used to define the referent statistics needed to perform receiver operating characteristics analysis that would determine the optimal diagnostic strategy.

Conclusion

Patients with LPR have significantly higher exposure to a pH <4 and a lower exposure to pH≥7 in their cervical esophagus than normal subjects. Using the threshold value of 19.7% for percent time pH≥7 rather than 0.9% threshold for the percent time pH<4 increases the sensitivity for diagnosis of the LPR from 69% to 84%. This approach switches the focus of pH monitoring in the cervical esophagus from measuring the ability to damage to the capacity to protect. When either or both an abnormal exposure to pH<4 and pH≥7 are used as a diagnostic criterion for abnormal cervical esophageal reflux, a sensitivity of 90% can be achieved.

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Discussant

Dr. Michael F. Vaezi (Nashville, TN): As you and your group knows, identifying more sensitive and more specific markers in LPR has been a challenge, limiting our ability to adequately diagnose and treat this difficult group of patients. I have a few questions, if you could clarify for us.

One is that you had mentioned that your patient population was mostly those that had concomitant typical symptoms and LPR. Were they patient mix and their chief complaints LPR symptoms, or were they predominantly typical symptoms but they had LPR complaints as well?

Number 2. As you know, when we increase the sensitivity of the test, this often is at the cost of specificity. Can you comment on that for me, whether or not you have increased sensitivity for LPR diagnosis but decreased the specificity for GERD?

Finally, since your cases were patients who responded to your surgical intervention, do you think the choice of using healthy controls was the correct one instead of choosing patients who had fundoplication without response to therapy?

Closing Discussant

Dr. Shahin Ayazi: Your first question referred to the chief complaint of our LPR patients. Eight out of 51 patients in our study had isolated LPR symptoms. The remaining 43 patients had combination of both typical and atypical reflux symptoms. The chief complaint in majority of the 43 patients was LPR symptoms, but there were also patients whose main driving force for treatment was typical reflux symptoms, and the LPR complaints were secondary or tertiary.

Your second question addresses the specificity of pH threshold of 7 in the diagnosis of LPR. This is a fair question since the effort of our study was to improve the sensitivity of the test. The accuracy of a diagnostic test depends on providing the best combination of sensitivity and specificity. We concur that improvement in sensitivity may result in sacrificing specificity. Unfortunately, the design of our study did not allow us to determine specificity. This would require having a true negative and a false positive group in our study population. For obvious reasons, it is difficult to identify such groups. Therefore, I cannot comment on the specificity of our approach. However, as you have correctly pointed out, there is a need to improve the accuracy of LPR diagnostic markers. The shortcomings of the different diagnostic tests vary; some lack sensitivity while others suffer from low specificity. The “achilles heel” of pH monitoring in the diagnosis of LPR is its low sensitivity, reflected by 50–60% sensitivity reported in publications on the subject, including the study from your group. The driving force in the design and conduct of our study was improving the sensitivity of pH monitoring in the diagnosis LPR.

This is in contrast to laryngoscopy that has a low specificity. Improvement in specificity of laryngoscopy requires identifying more specific laryngoscopic signs for reflux-related upper aerodigestive tract complaints. This is a task that needs our ENT colleagues’ attention.

Your last question is focused on our control group. I agree with you that from the methodology point of view, having a control group consisting of patients who did not benefit from a treatment might be a better choice than choosing healthy controls. The problem is identifying patients in whom reflux is the cause of laryngopharyngeal symptoms is challenging. Our goal was to validate our hypothesis in a clean and carefully selected group of patients. While it is reasonable to blame reflux as the cause of LPR symptoms in those who had complete relief of their LPR symptoms after antireflux surgery, the opposite is not

as true. This is because the etiology of LPR symptoms is multifactorial and LPR patients may have more than one factor as the cause of their symptoms. Antireflux surgery can stop reflux but has no impact on other factors such as ENT pathologies (sinusitis and etc.). In addition, antireflux surgery's ability in eliminating atypical reflux symptoms is not as effective as it is with typical reflux symptoms. Consequently, it might not be appropriate to exclude reflux as the cause of LPR symptoms based on unsatisfactory results of antireflux surgery. For these reasons, we selected healthy subjects as controls rather than patients who did not respond to surgical therapy.

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2010 SSAT PLENARY PRESENTATION

Potential Benefit of Resection for Stage IV Gastric Cancer: A National Survey

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Abstract
Introduction Controversy exists as to whether patients with stage IV gastric cancer should undergo surgical resection. We examined the association of gastrectomy with survival in this population.
Methods Stage IV gastric cancer diagnoses were identified using the SEER database (1988–2005). Analyses examined three subgroups divided on the basis of whether cancer-directed surgery was recommended and performed. Univariate analyses included chi-square and Kaplan–Meier survival analyses. Cox proportional hazards modeling was performed to assess independent determinants of survival.
Results Of 66,751 identified gastric cancer patients, 23,830 had stage IV disease. Resected patients had a significant survival advantage; survival outcomes of patients who had been recommended for, but had not undergone, surgery were identical to that of patients who had not been recommended (3 months vs. 9 months for resected, $p<0.0001$). Furthermore, resection status was the most significant independent predictor of increased risk of death (hazard ratios 2.0 for non-cancer-directed surgery groups).
Conclusions Patients with stage IV gastric cancer who undergo resection, a highly selected population, have significantly greater survival than unresected patients, including those who were recommended for, but did not receive, resection. Stage IV gastric cancer patients who are reasonable operative candidates should be offered resection.

Keywords Stage IV gastric cancer · Gastric resection · Survival

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Introduction

Gastric cancer is the second leading cause of cancer-specific mortality worldwide[1] and the tenth leading cause in the United States (stomach/esophagus).[2] The American Cancer Society estimated that cancer of the stomach had an incidence of 21,130 cases and caused 10,620 deaths in the United States in 2009.[3]

Previous investigators have suggested that palliative resection for gastric cancer may confer symptomatic and/or survival benefits. However, the survival benefit has been theorized to be limited to certain groups of patients or characteristics, e.g., younger age, Asian race, and limited spread of disease.[4–6] Data from the Dutch Cancer Trial showed that patients under 70 years of age with only one positive site of metastatic disease benefited from resection.[7,8] US-based studies analyzing data from the National Cancer Data Base (NCDB) have suggested that

gastric cancer may be undertreated in this country, especially with respect to surgical intervention.[9,10]

Many studies examining resections for gastric cancer are limited by the number of subjects or by a single-institutional design. The goal of this study was to use the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute, a national population-based database, to analyze survival rates for gastric resections for stage IV cancer. Our hypothesis was that the SEER database could be used to examine advantages of gastric resection and identify predictive factors for survival among patients with stage IV gastric cancer who had been recommended for treatment. We examined the relative effects of predictors of survival, including sex, age, race, and treatment.

Materials and Methods

Cohort Assembly

Patient data were collected from the SEER database from January 1, 1988 through December 31, 2005, the years for which complete American Joint Committee on Cancer (AJCC) staging and surgical resection information is available. SEER, sponsored by the National Cancer Institute, is a comprehensive US population-based database that includes stage of cancer at the time of diagnosis and patient survival data. Data are currently collected from 17 population-based cancer registries accounting for approximately 26% of the US population;[11] this applies to all of the 2000–2005 SEER data. The 1988–1999 SEER data are from 12 SEER registries, which comprised approximately 14% of the US population. Studies of the SEER database were approved from our institutional review board as exempt from the Committee for the Protection of Human Subjects in Research.

All patients ≥18 years of age at the time of first diagnosis of gastric cancer who underwent resection were identified through the SEERStat program (SEERStat 6.4.4[12]). These data were imported into SAS version 9.2 (SAS Institute, Cary, NC). We then further limited this group to those with the diagnosis of stage IV cancer using a combination of AJCC staging criteria and SEER historic stage. Patients were excluded if they were death certificate or autopsy only cases, were recorded as having died prior to recommended surgery, or had missing or unknown surgery type—all as recorded within SEER under "reason no cancer-directed surgery". Patients were also excluded on the multivariate analysis if they had missing race or M stage information (0.2% of total).

SEER captures cancer-directed surgery performed within 4 months of diagnosis. The SEER data include information regarding whether or not cancer-directed surgery was recommended and performed. To achieve "like-to-like" survival comparisons, using methods previously described by our group,[13] we divided patients with stage IV gastric cancer into three groups on the basis of surgery recommendation and performance. The three groups were: (1) recommended for and underwent cancer-directed surgery, (2) recommended for cancer-directed surgery, no surgery performed or underwent non-cancer-directed surgery, and (3) not recommended for cancer-directed surgery, no surgery performed or underwent non-cancer-directed surgery.

Statistical Analyses

Descriptive analyses included means and frequency distributions for patient and tumor characteristics—patient age, sex, race, marital status, disease M stage, tumor grade, and procedure type. Age was calculated as a mean and also divided into three groups to examine frequency distributions: <50, 50–69, and ≥70 years old. Procedure type for those patients who underwent cancer-directed resection was divided into seven groups: local tumor destruction ("local"), partial gastrectomy, total/near total gastrectomy, gastrectomy with en bloc resection, gastrectomy not otherwise specified (NOS), surgery NOS, and other cancer-directed surgery.

Analyses of Recommendation for Cancer-Directed Surgery

Univariate analyses were conducted using the above described characteristics, as well as year of diagnosis (divided into groups: 1988-1990, 1991-1993, 1994-1996, 1997-1999, 2000-2002, 2003-2005), on the outcome of being recommended for surgery. Multivariate analysis using a logistic regression model was also performed. Characteristics included in the model were those that were significant ($p<0.05$) on univariate analysis. These analyses evaluated the association of each characteristic as a predictor for being recommended for surgery, and then once recommended, for the probability of receiving surgery.

Survival Analyses

The primary outcome measure was overall survival, defined as time from date of diagnosis to death from any cause as recorded within the SEER database. Mortality data reported by SEER are provided by the National Center for Health Statistics. Survival was evaluated with univariate analyses using Kaplan–Meier (KM) estimates and survival curves[14] with comparisons across surgery groups. To examine the impact of the year of diagnosis

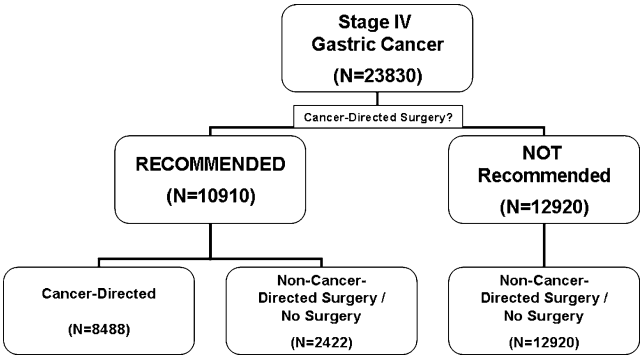

Fig. 1 Distribution of patients into recommendation/treatment groups

and surgery, given that advances in medical and surgical therapy for gastric therapy may have led to improved survival in more recent years, KM survival analyses were also performed across years. Multivariate analyses of survival were performed using Cox proportional hazard modeling with overall survival as the dependent variable. Independent variables adjusted for in this model included the patient and tumor characteristics described previously, as well as year of diagnosis (divided into groups: 1988-1990, 1991-1993, 1994-1996, 1997-1999, 2000-2002, 2003-2005).

Results

Patient Cohorts

There were 66,751 patients diagnosed with gastric cancer identified in the SEER database between 1988 and 2005. Of this total, 24,368 were diagnosed with stage IV disease; 538 patients were excluded, giving a final study cohort of 23,830. Among this cohort of patients, 10,910 were

Table 1 Patient characteristics for all patients diagnosed with stage IV gastric cancer

	Overall	Recommended		Not recommended
		Received cancer-directed surgery	Did not receive cancer-directed surgery	Did not receive cancer-directed surgery
Number of patients	23,830	8,488	2,422	12,920
Mean age (in years)	*66*	*65*	*68*	*67*
Age group				
<50	3,199	1,237	280	1,682
50–69	9,488	3,516	858	5,074
≥70	11,183	3,735	1,284	6,164
Sex				
Male	15,086	5,164	1,529	8,393
Female	8,744	3,324	893	4,527
Race				
White	17,195	5,825	1,848	9,522
Black	2,980	1,058	328	1,594
Other	3,634	1,598	245	1,791
Marital status				
Married	14,172	5,325	1,316	7,531
Single (never married)	2,821	937	285	1,599
Divorced/separated	1,980	673	189	1,118
Widowed	4,165	1,346	522	2,297
M stage				
M0	2,618	2,531	14	73
M1	21,184	5,931	2,408	12,845
Tumor grade				
Grade I	491	142	61	288
Grade II	4,194	1,479	437	2,278
Grade III	13,581	5,726	1,182	6,673
Grade IV	762	332	49	381
Unknown	4,802	809	693	3,300

Table 2 Operations performed on all stage IV gastric cancer patients who underwent cancer-directed gastric resection (N=8,488)

Procedure type	N (%)
Local tumor destruction	243 (2.9%)
Partial gastrectomy	4,358 (51.3%)
Total/near total gastrectomy	1,430 (16.8%)
Gastrectomy with en bloc resection	1,919 (22.6%)
Gastrectomy not otherwise specified (NOS)	126 (1.5%)
Surgery NOS	389 (4.6%)
Other cancer-directed surgery	23 (0.3%)

recommended for cancer-directed surgery, 8,488 underwent cancer-directed surgery, and 2,422 did not undergo recommended surgery—there was no surgery performed on them, including either cancer- or non-cancer-directed surgery. A total of 12,920 patients were not recommended for surgery, all of whom had either no surgery performed or underwent non-cancer-directed surgery (Fig. 1). Patient demographics are summarized in Table 1. Operations performed for the patients who underwent cancer-directed gastric resection are detailed in Table 2.

Univariate Analyses

Recommendation for Cancer-Directed Surgery

Patient age, sex, race, marital status, disease M stage, and tumor grade were all significantly associated with recommendation for cancer-directed surgery (regardless of whether procedure was performed). Patients who were recommended for surgery were more likely to be younger, male, white, married, have M1 disease, and have tumors of grade III. On further analysis of the subgroup both recommended for and receiving surgery, all of these characteristics continued to demonstrate a significant association. Patients undergoing recommended cancer-directed surgery were similarly more likely to be younger, male, white, married, have M1 disease, and have tumors of grade III (Table 3).

Table 3 Univariate analysis of patient characteristics for cancer-directed surgery recommendations and performance

	Recommended (N=23,830)		p	Performed (N=10,910)		p
	Yes	No		Yes	No	
No. of patients	10,910	12,920		8,488	2,422	
Age group						
<50	1,517	1,682	0.02	1,237	280	<0.0001
50–69	4,374	5,074		3,516	858	
≥70	5,019	6,164		3,735	1,284	
Sex						
Male	6,693	8,393	<0.0001	5,164	1,529	0.04
Female	4,217	4,527		3,324	893	
Race						
White	7,673	9,522	<0.0001	5,825	1,848	<0.0001
Black	1,386	1,594		1,058	328	
Other	1,843	1,791		1598	245	
Marital status						
Married	6,641	7531	0.0008	5,325	1,316	<0.0001
Single (never married)	1,222	1,599		937	285	
Divorced/separated	862	1,118		673	189	
Widowed	1,868	2,297		1,346	522	
Unknown	317	375		207	110	
M stage						
M0	2,545	73	<0.0001	2,531	14	<0.0001
M1	8,339	12,845		5,931	2,408	
Tumor grade						
Grade I	203	288	<0.0001	142	61	<0.0001
Grade II	1,916	2,278		1479	437	
Grade III	6,908	6,673		5726	1,182	
Grade IV	381	381		332	49	
Unknown	1,502	3,300		809	693	

Table 4 Kaplan–Meier survival estimates

Recommendation/treatment group	Number of patients (%)	Median survival (in months)
Recommended,cancer-directed surgery	8,488 (35.6%)	9
Local tumor destruction	243	6
Partial gastrectomy	4,358	9
Total/near total gastrectomy	1,430	8
Gastrectomy with en bloc resection	1,919	9
Gastrectomy not otherwise specified (NOS)	126	10
Surgery NOS	389	5
Other cancer-directed surgery	23	6
Recommended, no surgery/no cancer-directed surgery	2,422 (10.2%)	3
Not recommended, no surgery/no cancer-directed surgery	12,920 (54.2%)	3

Survival

KM survival analysis demonstrated an overall median survival of 4 months for the entire stage IV gastric cancer cohort. Analysis across the three groups showed that resected patients had a significant survival advantage, and that the survival outcome for patients who had been recommended for but had not undergone cancer-directed surgery was identical to that of patients who had not been recommended for surgery. Median survival of the cancer-directed surgery group was 9 months compared to 3 months in the other two groups ($p<0.0001$; Table 4 and Fig. 2). Within the cancer-directed surgery group, further analysis by type of surgery performed demonstrated that all types of cancer-directed surgery conferred some survival benefit over all other groups, in the range of 5–10 months. The greatest survival benefit (9–10 months) was observed among the patients who had undergone partial gastrectomy, gastrectomy with en bloc resection, and gastrectomy NOS (Table 4).

For the overall stage IV gastric cancer cohort, median survival throughout the years of the study was 4–5 months. For the cancer-directed surgery group, median survival ranged from 7–11 months, with 10–11-month survival times in the more recent years of the study (Fig. 2).

Multivariate Analyses

Receiving Cancer-Directed Surgery Once Recommended

When adjusted for in a logistic regression model, all included characteristics (patient age, sex, race, marital status, disease M stage, and tumor grade) remained independent predictors of undergoing recommended cancer-directed surgery. However, certain characteristics were associated with being more likely to receive cancer-directed surgery, while others decreased the probability of receiving surgery. Predictors associated with being more likely to receive recommended cancer-directed surgery were "Other" race, which includes Asian (odds ratio (OR), 1.74; 95% confidence interval (CI), 1.49–2.03) and tumor grades III and IV (III: OR, 1.68; 95% CI, 1.22–2.32; IV: OR, 2.75; 95% CI, 1.77–4.27). However, older age, male sex, marital status other than married, and M1

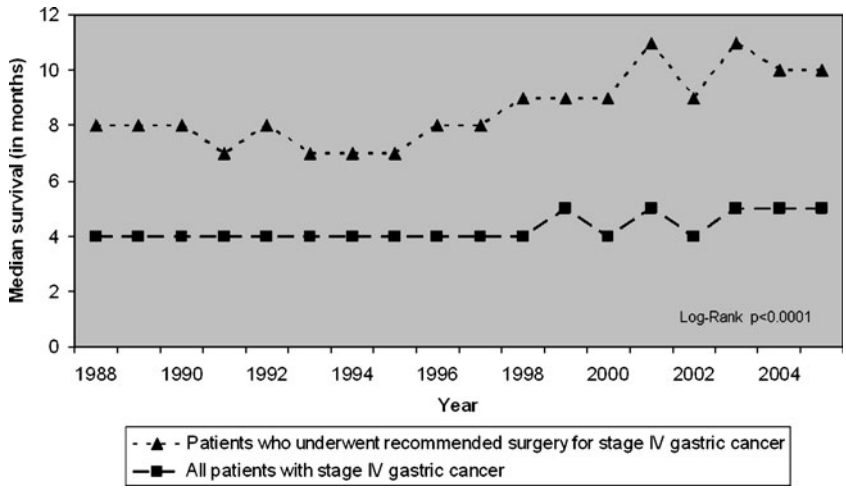

Fig. 2 Median survival over the time course of the study (1988–2005)

Table 5 Multivariate logistic regression analysis for probability of receiving surgery once recommended (N=10,910)

	Odds ratio Point estimate	95% Confidence interval
Age (vs. <50)		
50–69	0.93	0.79–1.10
≥70	0.68	0.58–0.80
Male (vs. female)	0.75	0.67–0.84
Race (vs. white)		
Black	1.12	0.96–1.30
Other	1.74	1.49–2.03
Marital status (vs. married)		
Single (never married)	0.84	0.72–0.99
Divorced/Separated	0.86	0.71–1.04
Widowed	0.69	0.60–0.80
M1 (vs. M0)	0.016	0.009–0.027
Tumor grade (vs. I)		
II	1.37	0.98–1.91
III	1.69	1.22–2.33
IV	2.68	1.72–4.18

disease were shown to be associated with patients being less likely to receive recommended surgery (Table 5).

Survival

Using Cox proportional hazard ratios to model survival, independent predictors including patient age, sex, race, marital status, M stage, tumor grade, year group, and surgery recommendation/performance were evaluated. When adjusting for independent variables, the most significant predictor of increased risk of death for stage IV gastric cancer patients was surgery recommendation/performance with patients who were not recommeded for and did not undergo cancer-directed surgery (NOT REC, No OR) as well as patients who were recommended for but did not undergo cancer-directed surgery (REC, No OR) having a nearly two-fold increased risk of death compared to patients who had undergone recommended cancer-directed surgery (REC, OR). Other factors independently predictive of increased risk of death included male sex, age older than 50 years, black race, marital status other than married, M1 disease, tumor grade higher than grade I, and year group prior to 2003-2005 (Fig. 3).

Discussion

In this study, we used national cancer data from SEER to demonstrate that patients with stage IV disease undergoing resection for gastric cancer have improved survival com-

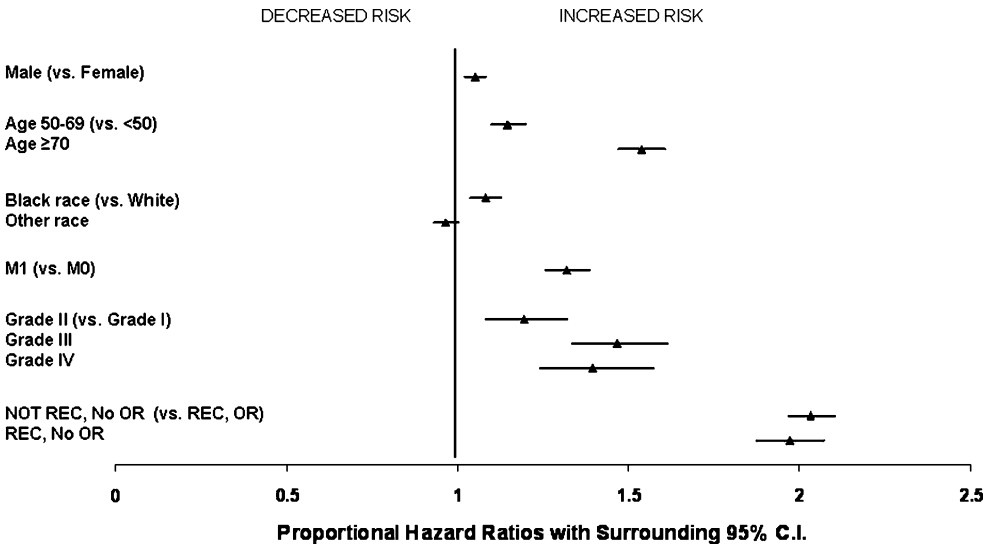

Fig. 3 Proportional hazard ratios for risk of mortality among all patients with stage IV gastric cancer

pared to patients not undergoing resection throughout the years 1988–2005. Patients who did not undergo recommended surgery had worsened survival compared to the operative cohort. Our analyses show that the hazard ratio (i.e., risk of mortality) for patients undergoing surgery compared to those patients who did not undergo recommended surgery was 2.0. Additionally, we found other factors that have significant influence on being recommended for surgery, as well as on overall survival including patient age, sex, race, marital status, and tumor/disease characteristics.

Our results, which demonstrate that there is a survival benefit to resection of stage IV gastric cancer, compare favorably with findings previously reported in the literature, which have reported improved 5-year survival rates,[15] as well as survival advantages of 3–10 months[7,16] for patients who have been resected compared to those who have not undergone resection for stage IV gastric cancer. Our results also suggest, as previous NCDB studies[9,10] have, that increased use of surgical resection in the treatment of gastric cancer may lead to improved outcomes for gastric cancer in the US.

This study is limited by the confines of the SEER database. In particular, in evaluating resections for stage IV disease, which may include palliative resections, SEER does not account for symptomatic or quality of life variables, therefore, palliative surgery, as studied here, can only account strictly for survival benefits. Another well-described limitation of registry data is the issue of non-random treatment assignment, which introduces selection bias into the study.[17] Regarding the defined patient cohorts, we recognize that patients who undergo surgical resection of stage IV cancer represent a highly selected group of patients. Therefore, some of the difference in survival may reflect that surgeons are appropriately selecting patients for surgery.

Despite these limitations, our data are from a national cancer database with both disease-and treatment-specific variables with a very large dataset, which contribute strength to these analyses. With these analyses, we have demonstrated that among all patients with stage IV gastric cancer recommended for surgery, patients who undergo gastric resection have improved survival over those who do not undergo resection.

Future studies would ideally analyze other outcome variables in addition to survival, including perioperative complications and quality of life. The previously mentioned limitation of only being able to focus on survival outcomes in this study is a limitation is shared by several studies of palliative resections.[7,15,16] Relatively few, small studies with conflicting results have been done examining the direct quality of life impact of gastric resection for cancer.[18,19] Additional larger studies are clearly needed to further elucidate quality of life factors in resected gastric cancer patients.

Conclusion

In conclusion, we have used the SEER database to demonstrate that patients with stage IV gastric cancer may benefit from cancer-directed resection. Surgical intervention is a treatment modality previously cited as being underutilized for gastric cancer in the US. Our results indicate that increased use of gastric resection in appropriate operative candidates would lead to improved outcomes for stage IV gastric cancer patients.

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Discussant

DR. MARTIN S. KARPEH (New York, NY): I wanted to thank you and your group for bringing up this very important topic and one that we are seeing more and more frequently. With the use of induction chemotherapy, we are seeing more of these patients that are potentially eligible for resection.

I believe this is the largest study of its type to address this question, and your group has very nicely tried to deal with the selection bias by identifying the patients who are recommended for cancer-directed surgery.

There are a couple of key issues that this topic brings up. Clearly, there are issues which are related to quality of life which I don't believe your data set was able to address and was not addressed in the paper. The other one, of course, is the potential bias in how the patients were selected.

Other investigators have pointed out that Asian ethnicity portends better survival. In your "other group" category, can you go back and tease out what percentage of those patients were of Asian ethnicity? It may be an interesting trend to identify.

Also, the use of induction chemotherapy is more recent, but your analysis goes back to 1988, when many of those patients weren't getting chemotherapy. Are you able to go back and look at the role of chemotherapy in the survival of these patients that ultimately got resected?

In some of the earlier published analyses, others have pointed out that the extent of resection has a negative impact in the patients that were resected in stage IV gastric cancers. Can you tell us how many patients had extended organ resection or total gastrectomy, and what impact did that have on their ultimate outcome?

There appears to be a greater percentage of M0 stage IVs in the patients that ultimately did get resected. Could that be an explanation for the differences in outcome?

Then lastly, is survival really the right endpoint? Should we really be looking at quality of life in these patients?

Closing Discussant

DR. JILLIAN K. SMITH: Regarding your first question about the survival advantage of gastric cancer patients of Asian race, we did not specifically examine this in our study. However, in our analysis of race, the category of "other" did include patients of Asian race. It would be interesting to take a further look at that analysis to see if a subset analysis of Asian race could be performed within the category of "other."

Regarding the question of chemotherapy, the use of neoadjuvant treatment for cancers is becoming a very highly discussed topic, and certainly relevant to anyone's survival. However, this was not studied in our patient cohort as chemotherapy is not recorded in the SEER database. Linkage of SEER data to Medicare does allow for chemotherapy on the basis of examining claims data for Medicare claims, but as we did not use linked Medicare data, I cannot speak specifically to a chemotherapy effect in this population; but I would certainly expect that there would be one with associated adjuvant or neoadjuvant treatment use in any of these populations.

With regard to the type of resection, in our first analysis, we looked at the treatment recommendations and then whether or not the patients underwent resection. We did also examine what type of resections those patients had, but we did not initially perform survival analysis pertaining specifically to each type of resection (these analyses were added to the revised manuscript).

With regard to the M0 versus M1 question, yes, it is possible that the higher percentage of M0 disease is contributing to the survival benefit among the patients who undergo resection. It is likely that among patients recommended for surgery, those that ultimately underwent a cancer-directed surgery were those with M0 disease. Whereas the patients who perhaps had unknown metastatic status and were recommended for surgery, were taken to the operating room, and then upon discovery of M1 disease, had aborted procedures—these patients would fall into the "recommended for, but underwent no surgery or non-cancer-directed surgery" category, who had worse survival.

Finally, your question about whether survival is the right endpoint brings up an important issue—ideally, any analysis of the potential benefit of surgical or any other treatment would examine the outcome of survival in the context of patients' quality of life. These large databases, unfortunately, are not able to be linked to any quality-of-life studies.

There have been several small series that have looked at quality-of-life questionnaires, even specifically for GI malignancies, examining patients' quality of life after resection. And those results have been mixed—some studies have shown an improved quality of life and extended survival with

resection, and other studies have indicated that patients are not reporting a better quality of that extended life, mostly due to the morbidity associated with such a major operation that they underwent. In any study of our treatment outcomes, quality of life is certainly something that we should always keep in the back of our minds.

Discussant

DR. JONATHAN CRITCHLOW (Boston, MA): I was struck by this interesting paper due to the fact that almost half of the patients with metastatic gastric cancer were recommended to have an operation. Although a number of them did not end up being operated, I find the percentage to be quite high, and I would say almost shocking. The question of selection bias is of interest, whether healthier patients were advised to have surgery. However, you got around this by showing similar survival in non-operated patients, whether they were advised to have resection or not. A major question of interest is if there is a difference in the ratio of M0 to M1 patients being resected.

It's going to be extremely difficult, but how many of these patients were symptomatic and operated on because they had obstruction or experienced bleeding? Or were they asymptomatic and operated in efforts to "prolong their survival"? I think that's an important part of this decision making.

Also, the type of operation is key. It's a whole different kettle of fish to be doing a subtotal gastrectomy for somebody who is obstructed, as opposed to a total gastrectomy for somebody who has no symptoms who may live an extra 6 months, but spend it convalescing and trying to learn how to use a new GI tract.

Those are questions that unfortunately you will have a difficult time answering, but are problems for me in trying to make sense of this. And I would actually say that your patient MH, who has metastatic disease with peritoneal studding, does not appear to be obstructed, and is probably going to need a total gastrectomy, needs to be looked at in a different way and not advised to have a resection.

Closing Discussant

DR. JILLIAN K. SMITH: Our data certainly have limitations with regard to knowing the symptomatology, as well as knowing exactly what the surgeon's decision process is and ultimately what the patient's decision process is. The point I would leave with this research is that, it is not meant to replace anyone's expert clinical judgment, but rather, inform clinicians that there are data to suggest that nearly half of these patients are being recommended for surgery, and nearly half of those are undergoing that surgery. Furthermore, undergoing surgery does appear to have some sort of survival benefit. The idea introduced by this research is that, if a surgeon, or perhaps a step back in the process, a primary care physician, has a patient that he or she believes is healthy enough to tolerate surgery, that patient should not be automatically dismissed from consideration for surgery just because of stage IV disease.

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2010 SSAT PLENARY PRESENTATION

Waist Circumference Predicts Increased Complications in Rectal Cancer Surgery

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Abstract
Background The impact of obesity on development of postoperative complications after gastrointestinal surgery remains controversial. This may be due to the fact that obesity has been calculated by body mass index, a measure that does not account for fat distribution. We hypothesized that waist circumference, a measure of central obesity, would better predict complications after high-risk gastrointestinal procedures.
Methods Retrospective review of an institutional cancer database identified consecutive cases of men undergoing elective rectal resections. Waist circumference was calculated from preoperative imaging.
Results From 2002 to 2009, 152 patients with mean age 65.2±0.75 years and body mass index 28.0±0.43 kg/m^2 underwent elective resection of rectal adenoma or carcinoma. Increasing body mass index was not significantly associated with risk of postoperative complications including infection, dehiscence, and reoperation. Greater waist circumference independently predicted increased risk of superficial infections (OR 1.98, 95% CI 1.19–3.30, $p<0.008$) and a significantly greater risk of having one or more postoperative complications (OR 1.56, 95% CI 1.04–2.34, $p<0.034$).
Conclusions Waist circumference, a measure of central obesity, is a better predictor of short-term complications than body mass index and can be used to identify patients who may benefit from more aggressive infection control and prevention.

Keywords Obesity · Rectal cancer · Complications

Introduction

The impact of obesity on development of postoperative complications after gastrointestinal surgery remains controversial. Several studies have shown that obese patients are

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at greater risk for death and short-term complications including wound infections, venous thrombosis, and anastomotic leaks.[1–3] However, other groups have shown no difference between obese and normal weight individuals or an effect limited primarily to those who are morbidly obese.[4–7] These contradictory findings may be partly explained by the fact that obesity is traditionally measured by BMI, which does not account for fat distribution.[8] By contrast, alternative measures of obesity including waist circumference can be used to measure fat distribution and to distinguish between central and other types of obesity.

Central obesity is an element of the metabolic syndrome and has been associated with changes in insulin regulation and mortality as well as increased incidence of colorectal cancer.[9,10] Central distribution of fat may be relevant for abdominal surgery since adipose tissue tends to be less well vascularized than skin and surrounding stroma. Consequently, having excess fat tissue in the abdominal region should be more likely to increase complications than having the same absolute quantity of fat distributed away from the operative field in the limbs or posterior region.

Several recent papers have looked at the effects of fat distribution by measuring intra-abdominal/visceral fat and subcutaneous fat area. These authors found that in laparoscopic colorectal surgery measuring fat distribution is better than BMI when it comes to predicting postoperative complications.[11–13] However, measuring visceral and subcutaneous fat requires specialized software and is time-consuming. By contrast, waist circumference is a simpler measure that reflects the presence of central obesity and has been associated with increased risk for parastomal hernia following abdominoperineal resection (APR).[14] We hypothesized that waist circumference would be an accurate predictor of other postoperative complications.

Materials and Methods

After obtaining approval from the Baylor College of Medicine and Veterans Affairs institutional review boards, consecutive patients undergoing rectal surgery from 2002 to 2009 were identified using an institutional database at the Michael E DeBakey Veterans Affairs Hospital. Patients were included in this study if they underwent elective resection for rectal adenoma or adenocarcinoma. Patients were excluded if they had a history of Crohn's disease, underwent emergency surgery, or had surgery purely for palliation. Demographics, comorbidities, surgical data, pathology, and information on complications were obtained from electronic medical records. Complications were defined according to VA National Surgical Quality Improvement Program criteria.[15]

Preoperative CT imaging was reviewed retrospectively to obtain images at mid-waist, defined as the midpoint between the last rib visualized and the top of the iliac crest.[9] Images were manually captured and de-identified prior to measuring circumference. Waist circumference was then measured at the mid-waist level using Photoshop© to determine abdominal circumference. Circumference was measured manually using the magnetic lasso tool within Photoshop© to trace the edge of the skin surface and record distance. To maximize sensitivity and reproducibility, image contrast and brightness were set to maximum in order to highlight differences between skin and surrounding air. Image scale was maintained by defining unit of measurement within Photoshop© based on visual record of the scale ruler from the original image. Abstraction of images and measurements were performed by one author (C.B.) who was blinded to patient outcomes. A second rater (W.B.) was blinded to previous measures of waist circumference and then measured waist circumference in a random sample of 50 patients in order to calculate the intraclass correlation coefficient.

Correlations between continuous variables were assessed using Pearson's correlation coefficient or Kendall's tau depending on normality of data distribution, and categorical variables were assessed using chi-square. The intraclass correlation coefficient was calculated as a two-way mixed effects model with raters classified as random effects. Comparisons of mean length of stay between tertiles of waist circumference and BMI were performed using ANCOVA with age as a covariate and taking the natural log transformation of the length of hospital stay as the dependent variable. Comparison between means was done using planned contrasts with quartile 1 as the reference category. Independent predictors of postoperative complications were calculated using univariable and multiple logistic regression. When adjusting for surgical approach comparing minimally invasive (laparoscopic or hand-assisted laparoscopic) to open surgery, cases were categorized as minimally invasive even when converted to open surgery. Comorbidities were controlled for individually (except for cardiac disease which was denoted as positive if patients had prior surgical or medical intervention for cardiac disease) by entrance into regression models as a dichotomous variable indicating either presence or absence of disease. The presence of effect measure modification was assessed by including a term for multiplicative interaction between obesity measures and variables coding for ethnicity and surgical approach. Model discrimination was assessed using the c-statistic and model fit evaluated using the Hosmer and Lemeshow test. All statistical comparisons were conducted using SPSS version 17 copyright SPSS Inc.

Results

Demographics and Comorbidities

From 2002 to 2009, 152 patients underwent elective resection for rectal adenoma or carcinoma under the supervision of 12 surgical attendings at a tertiary care Veterans Affairs hospital. A total of 129 patients (85%) had preoperative imaging available to determine waist circumference. There were no significant differences in age, comorbidities or complication rates between patients with available imaging and those without preoperative CT scans (data not shown). Mean patient age was 65±0.8 years, 98% were male and 93% were either Caucasian or African–American (Table 1). The most common surgeries were low anterior resection (LAR, 66%) and APR (30%), and 95% of cases revealed cancer on final pathology. An open surgical approach was utilized in 72% of cases with the remainder performed using laparoscopic-assisted or hand-assisted laparoscopic surgery. Conversion rate for laparoscopic-assisted and hand-assisted surgery was 23%. The most common comorbidities in this population were hypertension (68%) and diabetes (26%), and there was also a high smoking prevalence as 73% of patients were either current or former smokers.

Obesity Measurements

Previous studies have shown that measurements of visceral and subcutaneous fat are better predictors of postoperative complications than BMI, but none have evaluated whether increasing waist circumference is associated with overall complication rate or specific complications aside from parastomal hernia.[12–14] Consequently, we evaluated preoperative BMI and waist circumference to determine their association with postoperative complications. BMI was determined from preoperative medical records, and CT imaging was used to quantify waist circumference prior to surgery. Mean BMI was 28±0.43 kg/m^2, and mean waist circumference was 108.8±1.3 cm. Intraclass correlation coefficient for measuring waist circumference was assessed on a random sample of 50 cases and was found to be 0.999, indicating a high degree of reproducibility between raters.

Table 1 Demographics and comorbidities

	N or mean±SEM (*N*=128)	%
Age (years)	65.2±0.83	
Race		
Caucasian	94	73
African American	26	20
Other	8	7
Male	125	98
Surgical approach		
Open	97	76
Minimally invasive	31	24
Current or former smoker	94	73
Hypertension	87	68
Diabetes	33	26
Prior cardiac surgery	11	9
Prior PCI	6	5
Surgery performed		
Low anterior resection	84	66
Abdominoperineal resection	39	30
Other	5	4

Complications

During the 30 days following surgery, 55 patients (43%) had one or more postoperative complications (Table 2). The most common complication was superficial wound infection which occurred in 31%, and these infections resulted in wound opening and packing in 15% of patients. Additionally, 11% had an organ space infection and 13% required reoperation for complications. Dehiscence occurred less frequently at 7%, and deep wound infections (5%) or anastomotic leaks (4%) were the least common complications seen.

Predicting Complications

The univariable relationship between postoperative complications and BMI or waist circumference was assessed using logistic regression. Increasing BMI predicted a significantly greater risk of superficial surgical site infection along with the need for wound opening and packing (Table 3). For each 1 kg/m^2 increase in BMI, the odds of having a superficial infection increased 12% and the odds of having the surgical wound opened and packed increased by 9%. Larger BMI was also associated with increased risk for dehiscence and reoperation but neither achieved statistical significance. Overall, increasing BMI predicted significantly greater risk of one or more postoperative complications (HR 1.095, 95% CI 1.025–1.170). Increased waist circumference also predicted significantly increased risk of surgical site infection and need for wound opening as well as increased risk for any postoperative complication. For each 10 cm increase in waist circumference, the odds of infection increased 62% and the odds of having one or more complications increased by 51%. Additionally, greater values for waist circumference predicted a significantly greater risk of dehiscence and showed a trend towards higher risk of reoperation.

To further evaluate the relationship between obesity and risk of overall complication or infection, patients were divided into three groups (tertiles) for waist circumference

Table 2 Postoperative complications

Complication	*N* (*N*=128)	%
Superficial surgical site infection	40	31
Wound opened and packed	19	15
Reoperation	17	13
Organ space infection	14	11
Dehiscence	9	7
Deep surgical site infection	6	5
Anastomotic leak	5	4
Any complication	55	43

and BMI. Tertile one represents the reference category and consists of the thinnest individuals while tertile three represents more obese patients. As waist circumference increased from tertile one to tertile three, the chance of having some postoperative complication increased from 28% to 61% ($p<0.009$, Fig. 1a). Similarly, the likelihood of having any postoperative complication increased from 32% in patients with the lowest BMI to 54% in patients in the highest tertile of BMI, but this difference was not significant ($p<0.072$, Fig. 1b). When looking at superficial infections and waist circumference, those with the largest waist circumference developed infections in 46% of cases compared to 14% for the thinnest patients ($p<0.005$, Fig. 1c). Individuals with greater BMI also experienced a significantly greater chance of developing infections when compared to patients in tertile 1 for BMI ($p<0.019$, Fig. 1d).

Since increased operative time and bleeding have been associated with greater risk of complications, we also assessed correlations between these variables and both waist circumference and BMI. Neither BMI ($r=0.007$) nor waist circumference ($r=-0.007$) were significantly correlated with intraoperative bleeding. For operative time, BMI showed a weak positive correlation ($r=0.197$, $p<0.022$) but waist circumference was not significantly correlated with procedure length ($r=0.126$, $p<0.179$).

In order to adjust for potential confounders, multiple logistic regression was used to evaluate whether waist circumference and BMI independently predicted the risk of complications. After adjusting for age, ethnicity, smoking status, comorbidities, operative time, and laparoscopic versus open approach, BMI was associated with an increased risk of postoperative complications but these associations did not reach statistical significance (Table 4). However, waist circumference independently predicted an increased risk of superficial infection as well as a greater risk of encountering one or more postoperative complications. For each 10-cm increase in waist circumference, the odds of infection increased by 98% and odds of having one or more complication increased by 56%. Additionally, waist circumference was associated with an increased risk of dehiscence and reoperation but this did not achieve statistical significance. We also wanted to assess for interaction/effect measure modification between ethnicity and obesity measures as well as surgical approach and these measures. Consequently, the significance of the interaction term between these variables was also assessed and no significant interaction was seen.

Length of Hospital Stay

Given differences in complication rates based on waist circumference, we also wanted to evaluate whether increasing waist circumference or body mass index was associated with prolonged length of hospital stay. Neither waist circumference ($r=0.076$, $p<0.396$) nor body mass index ($r=0.034$, $p<0.679$) significantly correlated with length of stay (Fig. 2a and b). Additionally, differences in length of stay by tertile of waist circumference and BMI were compared after adjusting for age. Once again, length of stay did not significantly differ according to tertile of waist circumference (Fig. 2c, $p<0.447$) or tertile of BMI (Fig. 2d, $p<0.229$).

Discussion

An important issue in obesity research is determining the best way to actually measure obesity. The medical literature has increasingly made use of waist circumference, waist-to-hip ratio, visceral fat and subcutaneous fat ratios rather than relying solely on BMI.[16,17] This change stems from an evolving understanding of the biology and significance of

Table 3 Univariable odds ratios for complications

Complication	Body mass index		Waist circumference	
	Odds ratio	95% CI	Odds ratio	95% CI
Superficial Surgical Site Infection	1.12*	1.04–1.20	1.62*	1.20–2.17
Organ Space Infection	0.96	0.87–1.06	0.82	0.55–1.22
Wound Opened and Packed	1.09*	1.01–1.18	1.75*	1.21–2.54
Dehiscence	1.06	0.96–1.18	1.64*	1.02–2.63
Reoperation	1.05	0.96–1.14	1.13	0.79–1.61
Any Complication	1.10*	1.03–1.18	1.51*	1.15–1.99

Odds ratio reflects changes of 1 kg/m^2 for BMI and 10 cm for waist circumference

*$p<0.05$

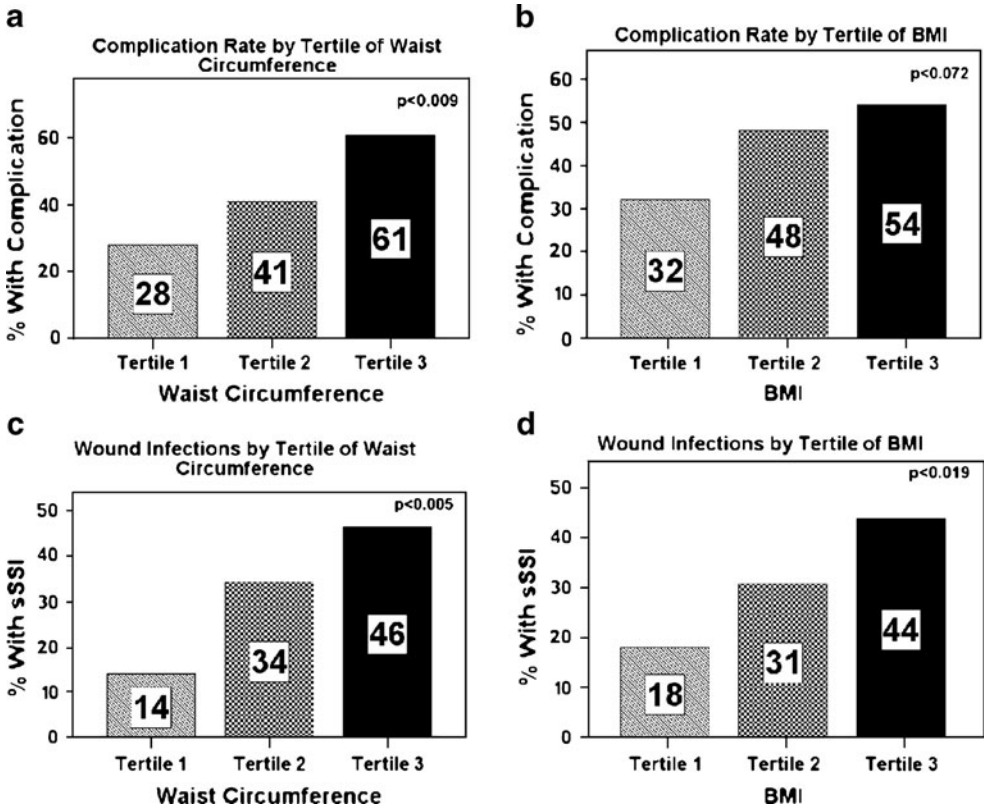

Fig. 1 Overall complication rate and rate of wound infections increase by tertile of waist circumference and BMI on univariable analysis. (**a**–**b**) Risk of having a postoperative complication increases by tertile of waist circumference (**a**) or BMI (**b**). (**c**–**d**) Risk of superficial surgical site infection increases by tertile of waist circumference (**c**) or BMI (**d**)

different types of adipose tissue and how fat distribution impacts outcomes.[18–20] Central obesity, in particular, is an important element of the metabolic syndrome and correlates strongly with incidence of cardiovascular disease as well as incidence of colorectal cancer.[18,21] Prospective studies have now shown that measuring adipose tissue quantity and distribution in addition to BMI offers valuable information when it comes to predicting medical complications of obesity.[18,22] Consequently, it is important to consider whether these measures have equal value in predicting surgical complications.

Multiple studies have attempted to evaluate obesity using BMI as an indicator, and this has generated mixed results. Merkow et al. used the American College of Surgeons NSQIP to examine 30-day outcomes following resection for colon malignancy.[4] They found that patients who were morbidly obese (BMI≥35 kg/m^2) were more than twice as likely as normal weight individuals to develop a surgical site infection and four times as likely to develop a deep wound infection. Other complications including pulmonary embolism and renal failure were also increased in the morbidly obese and the overall odds of having some

Table 4 Waist circumference predicts postoperative complications on multivariable analysis

Complication	Body Mass Index		Waist circumference	
	Odds Ratio	95% CI	Odds Ratio	95% CI
Superficial Surgical Site Infection	1.70	0.75–3.86	1.98*	1.19–3.30
Organ Space Infection	1.60	0.44–5.80	0.6	0.33–1.07
Wound Opened and Packed	2.45	0.92–6.55	1.47	0.82–2.62
Dehiscence	3.82	0.55–26.8	1.29	0.58–2.84
Reoperation	1.63	0.47–5.65	1.12	0.65–1.94
Any Complication	1.22	0.63–2.34	1.56*	1.04–2.34

All odds ratios adjusted for age, ethnicity, smoking, diabetes, hypertension, cardiac disease, operative time, and laparoscopic versus open approach

Odds ratio reflects changes of 1 kg/m^2 for BMI and 10 cm for waist circumference

*$p<0.05$

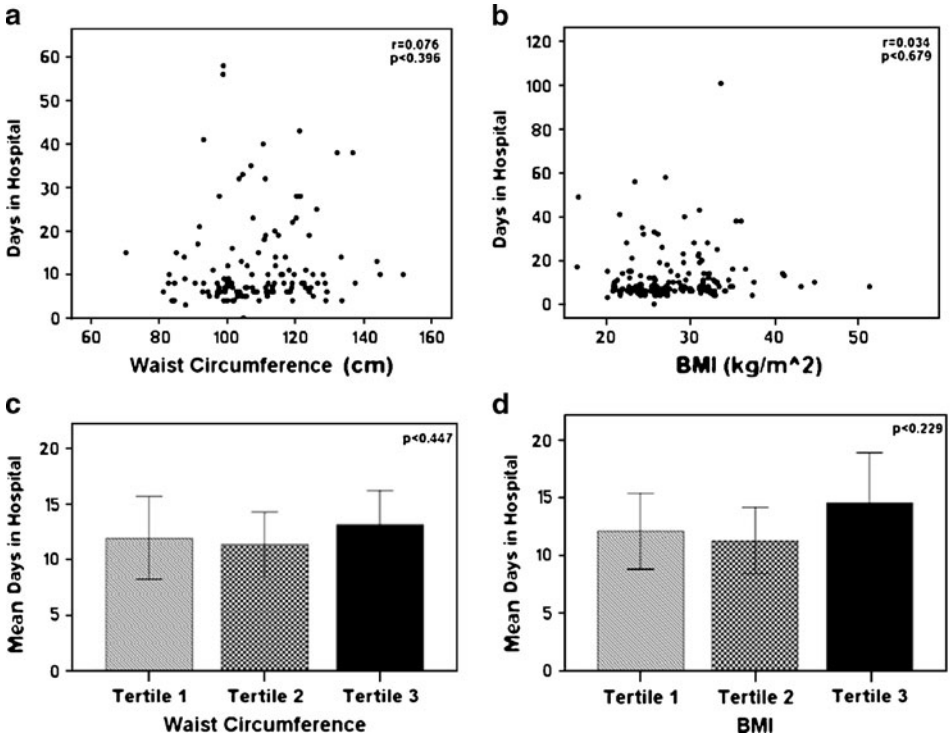

Fig. 2 Increasing waist circumference and BMI do not predict greater length of hospital stay. Waist circumference (**a**) and BMI (**b**) do not correlate with length of stay. There is no difference in length of stay by tertile of waist circumference (**c**) or BMI (**d**) after adjusting for age

postoperative complication were increased by 75%. By contrast, obese patients with a BMI of 30–34 kg/m^2 did not have significantly greater odds of infection when compared to normal weight individuals and their overall complication rate was similar. The authors did note, however that being overweight but not obese was associated with increased odds of perioperative complications. Benoist et al. evaluated 737 patients who underwent elective colorectal resection at their institution over a 7-year period of time and compared those with BMI>27 kg/m^2 to those with BMI≤27 kg/m^2.[1] After adjusting for other factors, this study did not find a significant difference in postoperative complications between the two groups undergoing rectal surgery. However, operative time was prolonged and mortality rate was increased in obese patients. Similarly, Hawn et al. evaluated the impact of obesity on resource utilization following colectomy and found that obesity was associated with increased operative time but did not predict length of stay.[23] Pikarsky et al. looked specifically at laparoscopic colorectal surgery and found increased risk of complications and conversions to open surgery in obese compared to non-obese patients.[2]

By contrast, several studies have found no difference in morbidity or mortality between obese and non-obese patients. Dindo et al. examined 6,336 consecutive patients undergoing elective general surgery and compared patients with BMI≥30 kg/m^2 to those with BMI<30 kg/m^2. The authors found no difference in complication rate after adjusting for confounding factors.[5] Schwandner et al. evaluated outcomes in laparoscopic colorectal surgery and found that obesity was not associated with postoperative morbidity or length of stay.[6] Another study looking specifically at laparoscopic rectal surgery also found no difference in mortality or overall morbidity despite prolonged operative time in obese patients.[24] Similarly, Leroy et al. looked at the effect of obesity on outcomes following laparoscopic left colectomy and found no difference in length of stay or postoperative complications.[7] Ballian et al. evaluated short- and long-term outcomes in obese patients undergoing surgery for rectal cancer and saw no difference in morbidity or length of stay, and actually saw improved overall survival.[25]

Since data based on BMI has generated conflicting results, other groups have asked whether measuring fat distribution can predict surgical complications. Ishii et al. used CT imaging to measure visceral fat area in 46 patients undergoing laparoscopic rectal cancer resection and found that visceral obesity was associated with prolonged operative time and increased risk of postoperative complications.[12] Similarly, Tsujinaka et al. found that visceral fat was a better predictor than BMI for wound infection, overall complications rate, and length of stay.[13] Seki et al. also looked at visceral fat as a predictor of technical difficulty in laparoscopic rectal sigmoid resections.[11] The authors found that increased visceral fat area relative to body surface area correlated with increased operative time and delayed resumption of a regular diet, but was not associated with increased complications.

One potential limitation of these newer obesity measurements is that quantification of adipose tissue on CT imaging is time-consuming and often uses specialized software. By contrast, calculating waist circumference ought to be more straightforward and less time-consuming. Additionally, if waist circumference proves to be a useful predictor it can easily be assessed without resorting to radiologic imaging. At least one group evaluated patients who underwent APR and found that waist circumference predicts parastomal hernia, but they did not assess other complications.[14]

Our study evaluated the predictive power of waist circumference in relation to the traditionally used measure of body mass index. On univariable analysis, we found that waist circumference was strongly associated with an increased risk of one or more postoperative complications as well as specific complications including wound infection and dehiscence. Even after adjusting for confounders including age, ethnicity, smoking status, comorbidities, operative time, and surgical approach we found that waist circumference predicted a twofold increase in risk of infection and greater than 50% increase in the odds of encountering one or more postoperative complications. By contrast, BMI was no longer significantly associated with risk of complication after adjusting for confounders. Since operative difficulty has been associated with increased risk of complications we also assessed whether surrogates for difficult surgery (operative time and blood loss) correlated with increasing waist circumference. We found that neither length of procedure nor intraoperative blood loss were significantly correlated with waist circumference, and this suggests that the increased rate of complications observed is not due simply to more difficult operations. The relationship between greater waist circumference and increased risk of complications may be due, at least in part, to greater quantities of adipose tissue in the abdominal region. Since adipose tissue tends to be poorly vascularized, one might expect central obesity to increase the risk of postoperative complications, especially wound infections. Since BMI does not specifically reflect an abdominal or central distribution of fat, this measure may be less sensitive to detecting differences between patients that are relevant for predicting complications.

Despite an increased risk of complications related to enlarging waist circumference, we did not find an associated increase in length of hospital stay. This finding may reflect the benefits of tightly integrated multidisciplinary care in the treatment of cancer patients. Close coordination with social work and case management allows surgical teams to continue care in the outpatient setting using home health agencies and other modalities. Additionally, early detection of infectious complications allows for initiation of antibiotics and wound opening so that patients are able to return home without significant delays.

Potential limitations of our study include its retrospective nature with an associated risk of differential misclassification bias. Additionally, selection bias cannot be ruled out since not all patients had preoperative imaging available for review. However, comparisons between patients with and without CT scans showed no significant differences. Moreover, since this was not a prospective study the timing of preoperative imaging was not standardized and it is conceivable that waist circumference as well as BMI may have fluctuated between time of measurement and time of surgery. Even though dramatic weight loss is not common in colorectal cancer patients, this possibility cannot be completely ruled out. Furthermore, although we attempted to control for relevant confounders, residual confounding cannot be entirely excluded. We are also limited by the single institutional nature of our study. Since all of the patients were part of the VA system, results may not be generalizable to other public or private institutions. At the same time, the vast majority of VA patients are men and it is possible that obesity has different impacts on complication rates depending on gender. Finally, our study has a relatively small sample size which makes it more difficult to determine predictors of complications that occur at low rates. It is also possible that a larger sample would result in smaller confidence intervals so that the trends we observed towards greater risk of dehiscence and reoperation on multivariable analysis would become significant given the larger sample population.

Conclusion

In spite of its potential weaknesses, our study is the first to demonstrate a link between waist circumference and postoperative complications. More importantly, waist circumference may be a better predictor of complications than BMI which has been the traditional measure of obesity. Since risk adjustment has begun to play an increasingly important role in surgery and may soon play a role in determining reimbursements for care, it is important to build models based on accurate predictors. Currently, no large prospective surgical databases are collecting measures of obesity other than BMI. Consequently, we are forced to rely on BMI and this measure may not accurately reflect what it means to be obese. Indeed, the medical literature has consistently shown the advantage of evaluating obesity measures other than BMI. Our study demonstrates that at least one of these measures, waist circumference, can be a useful predictor of surgical complications. Identification of high-risk patients helps delineate those who would benefit from more aggressive measures to prevent infection and other complications. This measure deserves further study and validation in a larger sample involving multiple patient populations.

Disclosure The views expressed in this article are those of the author(s) and do not necessarily represent the views of the Department of Veterans Affairs.

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Discussant

Dr. Stuart G. Marcus: Your presentation was excellent with good command of the data, and also you prepared a well-written manuscript. Your data challenges the accuracy of BMI in predicting surgical complications. Measuring waist circumference certainly seems simple. It's reproduc-

ible and it makes intuitive sense for patients undergoing abdominal surgery.

Your data joins a growing body of literature, including a paper presented this morning that highlights an important public policy issue. The concern is that surgeons will avoid operating on obese patients that are identified at high risk in order to keep their own quality report card more acceptable with regards to postop infections, readmissions, or returns to the OR, all potential financial disincentives to practitioners and hospitals.

Furthermore, a possible scenario that one could envision is the development of specialized obesity centers for the referral of high-risk obese patients for non-bariatric surgery similar to what we have seen for pancreatic and esophageal surgery.

With this in mind, I have several questions.

Are there strategies that you recommend to mitigate the risk of complications in patients identified preoperatively as being at high risk?

You mentioned some ranges, but where do you propose the cut-off is for waist circumference where we should begin to worry?

Can your results be extrapolated to women, who have a different body habitus than men? And also can they be extrapolated to patients undergoing non-rectal abdominal surgery?

Finally, can you comment on the use of neoadjuvant chemoradiation therapy and ostomies in your patients and how they contributed to your complication rates?

Closing Discussant

Dr. Courtney Balentine (Houston, TX): I'll try to take your first two questions together, since I see them as a little bit linked in terms of where the cut-offs are and then what you can actually do about it.

I think that one of the take-home messages from our data is that the effective waist circumference is relatively linear over the range of values we observed, meaning it kind of keeps getting worse as you add more. So there's not a really good, hard and fast cut-off you can say, this is great, this is bad. It's more if we can bring it back down to the lower end of the spectrum, it tends to be better.

I think extrapolating from the medical literature, we say someone is at increased risk for the metabolic syndrome and bad factors associated with diabetes at about 102 cm, and our average waist circumference was 108 cm. So I think we have, just in terms of the broad categories, quite a bit of room for improvement.

In terms of strategy, one of the nice things about rectal cancer, and again, one of the other reasons we focused on it, is you have sort of this extra time between identification of the patient coming to clinic, the setting up of the preop and neoadjuvant therapy before getting to the surgery. And looking at our population, about 80% of our patients are getting neoadjuvant therapy prior to the surgery. And that gives us a nice window in which we can say, hey, we know that if you can drop 10 cm off your waist between the next month and a half when we get you in from clinic to the OR, it will make a big difference.

At the same time, I think there's good data out there to say extra dosing or increasing the dosing of antibiotics in the OR can have some effect in the high-risk patients. And I think that's something we should probably explore in this group, since they certainly seem to be at risk specifically for infections.

I'm not sure from this data that we can really answer the question yet because there weren't enough women in our group to do a good subset analysis, or to do even a remotely robust test for interaction to figure that out.

One of the things we are looking to do is expand our data set and move into our county hospitals, where there are more females as well as different ethnic minority groups in which we can start getting sort of a broader picture and see how widely applicable this is.

In terms of looking outside of rectal cancer surgery specifically, that's something we are actually kind of in the process of doing now. We are looking at all the colon patients as well as the folks who were operated on purely for benign disease instead of cancer. And we are also sort of collaborating with our pancreatic surgeons at the Elkins Pancreas Center and looking at some of these different measures in the pancreatic patients as well to see if it's equally good at predicting risk in that population.

Discussant

Dr. Merril T. Dayton (Buffalo, NY): I have to stand and just commend the presenter on one of the cleanest presentations I think I've ever seen. I don't know if you noticed, but Dr. Balentine did not use any notes. His presentation was committed to memory. It really enhanced the quality of your presentation.

My first question is a simple one. It's a question about the technique that you used in CT scanning to measure the abdominal girth. Is there a scale on the CT scanner that tells you what the absolute size is relative to what one actually sees?

My second question is, what happens if one sees diastasis or, heaven forbid, an abdominal hernia that increases that girth artificially? Is there a way to factor that in?

The last question is, do you recommend that we have our

patients lose weight before we do their surgery, based on your findings here?

Closing Discussant

Dr. Courtney Balentine: For the last question, certainly, I think it's always a good idea, especially given the body habitus of most of the VA patients running through our group, they could all benefit with a little extra exercise and maybe a little thinning down.

In terms of the technique, what we did was took the image directly from the CT at mid waist level, essentially, and then imported it into sort of a preinstalled version of Photoshop, which allows you to sort of scale directly to the scale marker on the CT imaging from the hospital.

Take that, and then you can do it a couple of ways. You can actually sort of have it calculate to a certain extent for you, and you can guide it as well at the same time to kind of confirm it.

And that sort of helped us with the precision of the measurements. One of the things I didn't bring out in the presentation that did make it in the paper is we went back and had an MD PhD student who was rotating through on surgery do, basically, a subset. He took 50 random CTs that I had already scored and did a whole set of calculations on his own to repeat them to see what the intra-class correlation coefficient was. And it was 0.999. So it's about as reproducible as you can get in this sort of setting.

In terms of dealing with hernias or other things that are sort of adding extra space on CT without actually adding to waist circumference, I didn't run across it in this population. I did run across it a few times in the colon group. And I'm struggling internally on how to deal with that, to be honest.

My approach so far has been to try to approximate where the abdominal wall is and come across that as the true measure of circumference and not counting, sort of extruding viscera. Obviously, I'm not sure if that's the best way to do it, but it seemed reasonable that I'm basically measuring where the skin should be if nothing else were there. And that's kind of how I've been approaching it.

Discussant

Dr. David Greenblatt (Madison, WI): We have a lot of larger patients in our hospital, too. And in the really big patients, sometimes you can't even see the circumference of the waist. Was that a problem? And did you lose some super-obese patients because of that?

Number two, there's been several papers have come out on this visceral fat measure. And I'm wondering, have you had a chance to compare head to head your measure, this circumference, with the retro renal visceral fat thing and which is better.

Number three, in your analysis, it appears you treated BMI as a continuous variable. What happened if you tried to do it as a categorical variable barrier with a cut-off of like 30 or 35? Would/did it become significant in that case?

Closing discussant

Dr. Courtney Balentine: Actually, it worked out fairly well for the rectal patients, ironically. No one was so generally obese that I couldn't get a good image at the mid waist level that I was shooting. Where I got into trouble is I wanted to look at a waist-to-hip ratio at the same time and sort of adjust. And at that point, there was a little bit extra fat kind of distributed out over the hips. And for about 10 of those patients, it was cut off. So I didn't end up doing that for these patients.

For some of the colon patients, there were a couple people whose BMI was around the range of 45 to 50. And I just couldn't trust anything that I was getting. It was all folded and shaped around. So that is certainly a limitation of this particular measure.

In going forward, I wouldn't necessarily recommend irradiating people just to get a measure of their waist circumference. I think you put a tape measure around their waist, you get the same useful information. It's just as good. And that's actually something we are looking at exploring prospectively in another study that one of our attendings is doing looking at infections in patients undergoing cancer surgery. He agreed to add that variable for us.

The third question, looking at BMI, how to model it is always something I kind of struggle with when I'm doing it. And I tried it a few different ways in the model. Hard cut-offs in terms of overweight versus obese versus normal weight, tertiles, quartiles. And it seems that no matter how I did it, you kind of saw this nice stepwise trend, which kind of indicated to me there were major peaks and valleys over the range of our data. So I felt fairly comfortable modeling it as a linear continuous variable.

I did it both ways just because I'm paranoid, and the results are pretty much the same. Even if you compared the most obese just to the reference category at the beginning, once you adjust for other factors, the significance kind of starts to fade out of the picture.

The visceral fat, that actually is, ironically, the original hypothesis that I pursued that got me going in this direction. And we found something kind of interesting. We reported the

waist circumference data here and the visceral fat at SSO, because we found very different effects.

So when it came to complications, visceral fat, we measured the area at three different levels and took an aggregate average score. We measured the subcutaneous fat and took an aggregate score over three levels, looked at the absolute values of each and how it corresponded to outcomes. We looked at ratios between them and how they corresponded to outcomes.

What we found is, for short-term calculations, visceral and subcutaneous fat seemed to hint at a trend towards more significant complications as the values went up but it wasn't quite significant, whereas waist circumference, we saw, was significant, even after adjusting for other stuff.

The weird part—and I'm still trying to kind of make sense of this internally—is that in terms of long-term survival outcomes, visceral fat and subcutaneous fat seemed to matter, whereas waist circumference shows a trend but it's not quite significant.

So I'm still kind of monkeying around in my head how to explain that. We have some reasons that we are kind of exploring out long term, but it will be about 6 months to a year, I think, before I have enough data to really answer some of our hypotheses for why that turns out to be true.

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2010 SSAT PLENARY PRESENTATION

RAGE Signaling Significantly Impacts Tumorigenesis and Hepatic Tumor Growth in Murine Models of Colorectal Carcinoma

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Abstract
Background The receptor for advanced glycation end-products (RAGE) is a cell surface receptor implicated in tumor cell proliferation and migration. We hypothesized that RAGE signaling impacts tumorigenesis and metastatic tumor growth in murine models of colorectal carcinoma.
Materials and Methods Tumorigenesis: $Apc^{1638N/+}$ mice were crossed with $Rage^{-/-}$ mice in the C57BL/6 background to generate $Apc^{1638N/+}/Rage^{-/-}$ mice. *Metastasis*: BALB/c mice underwent portal vein injection with CT26 cells (syngeneic) and received daily soluble (s)RAGE or vehicle. $Rage^{-/-}$ mice and $Rage^{+/+}$ controls underwent portal vein injection with MC38 cells (syngeneic). $Rage^{+/+}$ mice underwent portal vein injection with MC38 cells after stable transfection with full-length RAGE or mock transfection control.
Results Tumorigenesis: $Apc^{1638N/+}/Rage^{-/-}$ mice had reduced tumor incidence, size, and histopathologic grade. *Metastasis*: Pharmacological blockade of RAGE with sRAGE or genetic deletion of *Rage* reduced hepatic tumor incidence, nodules, and burden. Gain of function by transfection with full-length RAGE increased hepatic tumor burden compared to vector control MC38 cells.
Conclusion RAGE signaling plays an important role in tumorigenesis and hepatic tumor growth in murine models of colorectal carcinoma. Further work is needed to target the ligand–RAGE axis for possible prophylaxis and treatment of primary and metastatic colorectal carcinoma.

Keywords RAGE · Receptor for advanced glycation end-products · Colorectal carcinoma · Colon cancer · sRAGE · *Rage* knockout mice

Introduction

Colorectal carcinoma is the most common gastrointestinal malignancy and the third-leading cause of cancer-related deaths in the United States.[1] Colorectal carcinoma com-

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monly metastasizes to the liver, after which 5-year patient survival is approximately 30%.[2] There is a need to identify novel targets for intervention in colorectal carcinoma tumorigenesis and metastasis; however, the cellular and molecular mechanisms involved are incompletely understood. Mutations in the *Apc* gene play a crucial, early role in the development of familial and sporadic intestinal tumors,[3] and there is mounting evidence that an inflammatory microenvironment supports tumorigenesis and metastasis by promoting cancer cell proliferation, invasion, and migration.[4–6]

The receptor for advanced glycation end-products (RAGE) is broadly implicated in both inflammation and cancer.[7–10] RAGE is a multi-ligand, transmembrane cell surface receptor of the immunoglobulin superfamily. Increased expression of RAGE and its ligands has been documented in various inflammatory diseases such as sepsis, diabetes, and inflammatory bowel disease.[7,8,11] Furthermore, up-regulation and co-localization of RAGE and many of its ligands in a range of human tumors, including colorectal tumors, suggest that the ligand–RAGE axis plays an important role in tumorigenesis and metastasis. RAGE ligands interact in complex autocrine and paracrine manners within the tumor microenvironment to promote cell survival, invasion, and migration.[9]

Among the RAGE ligands, two are widely implicated in tumorigenesis and metastasis: S100 proteins and high-mobility group box 1 (HMGB1). S100 proteins are small, calcium-binding molecules that can interact with RAGE and promote inflammation by activating endothelial cells, macrophages, and lymphocytes.[9] Increased expression of S100P has been documented in human colorectal carcinoma, and S100P has been shown to stimulate colon cancer cell proliferation and migration in vitro.[12] HMGB1, in part via its interaction with RAGE, can act as a potent pro-inflammatory cytokine to promote a microenvironment that is conducive to tumor growth, invasion, and metastasis.[13–15] Increased expression of HMGB1 has been demonstrated in colon adenomas and carcinomas,[16] and co-expression of RAGE and HMGB1 has been associated with tumor invasion, metastasis, and poor prognosis in colorectal cancer.[17–19]

Ligand–RAGE interactions activate multiple signaling pathways that are implicated in tumor proliferation and progression, including mitogen-activated protein kinase, c-Jun N-terminal kinase, and nuclear factor (NF)-κB pathways.[13,18] Depending on the cell type and biological context, RAGE-mediated activation of NF-κB primes cells for pro-inflammatory and anti-apoptotic signaling.[20,21] For example, NF-κB is known to play a critical role in the molecular pathogenesis of colon cancer associated with inflammatory bowel disease.[22] Other transcriptional targets of RAGE signaling include vascular cell adhesion molecule-1 (VCAM-1) and tissue factor, which contribute significantly to tumor cell interactions with the endothelium.[23,24] Finally, increased matrix metalloproteinase (MMP) activity in cells over-expressing RAGE has been shown to correlate with metastatic potential in colorectal and other tumor cells.[13,18,19]

In the current study, we examined the effects of RAGE signaling in murine models of colorectal carcinoma. We employed an established model of familial adenomatous polyposis (FAP) to test the impact of *Rage* gene deletion on tumorigenesis in $Apc^{1638N/+}$ mice. We then used pharmacological blockade and *Rage* gene deletion to evaluate the impact of loss of RAGE function on metastatic colorectal carcinoma cells. Finally, we used cell transfection with full-length RAGE to test the impact of cell-specific gain of RAGE function on metastatic tumor growth. Taken together, these data suggest that the ligand–RAGE axis plays an important role in the development of primary and metastatic colorectal carcinoma in mice.

Materials and Methods

Animals $Apc^{1638N/+}$ mice in the C57BL/6 background were kindly provided by Howard L. Kaufman, MD (Rush University Medical Center, Chicago, IL). *Rage* knockout ($Rage^{-/-}$) mice were generated in the C57BL/6 background as described previously.[25,26] $Rage^{-/-}$ mice develop normally and are reproductively fit. Absence of RAGE expression in $Rage^{-/-}$ mice has been documented previously at our institution.[27] Wild-type BALB/c and C57BL/6 mice were purchased from The Jackson Laboratory (Bar Harbor, ME). Animals were maintained in a specific pathogen-free facility of Columbia University (New York, NY), housed in a temperature-controlled room with alternating 12-h light/dark cycles in transparent cages with free access to food and water. Mice were acclimatized for at least 72 h prior to experimentation. Pups were weaned at 21 days. $Apc^{1638N/+}$ mice, $Rage^{-/-}$ mice, and their offspring were genotyped by using tail sample DNA extraction (Qiagen, Valencia, CA) for allele-specific polymerase chain reaction. Mice were euthanized with isoflurane followed by cervical dislocation at the time of autopsy and organ procurement. All animal experiments were approved by the Institutional Animal Care and Use Committee of Columbia University and conformed to the guidelines outlined in the National Institutes of Health Guide for Care and Use of Laboratory Animals.

$Apc^{1638N/+}$ model of tumorigenesis $Apc^{1638N/+}$ mice develop intestinal tumors that progress in an adenoma-carcinoma sequence similar to human FAP.[28] $Apc^{1638N/+}$ mice were crossed with $Rage^{-/-}$ mice to generate $Apc^{1638N/+}/Rage^{-/-}$

mice. In parallel, $Apc^{1638N/+}$ mice were bred with C57BL/6 mice to generate $Apc^{1638N/+}/Rage^{+/+}$ mice for controls. Mice were aged to 30 weeks and euthanized to harvest the intestine from duodenum to rectum. The lumen of the intestine was flushed with phosphate buffered saline (PBS) to remove fecal debris followed by 10% buffered formalin to preserve mucosal architecture. The intestine was divided into two halves of equal length, rolled into Swiss roll formations in tissue cassettes, and fixed for 24 h in 10% buffered formalin. Fixed intestine was then embedded in paraffin block, and 5-μm sections were cut at three successively deeper levels, discarding 100 μm between levels. Hematoxylin and eosin (H&E) stained sections at each level were viewed by two pathologists (H. Rotterdam and F. Bao) who were naïve to the treatment or genotype groups. Numbers of tumors per mouse were counted and sized by measurement of tumor greatest diameter in mm. Histopathology was graded as adenoma, adenoma with high-grade dysplasia, intramucosal carcinoma, or invasive adenocarcinoma. By definition, adenoma shows low-grade epithelial dysplasia, intramucosal carcinoma (carcinoma in situ) shows invasion of the lamina propria without extension through the muscularis mucosae, and invasive adenocarcinoma shows invasion beyond the muscularis mucosae into the submucosal tissue.

Tumor cell lines CT26 murine colon adenocarcinoma cells (BALB/c syngeneic) and MC38 murine colon adenocarcinoma cells (C57BL/6 syngeneic) were purchased from American Type Culture Collection (Manassas, VA). CT26 cells were maintained in RPMI-1640 medium and MC38 cells were maintained in DMEM medium, both supplemented with 10% heat-inactivated FBS, 100 units/mL penicillin, and 100 μg/mL streptomycin. Cells were incubated at 37°C in a humidified 5% CO_2 atm. To establish a full-length-RAGE-transfected MC38 cell line, complementary DNA for human full-length RAGE (FL-RAGE) was inserted into the pcDNA3 vector (Life Technologies, Carlsbad, CA). Purified plasmids and control vector (pcDNA3) were introduced into MC38 cells using Lipofectamine (Life Technologies). Cells were selected in the presence of Geneticin (G418) 1.5 mg/mL (Life Technologies), and individual clones were isolated by limiting dilution to obtain stable transfectants (MC38/FL-RAGE and MC38/mock). On the day of experiment, cells were harvested in their logarithmic growth phase using 0.25% trypsin–EDTA, washed with PBS three times prior to counting, and reconstituted in Hank's balanced salt solution at a cell concentration of 2.0×10^5 cells/mL. Cell viability exceeded 95% when assessed by trypan blue exclusion of cell suspensions before and after experiments.

Hepatic metastasis model Intrahepatic tumors were generated by direct portal vein injection of tumor cells using a standardized technique. Mice were anesthetized with a single intraperitoneal injection of ketamine (100 mg/kg) and xylazine (10 mg/kg) prior to abdominal shaving with clippers and prepping with betadine and alcohol. An upper midline incision was made, and the intestines were eviscerated and reflected to the right to expose the portal vein. A 30-gauge needle was used to cannulate the portal vein and inject 100 μL of the cell suspension, delivering a total inoculum of 2.0×10^4 cells per mouse. Hemostasis was achieved by gentle compression of the injection site with a cotton swab prior to closing the abdomen with clips.

Livers were excised, weighed, and assessed in a blinded manner without knowledge of treatment for tumor incidence, nodule count, and tumor burden. Tumor incidence was defined as the presence or absence of tumor by gross inspection of the liver. Individual tumor nodules were counted on the liver surface. To calculate tumor burden, the expected weight of the liver was subtracted from the actual weight of the liver. The expected liver weight was calculated using the ratio of average liver to body weight from 25 normal mice of equivalent age, multiplied by the body weight at the time of sacrifice of the experimental mouse $\left(\left[\text{average liver weight}_{\text{normal mice}}/\text{average body weight}_{\text{normal mice}}\right]\times \text{body weight}_{\text{experimental mouse}}\right)$.

Pharmacological blockade of RAGE in the CT26 model Pharmacological blockade of RAGE was achieved by treating mice with a soluble form of the receptor which lacks the transmembrane and cytosolic components of the molecule. Despite these deletions, the truncated receptor maintains its ability to bind ligands and functions as a competitive inhibitor. Soluble RAGE (sRAGE) was prepared in a baculovirus expression system as previously described.[29] Prior pharmacokinetic experiments have demonstrated effective receptor blockade without toxicity at a dose of 100 μg daily.[30] The agent is dissolved in PBS and delivered by intraperitoneal injection in a total volume of 100 μL. BALB/c mice were randomly assigned to treatment with sRAGE (experimental group) or vehicle (control group). Mice then underwent portal vein injection with 2.0×10^4 CT26 cells as described above. Beginning on the day of portal vein inoculation, the experimental group received daily intraperitoneal injections of sRAGE and the control group received daily intraperitoneal injections of PBS. The initial treatment with sRAGE was administered after portal vein inoculation, but before the mice awoke from anesthesia. Six mice from each group were euthanized on postoperative days 21 and 28 for evaluation of hepatic tumors as described above.

Host Rage deletion in the MC38 model Twenty $Rage^{-/-}$ mice and 20 C57BL/6 controls underwent portal vein injection of 2.0×10^4 MC38 wild-type cells. Ten mice from

each group were euthanized on postoperative days 21 and 28 for evaluation of hepatic tumors as described above.

Tumor cell Rage up-regulation in the MC38 model Thirty C57BL/6 mice underwent portal vein injection of 2.0×10^4 MC38/FL-RAGE, MC38/mock cells, or MC38 wild-type cells, ten mice in each group. Mice were euthanized on postoperative day 28 for evaluation of hepatic tumors as described above.

Western blot analysis Protein extracts were prepared from tumors harvested from the livers of the above mice and from CT26 wild-type, MC38 wild-type, MC38/FL-RAGE, and MC38/mock cells using cell lysis buffer (Cell Signaling, Beverly, MA). Protein concentration was determined using the Bio-Rad protein assay (Bio-Rad Laboratories, Hercules, CA). Equal amounts of protein were placed in each lane and separated by SDS polyacrylamide gel electrophoresis and transferred to nitrocellulose. Nonspecific binding was blocked by incubation of membranes with nonfat dry milk (5%) in Tris-buffered saline containing Tween 20 (0.1%; blocking buffer) for 1 h at room temperature or overnight at 4°C. RAGE was detected by incubating the transferred membrane overnight at 4°C with rabbit polyclonal antibody (Gene Tex, Irvine, CA) at 1:500 dilution. HRP-conjugated donkey anti-rabbit IgG secondary antibody (1:2,000; Amersham Biosciences) was used to identify sites of binding of primary antibody. Final detection of immunoreactive bands was performed using the enhanced chemiluminescent Western blotting system (Amersham Biosciences).

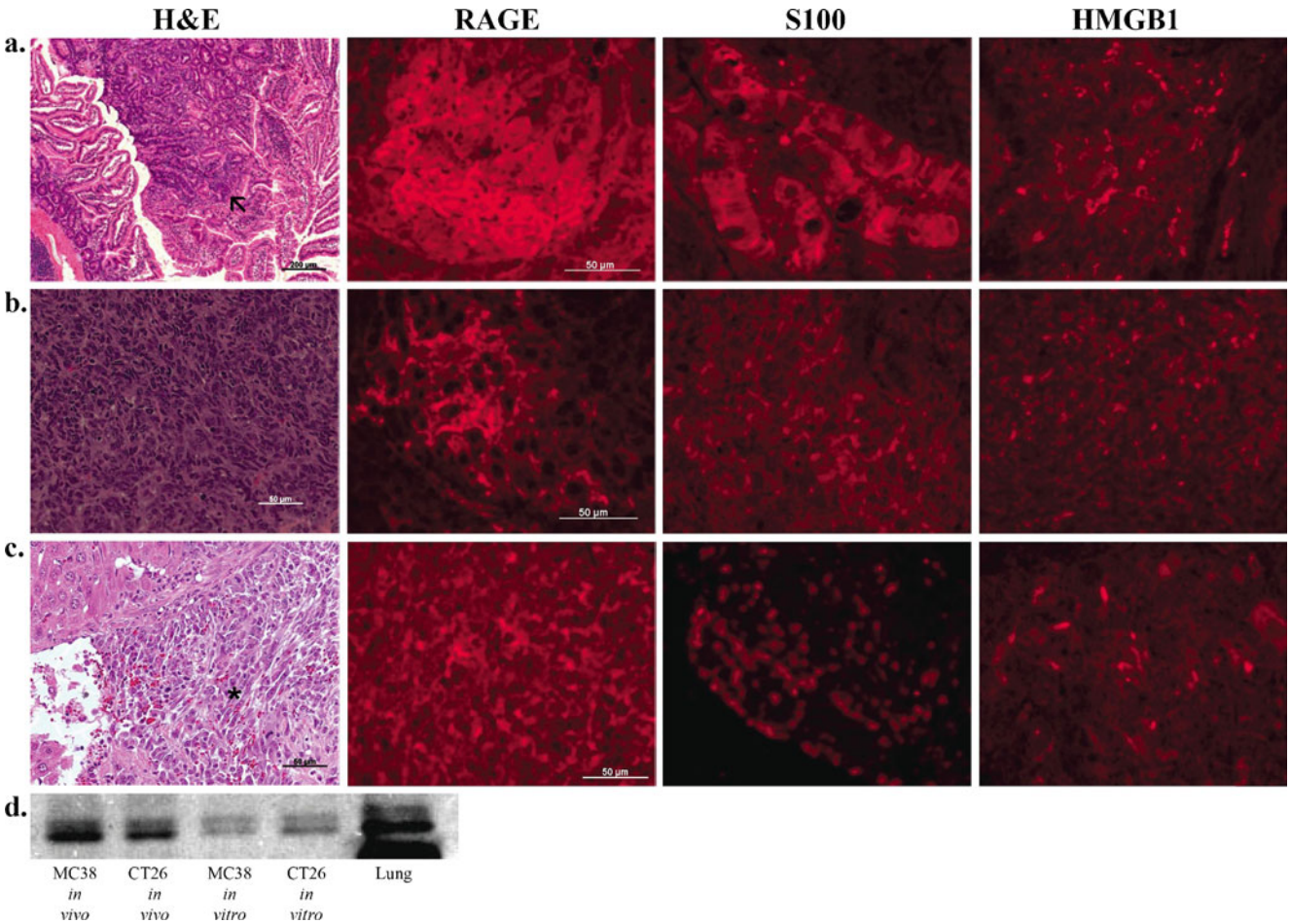

Fig. 1 RAGE and its ligands, S100 and HMGB1, are expressed in intestinal neoplasia in *Apc*$^{1638N/+}$ mice and in CT26 and MC38 murine colorectal carcinoma cells in vitro and in vivo. **a** An H&E-stained section of intestine from a 30-week-old *Apc*$^{1638N/+}$ mouse demonstrates an adenoma with high-grade dysplasia (*arrow*) adjacent to normal mucosa. Immunofluorescent staining of representative sections demonstrates the presence of RAGE, S100, and HMGB1 in the neoplasm. **b** and **c** H&E-stained sections of livers from *Rage*$^{+/+}$ mice demonstrate metastatic CT26 and MC38 colorectal carcinoma tumors. An *asterisk* marks MC38 tumor bounded by normal liver. Immunofluorescent staining demonstrates the presence of RAGE, S100, and HMGB1 in the metastatic tumors. *Magnification scale bars* are indicated. **d** Expression of the RAGE protein (~55 kDa) is demonstrated by immunoblotting of CT26 and MC38 cells in vitro and in vivo. Murine lung tissue serves as the control

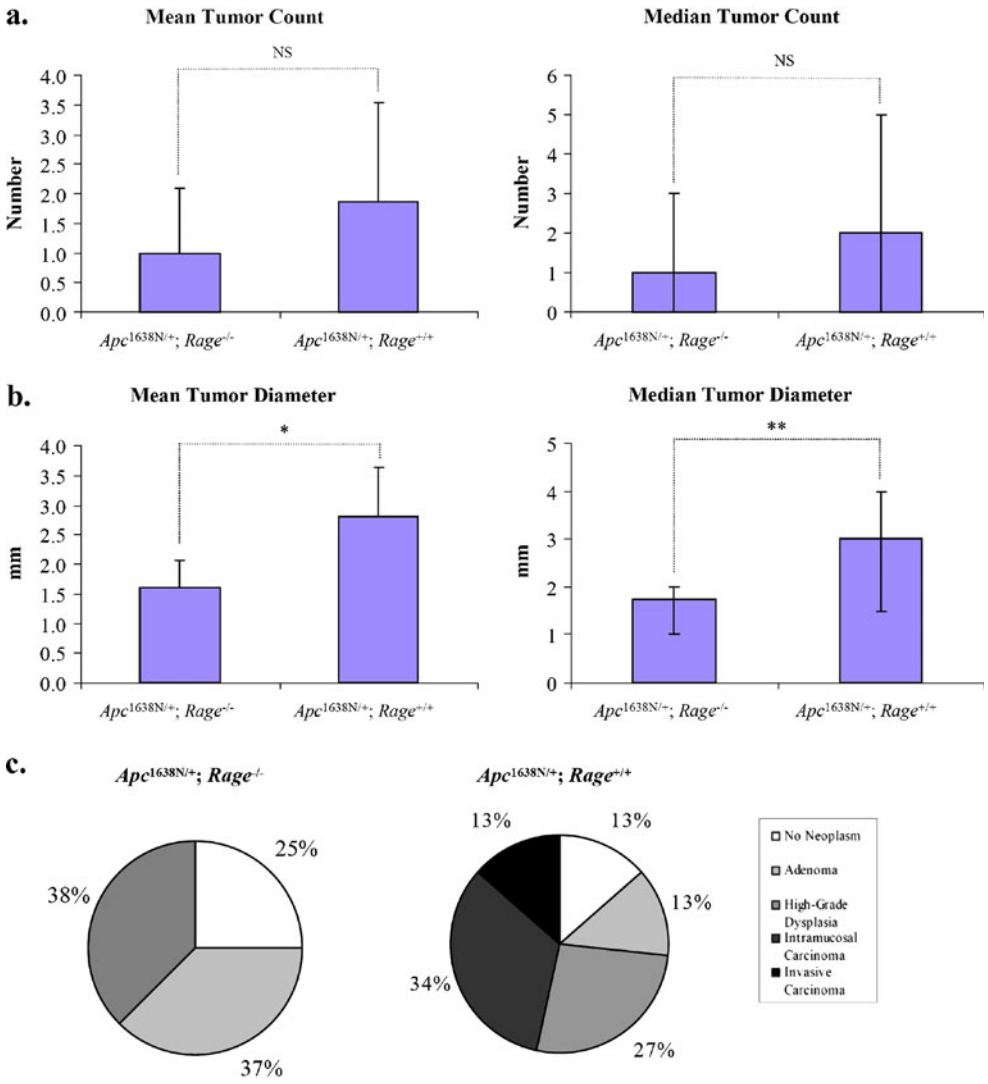

Fig. 2 *Rage* deletion inhibits tumor development and progression in $Apc^{1638N/+}$ mice. $Apc^{1638N/+}/Rage^{-/-}$ mice (n=6) had reduced tumor count, smaller tumor size, and more benign histopathologic grade of intestinal neoplasia compared to $Apc^{1638N/+}/Rage^{+/+}$ mice (n=7) at 30 weeks of age. **a** Mean and median tumor count are shown. **b** Mean and median tumor diameter are shown. **c** The incidences of adenoma, high-grade dysplasia, intramucosal carcinoma, and invasive carcinoma as seen on histopathologic examination are shown. *p<0.0001, **p=0.01, NS=not significant

Immunohistochemical analysis Intestine and liver tumors from the above mice were harvested and fixed in 10% buffered formalin, followed by paraffin-embedding and generation of sections (5 μm thick). The sections were deparaffinized and rehydrated in graded alcohols. Certain sections were stained with H&E. Sections to be stained with the antibodies to RAGE or HMGB1 were pretreated with trypsin for 20 min. Sections to be stained with the antibody to S100 were heated by boiling in 10 mM citrate buffer, pH 6.0 for 10 min followed by cooling at room temperature for 20 min before immunostaining. After blocking with 10% normal goat serum (Vector Laboratories, Burlingame, CA), serial sections were stained with the rabbit polyclonal antibodies to RAGE (1:100),[13] HMGB1 (1:50; ProteinTech Group, Chicago, IL), S100 (1:300; Abcam, Cambridge, MA) and were incubated overnight at 4°C in a humidified chamber. After washing with PBS, sections were stained with biotinylated secondary goat anti-rabbit antibody (1:200; Vector Laboratories) followed by incubation with Texas Red–avidin D. Sections were mounted. The signals of images for antigen detection were performed using a Zeiss Fluorescent Scope equipped with a filter specific for Texas Red. Negative controls consisted of serial sections stained with equivalent concentrations of preimmune IgG in place of the primary antibody.

Statistics Continuous variables were compared using Student's t test or Mann–Whitney U test. Group means were compared using ANOVA followed by Student's t test where indicated. Categorical variables were compared using Fisher's exact test. A p value of less than 0.05 was considered statistically significant.

Results

RAGE and RAGE ligand expression in $Apc^{1638N/+}$, CT26, and MC38 models Histologic examination of H&E-stained

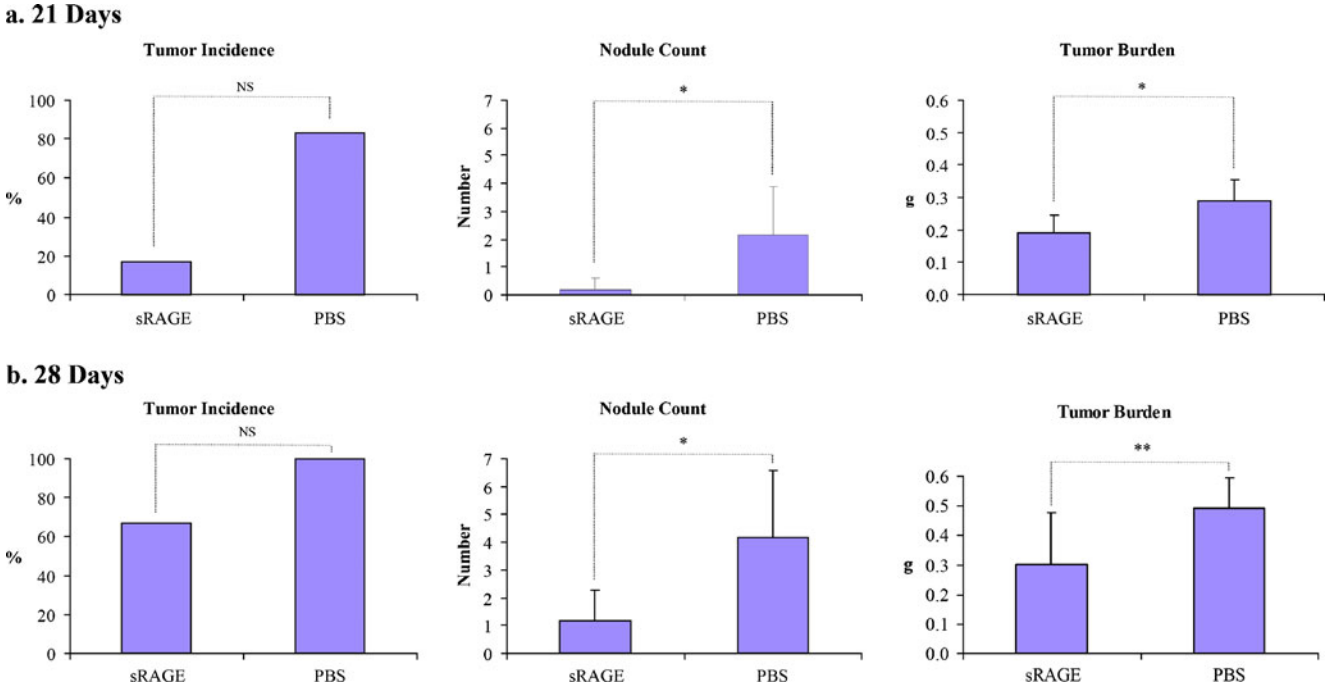

Fig. 3 Pharmacological blockade of RAGE inhibits intrahepatic CT26 tumor growth. **a**. Twenty-one days after portal vein injection of 2.0×10^4 CT26 colorectal carcinoma cells, sRAGE-treated mice (n=6) had lower tumor incidence and significantly lower hepatic nodule count and tumor burden compared to controls (n=6). **b** This difference persisted on day 28 with lower tumor incidence and significantly lower nodule count and tumor burden in sRAGE-treated (n=6) versus control (n=6) mice. *p=0.02, **p<0.05, NS=not significant

sections of intestine from $Apc^{1638N/+}$ mice showed a spectrum of neoplasia, ranging from benign adenoma to invasive carcinoma. Representative sections of an adenoma with high-grade dysplasia demonstrated strong staining for RAGE and its ligands, S100 and HMGB1 (Fig. 1a). Representative sections of intrahepatic CT26 and MC38 tumors also demonstrated strong staining for RAGE, S100, and HMGB1 (Fig. 1b and c). Western blot analysis of CT26 and MC38 cells in vitro and in vivo demonstrated RAGE protein expression (Fig. 1d).

Rage deletion inhibits intestinal tumor development and progression in $Apc^{1638N/+}$ mice At 30 weeks, $Apc^{1638N/+}$/$Rage^{-/-}$ mice (n=6) had fewer tumors compared to $Apc^{1638N/+}$/$Rage^{+/+}$ mice (n=7), though these results were not statistically significant (1.00±1.10 tumors vs. 1.86±1.68 tumors, p=0.31). However, mean tumor diameter was significantly smaller in $Apc^{1638N/+}$/$Rage^{-/-}$ mice (1.62±0.45 mm vs. 2.81±0.83 mm, p<0.001). Most importantly, no $Apc^{1638N/+}$/$Rage^{-/-}$ mouse displayed pathological evidence of carcinoma, whereas there was a significantly higher 46.7% incidence of carcinoma noted in $Apc^{1638N/+}$/$Rage^{+/+}$ mice (p=0.03; Fig. 2).

Pharmacological blockade of RAGE inhibits intrahepatic CT26 tumor growth To further establish the role of RAGE in tumor growth, we treated mice inoculated with CT26 tumors with sRAGE or vehicle as described above. On day 21, 16.7% of sRAGE-treated mice (n=6) versus 83.3% of control mice (n=6) had intrahepatic tumors (p=0.08). There was a greater than tenfold lower nodule count in sRAGE-treated mice compared to control mice (0.17±0.41 nodules vs. 2.17±1.72 nodules, p=0.02). sRAGE-treated mice had significantly lower mean tumor burden compared to control mice (0.19±0.05 g vs. 0.29±0.06 g, p=0.02). On day 28, 66.7% of sRAGE-treated mice (n=6) had tumors whereas 100% of control mice (n=6) had tumors (p=0.45). Finally, there was a fourfold lower nodule count (1.17±1.17 nodules vs. 4.17±2.40 nodules, p=0.02) and significantly lower mean tumor burden in sRAGE-treated mice compared to control mice (0.30±0.18 g vs. 0.49±0.11 g, p<0.05; Fig. 3).

Rage deletion inhibits intrahepatic MC38 tumor growth On day 21, $Rage^{-/-}$ mice (n=8) had a lower incidence of intrahepatic tumors compared to $Rage^{+/+}$ mice (n=9), though this difference was not statistically significant (75% vs. 100%, p=0.21). Mean nodule count was significantly lower in the $Rage^{-/-}$ mice compared to $Rage^{+/+}$ mice (3.88±7.83 nodules vs. 30.00±28.92 nodules, p=0.03). There was a 30-fold reduction in mean tumor burden in $Rage^{-/-}$ mice compared to $Rage^{+/+}$ mice (0.03±0.06 g vs. 0.94±0.94 g, p=0.02). On day 28, significantly fewer $Rage^{-/-}$ mice (n=10) had tumors compared to $Rage^{+/+}$ mice (n=9; 50% vs.

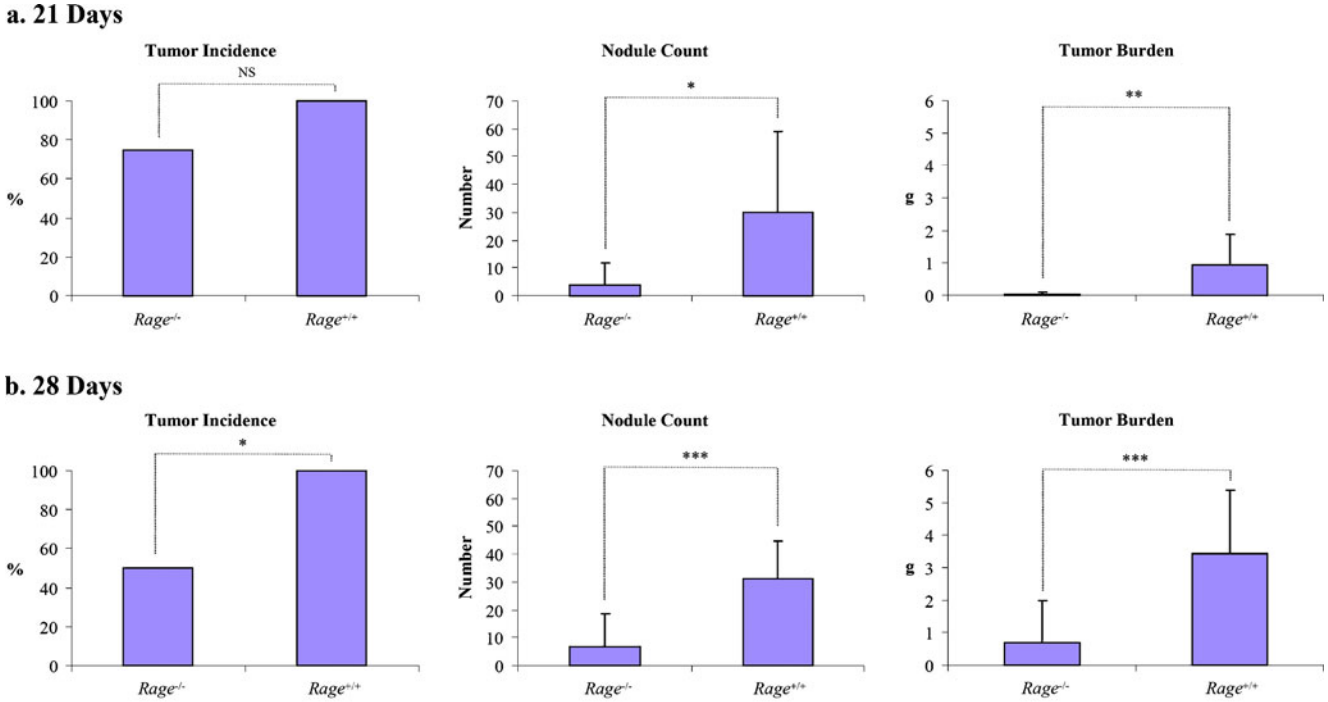

Fig. 4 Host *Rage* deletion significantly inhibits intrahepatic MC38 tumor growth. **a** After portal vein injection of 2.0×10^4 MC38 colorectal carcinoma cells, $Rage^{-/-}$ mice (n=8) had lower tumor incidence and significantly lower nodule count and tumor burden on day 21 compared to $Rage^{+/+}$ mice (n=9). **b** This difference was more pronounced on day 28 with significantly lower tumor incidence, nodule count, and tumor burden in $Rage^{-/-}$ mice (n=10) compared to controls (n=9). *p=0.03, **p=0.02, ***p<0.01, NS=not significant

100%, p=0.03). Mean nodule count was significantly lower in $Rage^{-/-}$ mice compared to $Rage^{+/+}$ mice (6.70±12.00 nodules vs. 31.00±13.70 nodules, p<0.01). Finally, there was a fivefold lower mean tumor burden in $Rage^{-/-}$ mice compared to controls (0.70±1.29 g vs. 3.44±1.93 g, p<0.01; Fig. 4).

RAGE gain of function increases intrahepatic MC38 tumor growth Western blot analysis confirmed RAGE protein overexpression in vitro in the MC38/FL-RAGE cells compared to MC38/mock and MC38 wild-type cells. On day 28 after intraportal injection of transfected cells, mice in all experimental groups (n=9/group) developed tumors. There were no statistically significant differences in mean nodule count between groups (p=0.13). Mice injected with MC38/FL-RAGE cells had significantly increased mean tumor burden compared to mock-transfected controls (1.33±1.34 g vs. 0.46 +/0.37 g, p=0.04) and MC38 wild-type cells (1.33± 1.34 g vs. 0.27±0.25 g, p=0.02). There was no difference in tumor burden between mock-transfected controls and MC38 wild-type cells (p=0.23; Fig. 5).

Discussion

Colorectal carcinoma is a leading cause of cancer-related deaths worldwide. The liver is the most frequent site of metastasis, and patients with metastatic disease have significantly worse survival.[2] The molecular mechanisms of tumorigenesis and metastasis in colorectal carcinoma are incompletely understood, although genetic mutation and

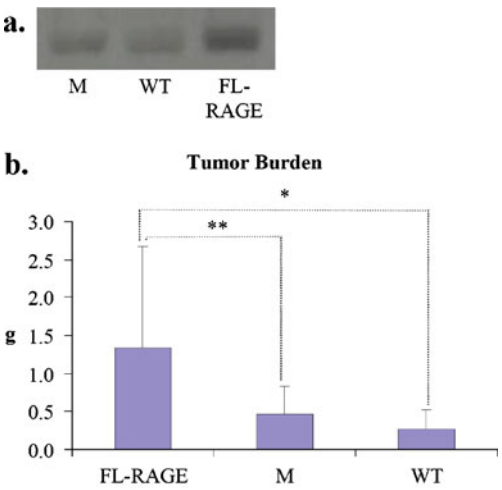

Fig. 5 RAGE gain of function increases intrahepatic MC38 tumor growth. **a** Stably transfected MC38/full-length RAGE (*FL-RAGE*) cells demonstrated increased expression of RAGE protein (~55 kDa) in vitro compared to MC38/mock (*M*) and MC38 wild-type (*WT*) cells examined by immunoblot analysis. **b** Intraportal injection (n=9 mice/group) of 2.0×10^4 MC38/FL-RAGE cells resulted in increased mean tumor burden compared to MC38/M and MC38 WT cells. *p=0.02, **p=0.04

inflammation are known potentiating factors. Mounting evidence suggests that the ligand–RAGE axis is a link between inflammation and the initiation and progression of intestinal neoplasia. Fuentes and colleagues [12] documented expression of S100P in human colon tumor tissue. They further showed that the S100P-RAGE interaction stimulated cell proliferation, cell migration, and NF-κB activation in in vitro studies employing human colon cancer cell lines. Using a competitive RAGE ligand antagonist, amphoterin peptide, they demonstrated that blockade of RAGE significantly inhibited cell proliferation. Turovskaya and colleagues [22] demonstrated that the ligand–RAGE axis mediated inflammation-associated colon cancer through activation of NF-κB. Using a murine model of colitis-associated cancer (CAC), they found increased expression of S100 proteins in the tumor microenvironment and dramatically reduced incidence of CAC in $Rage^{-/-}$ compared to $Rage^{+/+}$ mice.

In the current study, we used the $Apc^{1638N/+}$ mouse model of FAP to evaluate the effects of RAGE signaling on the development of intestinal neoplasia. Mutation of the *Apc* gene is a known early event in the progression from normal intestinal mucosa to adenoma to carcinoma. Various *Apc* mutant mouse models exist, and we chose $Apc^{1638N/+}$ model for several reasons. $Apc^{1638N/+}$ mice have a reduced tumor burden and consequently increased lifespan compared to other *Apc* mutant mice. This increased lifespan allows time for more advanced tumors to develop and provides a spectrum of benign to malignant intestinal neoplasia. The progression of tumors in $Apc^{1638N/+}$ mice thus more accurately models the development of colorectal carcinoma in humans.[3]

We observed the complete spectrum of intestinal neoplasia in $Apc^{1638N/+}$ mice, ranging from benign adenoma to invasive adenocarcinoma. Similar to prior reports,[3,28] we observed a majority of lesions in the small intestine. We first documented the presence of RAGE and its ligands in these lesions by immunofluorescent staining. We then examined how intestinal neoplasia develops and progresses in the absence of RAGE by breeding the $Rage^{-/-}$ locus into the $Apc^{1638N/+}$ mouse. The $Apc^{1638N/+}/Rage^{-/-}$ mice tended to have fewer tumors of markedly decreased size. Strikingly, the tumors in the $Rage^{-/-}$ mice had more benign histopathologic grade with no $Rage^{-/-}$ mouse harboring carcinoma compared to a nearly 50% incidence of carcinoma in control mice. Our findings support the hypothesis that RAGE signaling plays an important role in the initiation and progression of intestinal neoplasia. In future work, it will be interesting to examine the intestines of $Apc^{1638N/+}/Rage$ heterozygous ($Rage^{+/-}$) mice to study the effects of partial allelic loss on tumorigenesis in the model.

The role of the ligand–RAGE axis in the development and growth of metastatic tumors is becoming increasingly evident. It is known that an influx of tumor cells into the liver causes an acute inflammatory response characterized by ligand–RAGE interactions and release of TNF-α.[31] Expression of RAGE and its ligands has been correlated with metastatic disease in colorectal carcinoma. Kuniyasu and colleagues [17] observed that RAGE expression increased in parallel with Dukes' stage. Over-expression of RAGE was observed in 19%, 81%, and 100% of the Dukes' B, C, and D cases, respectively. In addition, the authors reported significantly reduced survival in Dukes' B and C cases with co-expression of RAGE and HMGB1 compared to those without co-expression. Similarly, Kostova and colleagues [32] observed intense signal for RAGE and HMGB1 in immunohistochemical studies of primary and metastatic human colorectal carcinoma specimens.

These data led us to hypothesize that blockade of the RAGE signaling pathway would reduce tumor growth in mouse models of colorectal liver metastasis. First, we demonstrated expression of RAGE and its ligands in CT26 and MC38 cells in vitro by western blot. In vivo CT26 and MC38 cells also expressed RAGE on western blot and stained strongly for RAGE and its ligands by immunohistochemical analysis of hepatic tumors. Having established RAGE expression in these tumor cells, we tested the impact of pharmacological blockade of RAGE by administering sRAGE after intraportal injection of syngeneic CT26 tumor cells in BALB/c mice. sRAGE is the extracellular domain of RAGE and acts a competitive inhibitor of receptor activation by binding RAGE ligands.[29] Treatment with sRAGE had a potent protective effect as development of liver metastases was delayed and tumor burden was significantly reduced. A limitation of long-term pharmacological blockade is the potential for tumor burden to overwhelm the competitive inhibitory effects of sRAGE via the increased release of RAGE ligands by necrotic cells.[32]

To overcome the limitations of long-term pharmacological blockade, we performed intraportal injections with syngeneic MC38 cells in $Rage^{-/-}$ mice. At the early time point, $Rage^{-/-}$ mice had a similar incidence of hepatic disease, but significantly fewer nodules and lower tumor burden compared to $Rage^{+/+}$ mice. Interestingly, these differences became more pronounced at the later time point. Intraportal injection in $Rage^{-/-}$ mice thus allowed us to examine host effects on tumor growth in the liver. Previous work by Liang and colleagues [31] demonstrated similar host effects on tumor growth in $Rage^{+/+}$ mice. They showed that administration of ethyl pyruvate prior to intraportal MC38 injection significantly reduced serum levels of inflammatory cytokines and resulted in reduced number of tumor nodules. A potent anti-inflammatory agent, ethyl pyruvate exerts its effects in part via inhibition

of inflammatory cytokines such as TNF-α and HMGB1. In light of that work, our current data suggest that absence of RAGE in the host liver dampens the deleterious effects of the inflammatory response elicited by metastatic tumor cells.

As our findings indicated that RAGE loss of function inhibited tumor growth, we then assessed the impact of RAGE gain of function on tumor growth. We stably transfected MC38 clones with full-length RAGE to mediate over-expression and injected C57BL/6 mice with syngeneic full-length RAGE-transfected or mock-transfected control MC38 cells. We noted significantly increased tumor burden compared to mock and wild-type MC38 cells. These results mirror earlier work with full-length RAGE-transfected C6 glioma, which exhibited markedly increased tumor growth compared to mock-transfected glioma.[13] The full-length RAGE-transfected C6 glioma also demonstrated enhanced proliferation, invasion, and migration in vitro. In future work, it will be interesting to examine the in vitro effects of RAGE over-expression in the full-length RAGE-transfected MC38 cells. Assays measuring cell proliferation, invasion, and apoptosis will help characterize the mechanisms by which RAGE signaling impacts tumor growth in this model.

Our data thus show the key finding that both host and tumor cell RAGE expression contribute significantly to tumor growth in a murine model of colorectal carcinoma metastasis. Further work is needed to evaluate the relative contributions of host and tumor cell RAGE interactions and to elucidate the mechanisms by which RAGE signaling influences tumor development and progression.

Conclusion

These studies provide further evidence that RAGE signaling plays an important and complex role in the biology of intestinal neoplasia. Using an established murine model of intestinal neoplasia, we demonstrated significant inhibition of tumor growth and delay of progression to carcinoma in $Apc^{1638N/+}/Rage^{-/-}$ mice. We showed that loss of function via pharmacological blockade of RAGE and genetic deletion of the *Rage* gene had profound effects on growth of colorectal carcinoma cells in murine models of metastasis. Finally, we showed that RAGE gain of function by direct manipulation of murine colorectal carcinoma cells significantly increased tumor growth in the liver. Further cellular and molecular work is needed to target the ligand–RAGE axis for possible prophylaxis and treatment of primary and metastatic colorectal carcinoma.

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Discussant

Dr. Emina H. Huang (Gainesville, FL): This is the lab where I started as faculty, and it's really nice to see you guys progress with your work. So I would like to congratulate you for continuing this investigation of RAGE and colorectal cancer.

As you point out, RAGE activation has been implicated in a broad range of disease processes, including inflammation and diabetes as well as cancer. In the current studies, your team uses two different murine models.

In the first model, you have spontaneous development of adenomas and adenocarcinoma. However, this model bears the shortcomings of many murine polyposis-like models, in which tumors are dominantly present in the small bowel rather than in the colon.

In your second model, you directly inject the portal vein, which results in the development of liver lesions. Despite shortcomings associated with any model system, the significance of your studies reveals the potential for future translation. So I have a couple of questions:

Number one, would you posit that an orthotopic metastatic model of colorectal cancer might demonstrate different results? And number two, chronic inflammation is involved in 15% of the world's malignancies. Certainly, these relationships are seen in the GI tract, including Barrett's esophagus, hepatitis, and ulcerative colitis. Would you envision RAGE antagonism as having a role in chemo prevention or in an adjuvant cancer treatment?

Thank you. Keep up the great work.

Closing Discussant

Dr. Joseph DiNorcia: Thank you, Dr. Huang, for your gracious comments and thoughtful questions. To answer the first, it's true that the majority of tumors we saw in the Apc 1638 model developed in the small intestine, as is reported in literature. Though of small intestine origin, these tumors follow the same adenoma to carcinoma progression as a colon lesion. So I hope an orthotopic model would demonstrate similar effects. A colleague at the resident research conference suggested using a chemical-induced model of colon carcinogenesis to test the effects of RAGE. Using AOM/DSS, for example, we might induce colon cancer in both RAGE knockout and RAGE wild-type mice and compare results.

To answer the second question, I think the ligand–RAGE axis is an exciting potential target for both prevention and treatment of cancer. In terms of treatment, it's known that when they outgrow their blood supply, tumor cells necrose and release HMGB1. HMGB1 then feeds back on RAGE to create a pro-survival environment that supports the remaining tumor cells. So it's very possible that a RAGE antagonist could inhibit that feedback mechanism and act either as a primary therapy

or as an adjunct agent that might make chemotherapy even more effective. Still, we have a lot more work to do before we get to the point of using a RAGE antagonist in clinical practice.

Discussant

Dr. Merril Dayton (Buffalo, NY): A group at my home institution in Buffalo is studying RAGE in trauma and has found that animals that have a high RAGE diet do much more poorly after trauma. My question for you is, what are the implications of diet on advanced glycosylation end products and so forth? Have you had any opportunity to pre-feed animals RAGE products and see how that impacts cancer? Obviously, there is concern about carbonized food products and its implications in colon cancer.

Closing Discussant

Dr. Joseph DiNorcia: We haven't studied any of the potential dietary effects in these mouse models of cancer. It's true that most of the original work on RAGE was done in diabetes. And certainly in the tumor microenvironment, there are increased levels of advanced glycosylation end products, as tumor cells have increased rates of glycolysis. It follows then that diets high in refined carbohydrates might predispose to the development of cancer, perhaps mediated through the ligand–RAGE axis. It would be an interesting area for future study.

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2010 SSAT PLENARY PRESENTATION

Disappearing Colorectal Liver Metastases after Chemotherapy: Should we be Concerned?

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Abstract
Background With increasing efficacy of preoperative chemotherapy for colorectal cancer, more patients will present with one or more disappearing liver metastases (DLM) on preoperative cross-sectional imaging.
Patients and Methods A retrospective review was conducted evaluating the radiological response to preoperative chemotherapy for 168 patients undergoing surgical therapy for colorectal liver metastases at Johns Hopkins Hospital between 2000 and 2008.
Results Forty patients (23.8%) had one or more DLM, accounting for a total of 127 lesions. In 22 patients (55%), all DLM sites were treated during surgery. Of the 17 patients with unidentified, untreated DLM, ten patients (59%) developed a local recurrence at the initial site, half of which also developed recurrences in other sites. While the intrahepatic recurrence rate was higher for patients with DLM left in situ ($p=0.04$), the 1-, 3-, and 5-year overall survival rate was not significantly different for patients with DLM left in situ (93.8%, 63.5%, and 63.5%, respectively) when compared to patients with a radiological chemotherapy response in whom all original disease sites were surgically treated (92.3%, 70.8%, and 46.2%, respectively; $p=0.66$).
Conclusions DLM were frequently observed in patients undergoing preoperative chemotherapy for liver metastases. Survival was comparable in patients with untreated DLM, in spite of high intrahepatic recurrence rates seen in these patients. Therefore, aggressive surgical therapy should be considered in patients with marked response to chemotherapy, even when all DLM sites cannot be identified.

Keywords Colorectal liver metastases · Chemotherapy · Liver resection

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Introduction

Approximately half of all patients diagnosed with colorectal cancer will develop liver metastases during the course of their disease. For these patients, hepatic resection offers the best chance for long-term survival, with reported 5-year survival rates over 50%.[1–5] An increasing number of patients are treated with systemic chemotherapy prior to liver resection, either administered as neoadjuvant treatment for initially resectable disease or in attempt to convert patients with unresectable disease into surgical candidates.[6,7] With the introduction of new chemotherapeutic regimens and targeted therapies, the radiologic response rates are high with an increasing number of patients showing a disappearance of one or more liver metastases on preoperative cross-sectional imaging.[8,9] Previous reports have shown variable results with regard to the proportion of these disappearing liver metas-

tases (DLM) that represents a true complete remission (e.g., a complete pathological response or a durable remission on repeat imaging), ranging from 17% to 69%.[8–11] The current paradigm is therefore to aim for complete resection or ablation of all areas in the liver where disease was observed prior to chemotherapy, perhaps including resection of regions in which disease originally occurred but cannot be found intraoperatively. However, limitations in the ability to visualize or locate these DCM intraoperatively may result in leaving these metastases untreated.[9]

Current studies which have reported on the fate of missing metastases have primarily focused on per lesion analyses, whereas information regarding patient-specific findings, management, and outcomes in those with DLM is limited. Therefore, in this study, we aimed to determine the proportion of patients developing DLM following preoperative chemotherapy, characterize the fate of these DLM during surgery, and to investigate the impact of undetected, untreated DLM on recurrence-free and overall survival.

Methods

Patients

A retrospective analysis was conducted on 366 patients undergoing curative intent surgery for colorectal liver metastases at Johns Hopkins Hospital between January 1, 2000 and December 31, 2008 in order to identify those who developed DLM following chemotherapy. Of the patients, 189 (51.6%) received preoperative chemotherapy. Of these, 21 were excluded (non-therapeutic laparotomy or incomplete staged procedure, $n=10$; incomplete imaging data available, $n=9$; non-surgical locoregional treatment prior to liver surgery, $n=2$), leaving 168 patients included in the study. The protocol was approved by the Johns Hopkins Hospital Institutional Review Board.

Preoperative Chemotherapy

Various preoperative chemotherapy regimens were utilized in these patients for their metastatic disease. One hundred forty-nine patients (88.7%) underwent only a single regimen of chemotherapy prior to surgery, and 21 patients (11.3%) received two or more lines of preoperative chemotherapy, excluding prior use for adjuvant therapy of primary disease. These included oxaliplatin-based, irinotecan-based, or fluoropyrimide monotherapy (5-fluorouracil or capecitabine) regimens. Targeted biologic therapies (bevacizumab and/or cetuximab) were incorporated preoperatively in 69 patients. The average number of chemotherapy cycles administered before surgery was 6.0 (SD 3.68). In 54 patients (32.1%), chemotherapy was initiated for initially unresectable disease (conversion intent). Reasons for initially unresectable disease included distribution of bilateral metastases in 39 patients, size or location in nine patients, or suspected unresectable extrahepatic disease in six patients. In the other 114 patients (67.9%), resectable disease was observed prior to chemotherapy and chemotherapy was administered as a neoadjuvant strategy. When multiple regimens were used, the active preoperative regimen was defined as the last regimen to which the patient responded or that which was administered immediately prior to liver surgery. Determination of resectability and timing to proceed to surgery was left to the discretion of the treating physicians as part of a multidisciplinary management team. In general, resectability was defined as the ability to completely resect all metastatic sites while leaving sufficient volume of the hepatic remnant (>20–30%) and adequate remnant vascular/biliary inflow and vascular outflow.

Imaging

All patients were initially staged prior to chemotherapy using contrast-enhanced multi-detector computerized tomography (CT). Positron emission tomography (PET) or PET/CT was utilized selectively at the discretion of the treating physicians. Imaging following chemotherapy was performed using CT in the majority of patients, with contrast-enhanced MRI only obtained in 22 (13%) patients. The majority of imaging studies were performed at Johns Hopkins Hospital. All imaging studies were reviewed by experienced radiologists and hepatic surgeons, and repeated when considered inadequate. Post-chemotherapy imaging was all conducted within 60 days of surgery. A disappearing liver metastasis (DLM) was defined as that in which no radiologically visible lesion or abnormality was seen at a site initially identified as a liver metastasis. Postoperative surveillance for recurrence was determined using CT, PET, or MRI every 3–6 months, at the discretion of the treating physician. If a DLM was identified and left surgically untreated, follow-up imaging studies were examined specifically for in situ recurrence as determined by comparison to the initial CT.

Hepatic Surgery

All patients underwent open surgical exploration with curative intent. Intraoperative assessment included examination for extrahepatic metastatic disease as well as careful visualization and palpation of the mobilized liver. Intraoperative ultrasound (IOUS) was performed by the hepatobiliary surgeon using a 4.0–8.0 MHz curvilinear transducer (Phillips ATL HDI 5000) based on a standardized protocol.[12] All known metastatic sites were known to the surgeon, including information regarding location and number of original and persistent lesions, as well as DLM. Findings and IOUS imaging of

regions of interest were documented. The goal of surgery when possible was to completely resect or ablate all sites of disease found during surgery as well as originally detected sites prior to chemotherapy. In five patients, preoperative right portal vein embolization or ligation was applied to allow for an adequate remnant liver volume after resection. Resection was combined with radiofrequency ablation (RITA-XL or XLie, Angiodynamics, Queensbury, NY, USA) in 53 patients and microwave ablation (Microsulis Inc.) in one patient.

Histopathologic Examination

Resected specimens were serially sectioned in 0.5 cm slices and examined for metastatic deposits. Regions within the resected liver in which intraoperative lesions were identified or where prior metastases were felt to be present were pointed out to the pathologist for identification. Samples embedded and fixed in paraffin, sliced, stained with hematoxylin and eosin were examined microscopically for the presence of metastatic colorectal cancer. A complete pathological response was defined as the absence of any viable tumor cells at the sites of macroscopically visible tumors or if no evidence of any tumor was found at the site of previously identified DLM.

Statistics

Statistical analysis was performed using Stata 10.0 (Collegetown, TX, USA). Summary statistics were obtained with established methods using χ^2 squared test and Fisher's exact test for categorical data and Student's t test for continuous data. Factors predictive of the development of one or more DLM were investigated using univariate and multivariate logistic regression analysis. Differences in recurrence-free and overall survival were calculated with the log rank test and Kaplan–Meier curves. A p value of <0.05 was considered statistically significant.

Results

Patient and Tumor Characteristics

Clinicopathological and morphologic characteristics of the 168 patients are summarized in Table 1. The majority of patients included were male (n=94; 55.9%) with a median age of 57 years (range 23–84 years). At the time of resection of the primary tumor, 114 patients (67.9%) were found to have nodal metastases. Diagnosis of metastatic disease was synchronous with the primary tumor in 128 patients (76.2%). Eighty-seven patients (51.6%) had bilateral disease at the time of presentation with a median number of metastases of 2.0 (range 1–24). Sixty-one patients (36.3%) had a solitary metastasis before chemotherapy, 54 patients (32.1%) had two or three metastases, and 53 patients (31.6%) had four or more metastases prior to chemotherapy.

Table 1 Clinicopathologic and morphologic characteristics of 168 patients treated with chemotherapy prior to surgery

Variable	N=168
Median age in years (range)	57 (23–84)
Gender	
Male	94 (55.9)
Female	74 (44.1)
Diagnosis of liver metastases	
Synchronous	128 (76.2)
Metachronous	40 (23.8)
Node status primary	
Positive	114 (67.9)
Negative	47 (27.9)
Missing values	7 (4.2)
Median tumor number (range) pre-chemotherapy	2 (1–24)
Median size largest tumor in cm (range) pre-chemotherapy	3 (1–17)
Disease spread	
Bilateral	87 (51.6)
Unilateral	81 (48.2)
Indication for chemotherapy	
Neoadjuvant	114 (67.9)
Conversion	54 (32.1)
Preoperative chemotherapy regimen	
Fluoropyrimidine monotherapy	15 (8.9)
Irinotecan-based	55 (32.7)
Oxaliplatin-based	96 (57.2)
FOLFOXIRI	2 (1.2)
Bevacizumab or Cetuximab	
Yes	69 (41.1)
No	99 (58.9)
Radiological response (RECIST)	
Complete	11 (6.5)
Partial	88 (52.4)
Stable disease/progressive disease	68 (40.5)
Missing data	1 (0.6)

Incidence and Predictors of DLM

Forty (23.8%) patients were observed to have a total of 127 DLM at the time of surgery. When compared to patients in whom all original disease sites were still visible, patients with one or more DLM presented more often with synchronous disease (OR 8.02; p=0.006) and initially unresectable disease (OR 4.09; $p<0.001$) (Table 2). Moreover, DLM were more common in patients with four or

more metastases (25/53; 47.2%) when compared to patients with three or less metastases (15/115; 13.0%) detected prior to chemotherapy (OR 5.59; $p<0.001$). While no correlation between the last regimen of preoperative chemotherapy and the probability of developing DLM was seen, patients with a complete radiological response in one or more metastases received more cycles of preoperative chemotherapy (7.7± 5.1 courses) than their counterparts without DLM (5.5±3.1 courses; OR 1.14; $p=0.01$). On multivariate analysis of factors predictive for the development of a complete radiologic response in one or more metastases, only tumor number >3 (OR 13.1; $p<0.001$) and the number of courses of preoperative chemotherapy (OR 1.18; $p=0.03$) had an independent association with the development of one or more DLM. In addition, the median size of metastases prior to chemotherapy was significantly smaller in metastases that disappeared (median 1.0 cm; range 0.3–3.5 cm) when compared to the size of metastases that did not disappear during chemotherapy (median 2.1 cm; range 0.4–16; $p<0.001$; Fig. 1).

Intraoperative Detection and Management of DLM

In 18 of the 40 patients (45.0%) with one or more DLM, all sites of metastatic disease identified prior to chemotherapy were detected during surgery, and in all cases, all sites were resected or ablated (Fig. 2). In 22 patients with DLM (55.0%), detection of all DLM was not achieved during surgery. Of these, five patients underwent resection of regions in which the original tumors existed, all of which were achieved by incorporating these sites in a hemihepatectomy. In no cases was a separate resection performed of an undetected DLM.

Seventeen patients (42.5%) had DLM that were not detected and remained untreated during surgery. The median number of untreated metastases in these patients was two (range 1–11). Specifically, in eight patients, one DLM was left untreated, in four patients two DLM were left untreated, and in three patients three DLM were left untreated. In two patients, ten and 11 metastases were left untreated, respectively. The characteristics of these patients are outlined in Table 3. Patients in which DLM were left untreated were more likely to have unfavorable prognostic factors when compared to patients in which all original disease sites were treated. More specifically, all patients with untreated DLM presented with synchronous disease and 11 of these patients (64.7%) had more than four metastases diagnosed prior to chemotherapy. Also, the majority of these patients ($n=13$; 76.5%) were initially considered unresectable, and only became surgical candidates after a significant response to chemotherapy (all $p<0.05$).

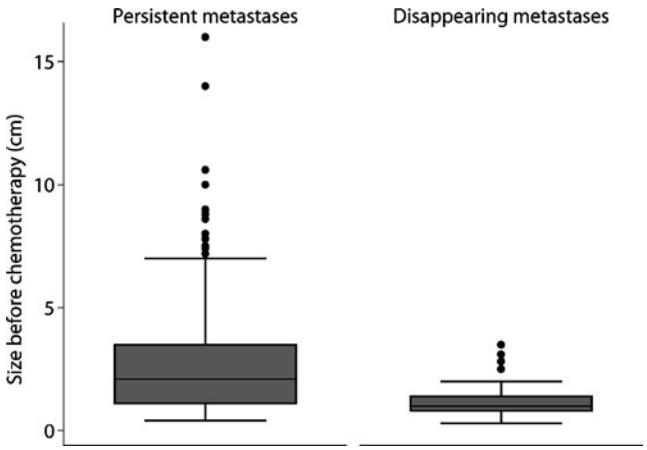

Fig. 1 Box plot comparing the size of metastases prior to chemotherapy among those that radiologically disappeared versus those that remained visible following chemotherapy. Median diameter (range): persistent=2.1 cm (0.4–16 cm) vs. 1.0 cm (0.3–3.5 cm; $p<0.001$)

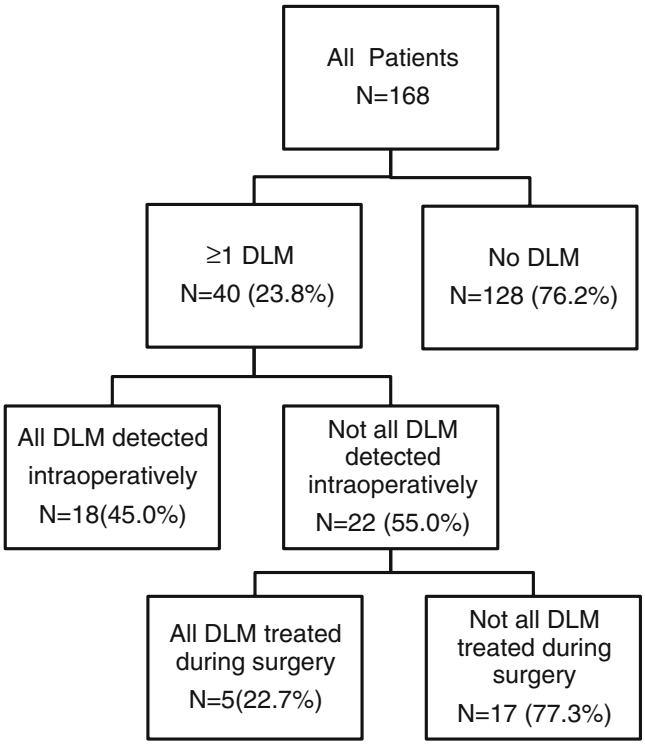

Fig. 2 Flowchart depicting the findings and management of patients with one or more disappearing liver metastases (DLM)

Recurrence-Free and Overall Survival

Thirteen (76.5%) of the 17 patients with DLM that were left untreated developed an intrahepatic recurrence. Moreover, in ten of these 13 patients (76.9%), this intrahepatic recurrence was observed at the site of an untreated DLM. While five of these ten patients (50.0%) developed concomitant intra- or extrahepatic recurrences (intrahepatic $n=1$, extrahepatic $n=2$, both intrahepatic and extrahepatic $n=2$), in five patients recurrence was truly local and limited

Table 2 Univariate and multivariate logistic regression analysis of factors associated with the development of one or more DLM

Variable	OR	95% CI	*p* value	OR	95% CI	*p* value
Gender (male)	0.95	0.46–1.94	0.89	–		
Age	0.99	0.97–1.03	0.73	–		
Synchronous presentation	8.02	1.84–34.9	0.006	3.90	0.77–21.6	0.13
Positive node status	0.91	0.41–1.98	0.80			
Tumor number>3	5.95	2.77–12.8	<0.001	13.1	3.50–49.3	<0.001
Pre-operative chemotherapy						
5-Fluoropyrimidine only	–	–	–			
Irinotecan-based regimen	1.12	0.27–4.60	0.88	–		
Oxaliplatin-based regimen	1.33	0.34–5.12	0.67	–		
FOLFOXIRI	4.00	0.19–84.2	0.37	–		
Biological added	1.84	0.89–3.77	0.09	2.25	0.75–6.73	0.15
Total number of cycles	1.14	1.03–1.28	0.013	1.18	1.02–1.37	0.03
Initially unresectable disease	4.90	2.31–10.4	<0.001	1.76	0.52–6.01	0.36

Table 3 Characteristics of patients with residual untreated DLM versus all original sites treated after surgery

Variable	Residual untreated DLM *n*=17 (10.1%)	All original sites treated *n*=151 (89.9%)	*p* value
Gender			
Male	11 (64.7)	83 (54.9)	0.44
Female	6 (35.3)	68 (45.1)	
Diagnosis of liver metastases			
Synchronous	17 (100)	111 (73.5)	0.015
Metachronous	–	40 (26.5)	
Primary nodal status			
Positive	8 (47.1)	106 (73.6)	0.023
Negative	9 (52.9)	40 (26.4)	
Unknown (*n*=7)	0	7	
Tumor number pre-chemotherapy			
1	0	61 (40.4)	0.001
2–3	6 (35.3)	48 (31.8)	
≥4	11 (64.7)	42 (27.8)	
Indication for chemotherapy			
Neoadjuvant	4 (23.5)	110 (72.9)	<0.001
Conversion	13 (76.5)	41 (27.2)	
Complete pathological response in any CLRM			
Yes	12 (70.6)	129 (85.4)	0.131
No	4 (23.5)	17 (11.3)	
RFA only	1 (5.9)	5 (3.3)	
Resection margin			
R0	15 (88.2)	134 (88.8)	0.78
R1	1 (5.9)	12 (7.9)	
RFA only	1 (5.9)	5 (3.3)	
Postoperative adjuvant chemotherapy			
None	8 (47.1)	70 (46.4)	0.19
Systemic	6 (35.3)	72 (51.4)	
Intra-arterial	3 (17.7)	9 (6.4)	

to the site of an untreated DLM. All of these patients successfully underwent repeat surgical treatment for this recurrent disease. Of the five patients in whom three or more DLM were left behind, all recurred in within the liver with a median time to recurrence of 7 months [range 4–14]. In two of these patients, recurrence was limited to the site of a DLM and repeat surgery was performed.

When compared to patients in whom all original disease sites were surgically treated, patients with untreated DLM had a significantly higher rate of intrahepatic recurrence. More specifically, 1- and 3-year intrahepatic recurrence-free survival rates were 40.2% and 16.1% for patients with untreated DLM (median; 11 months) compared to 68.8% and 35.1% for those patients in which all original disease sites were treated (median; 20 months; p=0.04; Fig. 3a). In addition, 1- and 3-year any site recurrence-free survival were 33.1% and 13.2% in patients with untreated DLM (median=10 months) and 59.7% and 22.7% in patients in which all original disease sites were treated (median= 15 months; p=0.06; Fig. 3b).

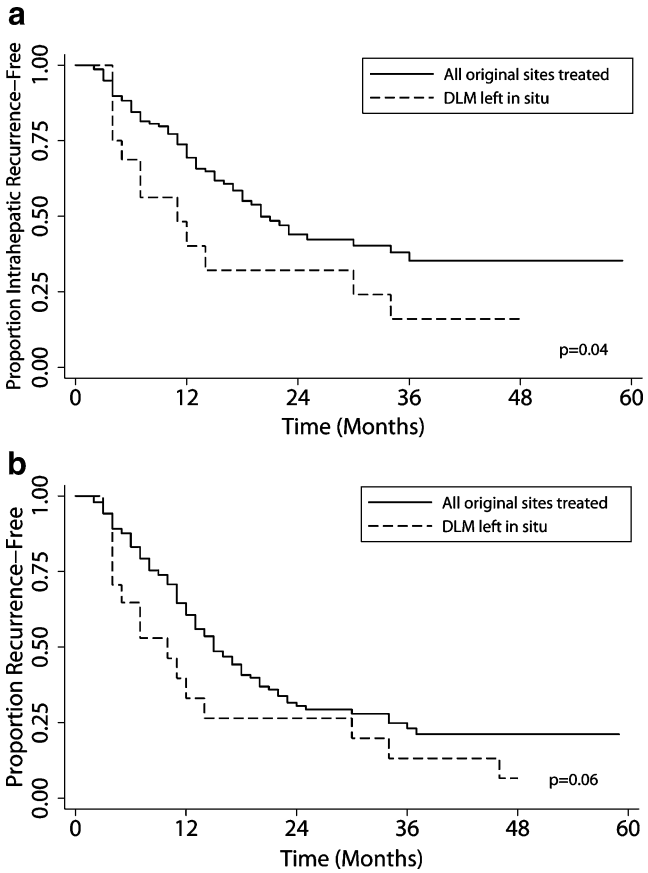

Fig. 3 **a** Kaplan–Meier curve of intrahepatic recurrence-free survival in patients with untreated DLM when compared to patients in whom all original disease sites were resected. **b** Kaplan–Meier curve of any site recurrence-free survival in patients with untreated DLM when compared to patients in whom all original disease sites were resected

We then investigated the impact of untreated DLM on overall survival. The median overall survival was 45 months for the entire cohort, corresponding to a 93.2 %, 59.0% and 40.0% 1-, 3-, and 5-year overall survival (median; 55 months). For patients in which DLM sites were left untreated, 1-, 3-, and 5-year survival rates were 93.8%, 63.5%, and 63.5%, respectively with a median survival of 65 months. For those in which all original disease sites were treated, 1-, 3- and 5-year survival rates were 93.1%, 58.5% and 37.5%, respectively with a median survival of 45 months. When comparing those groups, no statistically significant difference in overall survival was observed (logrank; p=0.31; Fig. 4a).

To adjust for the potential prognostic influence of a radiological response to chemotherapy on overall survival, a stratified survival analysis was performed in a subgroup of patients with a complete or partial radiological response to chemotherapy (n=99). When comparing overall survival for patients with untreated DLM (median; 65 months) and patients in which all disease sites diagnosed prior to chemotherapy were treated (median**;** 54 months), no statistically significant difference was found with corresponding 1-, 3-, and 5-year survival rates for patients without untreated DLM of 92.3%, 70.8% and 46.2%, respectively and 93.8%, 63.5%, and 63.5% respectively for those with untreated DLM (p=0.66; Fig. 4b).

Analysis of True Complete Response

The true complete response rate of DLM lesions was examined by determining both the complete pathological response in resected lesions as well as the durable remission in those lesions left in situ. Of the 126 DLM observed, 69 (54.7%) were detected during surgery and concomitantly treated (resection n=55; ablation n=14). Of the 55 DLM that were detected and resected (excluding ablated lesions), 19 metastases (34.5%) showed a complete pathological response. In contrast, complete pathological response was observed in seven of the 12 DLM (58.3%) that were not detected during surgery but were incorporated in the resection of one hemiliver. Of the 45 DLM that were left untreated, 24 (53.3%) did not recur during a median follow-up of 20 months (range 7–88; Fig. 5). Therefore, a true complete response was observed in 50 of the 112 DLM available for analysis (44.6%).

Discussion

In this study, one or more disappearing liver metastases were found to occur in 23.8% of patients receiving preoperative chemotherapy. We found that only approximately half of these could be indentified during surgery and

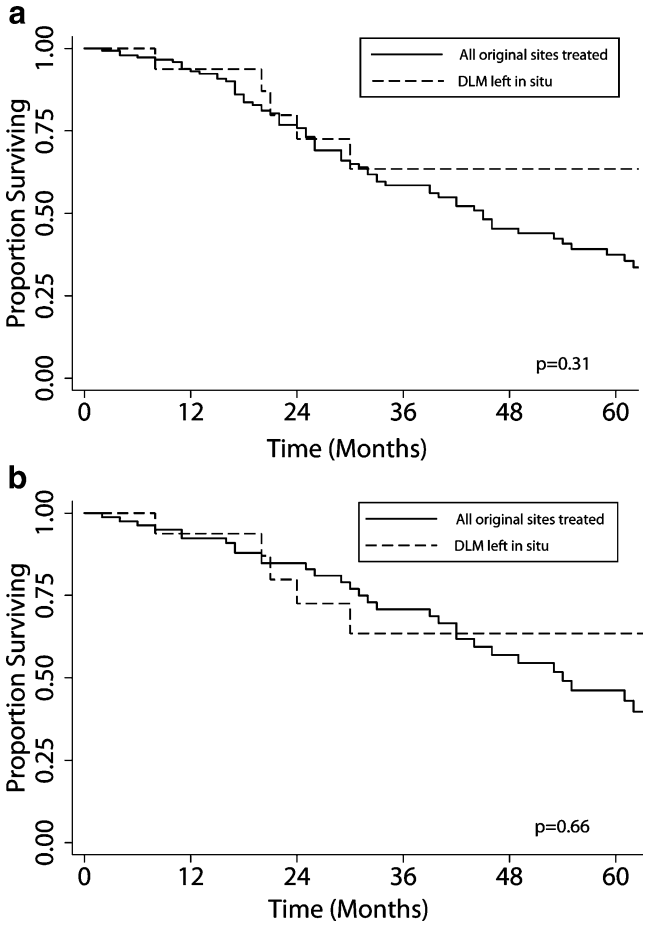

Fig. 4 **a** Kaplan–Meier curve of overall survival in patients with untreated DLM when compared to patients in whom all original disease sites were resected. **b** Kaplan–Meier curve showing overall survival in 99 patients with a complete or partial radiological response (RECIST) to preoperative chemotherapy stratified by the presence of untreated DLM

if so, all of these sites were able to be resected or ablated. In 42.5% of these patients, one or more DLM remained untreated at the time of surgery, resulting in potential increased risk of intrahepatic recurrence. However, overall survival did not seem to be significantly impacted in these highly selected patients and was comparable when compared to patients in whom all original disease sites were detected.

The number of patients developing DLM in our study was higher than that reported in other series.[9] This likely reflects an aggressive policy towards our patients with initially unresectable disease and tendency towards surgical therapy if a radiological response is observed.[13] Indeed, many patients that developed DLM in this study were considered initially unresectable (61%), with utilization of longer duration and more aggressive chemotherapeutic regimens. In addition, the majority of the patients had multiple metastases, increasing the probability of developing DLM.

In this study, we found that patients with multiple tumors and those undergoing longer duration of chemotherapy were associated with a higher risk of developing DLM. More than 60% of patients with at least one DLM had four or more metastases prior to chemotherapy. In addition, small metastases (median size 1 cm) were more likely to disappear. These findings are not surprising but may be useful when planning use of chemotherapy prior to plan surgical therapy in order to avoid a complete radiologic response when possible. When a patient is initially resectable and the intent of chemotherapy is as a neo-adjuvant approach, limiting the duration may be prudent. Small tumors in sites which may prove to be problematic if not operatively detectable following a response may be considered for initial surgical intervention. In initially unresectable patients in whom preoperative chemotherapy is being employed to convert to a resectable status, careful serial imaging is important, proceeding to surgical therapy as soon as resectability is achieved rather than waiting for maximum response. In addition, marking a small tumor which is in a potentially difficult location with a radiologically placed fiducial can be considered, either prior to chemotherapy [14] or using post-response marking based on the initial imaging studies.

We found that upon surgical exploration, including IOUS, an identifiable lesion was found in 55% of the metastases that had disappeared on cross-sectional imaging. The rate of intraoperative DLM detection rate found in our study was higher than that in most other reported series. Benoist et al.[9] reported only 20 of 66 lesions (31%) with complete radiologic response could be found operatively. Tanaka et al.[11] reported a 36% operative detection rate of DLM. Reasons for these differences are likely multifactorial, in part related to the choice of imaging technique and perhaps time lapse between chemotherapy

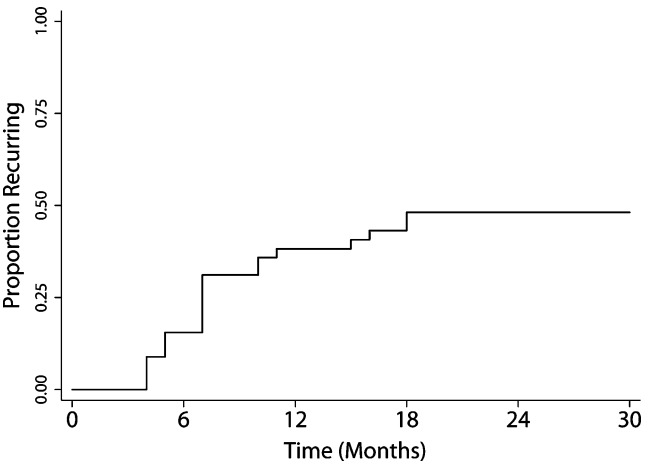

Fig. 5 Kaplan–Meier plot illustrating the proportion of undetected DLM recurring locally when left untreated

and surgery. In addition, lesions located near the surface or which become more conspicuous on IOUS may be detected more easily. Several studies have established the importance of detecting and identifying all macroscopic disease when possible in order to offer improved outcome for patients undergoing surgical therapy of colorectal metastases.[8,9,11] Implementation of preoperative chemotherapy may have a variable effect on the ability to detect and therefore treat all sites of disease. While in some cases, reduction in tumor size may limit detection, changes in lesion echogenicity may paradoxically improve detection rate in other situations.[15–17]

A true complete response, either no viable disease on pathologic assessment or a durable local remission of an unresected site, was observed in 43% of DLM in our study. Some studies have reported true complete responses in excess of 50% of cases, but these have included those receiving regional intrahepatic chemotherapy.[8,10,11] Benoist et al. reported complete durable responses to be found in only 17% of lesions with radiologic complete response. Likely, observed differences may reflect various confounding factors, including chemotherapy duration and choice of agents, as well as differences in the waiting period between the development of DLM and surgical intervention. Yet, with the higher observed rate of true complete responses seen in this and other studies using aggressive chemotherapeutic regimens, the dogma that viable disease exists in most DLM might be reconsidered.

An important question arises regarding the optimal management of patients in which DLM occur. Given the relatively low rate of true complete pathological responses in these DLM and the high rate of intrahepatic recurrences observed in patients with untreated DLM, we still recommend that complete surgical treatment of all original sites should be done when possible, even if undetected intraoperatively. When a lesion cannot be identified, incorporation of the original sites into the hepatectomy should be done when possible. Such "blind" resections may include a major hepatectomy, for example, when lesions were originally contained within one hemiliver, even if persistent sites can be treated with limited resection or ablation. However, this may not be safe or possible in all cases. We found that in such patients, leaving undetected lesions untreated can still be associated with reasonable long-term outcome when repeat resection or ablation of an isolated local recurrence is possible.[18]

The retrospective design of the current study presents some limitations to the analysis which necessitate some tempering of definitive conclusions based on these findings. Imaging methodology had evolved over the study period. In addition, while management decisions were based on radiologic assessment at the time, this study did not incorporate a systematic re-review of the cross-sectional studies.

In summary, disappearing metastases were commonly observed in patients receiving preoperative chemotherapy. With increasingly aggressive multimodality strategies being offered to patients with advanced colorectal cancer, including liver resection following chemotherapy, this is likely to become an increasingly common problem facing the hepatic surgeon. Anticipating the occurrence of DLM in patients with small, multiple metastases may alter management strategies regarding choice and duration of chemotherapy before surgery. When DLM develop, one can anticipate finding and treating these lesions in many cases with careful intraoperative assessment. In those circumstances in which all sites cannot be identified and when incorporation of undetected original sites in a resection is not safe or possible, leaving them behind can be considered in selected cases. However, these untreated sites have a high risk of in situ recurrence and therefore we advise that one must only consider surgical therapy for those in whom all original sites can be treated, either at the time of initial surgery or when a recurrence occurs after initial liver surgery.

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Discussant

Dr. Eddie K. Abdalla (Houston, TX, USA): This question of what to do with disappearing metastases is an important one. I have a comment and a couple of questions. It seems to me your title with regard to disappearing metastases must be "we should be concerned." Your paper develops a proposal for a new (perhaps dangerous) goal of surgery to debulk or palliate liver metastases and leave some lesions behind to be followed. So I want to be careful about the data before we go down the road of debulking as you propose, because your data strongly suggest this proposed path is the wrong way right now.

My first question is with regard to the median follow-up, which is only 19 months. Is that long enough to declare the missing lesions gone? Because your reported 16% 3-year recurrence-free survival in the "debulked group" is by no means cured, and it's far lower than the recurrence-free survival in the group where you resected all the disappearing lesions. Worse, you only salvaged a few of them. So, in fact, you've shown that leaving lesions in place led to poor outcomes. Thus, the proposal to leave "disappearing lesions" in place and to follow and wait for recurrence (or hope for no recurrence) does not seem to be a rational conclusion from your data or a reasonable oncologic approach, does it?

Leaving disappearing lesions in place is basically hoping for a complete pathologic response. So I will try to sum up some issues regarding pathologic response. When we look at pathologic response to chemotherapy, we know that this is an extremely powerful predictor of survival. There are two explant studies that show the pathologic complete response rate overall is about 10%, even with the use of biologic agents. Bottom line, it's a matter of time before nearly all the patients will recur if you don't resect all the sites of disease ever present.

In these two studies in the Journal of Clinical Oncology, one from our group authored by Blazer et al. (J Clin Oncol. 2008 Nov 20; 26 (33):5344–51), and the other from the Paul Brousse authored by Adam et al. (J Clin Oncol. 2008. Apr 1; 26 (10):1653–41), the 5-year overall survival following resection with a finding of pathologic complete response is about 75%, and the disease-free survival is about 70%. So how do you reconcile only a 58% three-year overall survival in this cohort with a so-called complete response (lesions disappeared) when the 5-year survival should be nearly 75%? You cannot draw that conclusion. Rather, I think it proves that we have to go after every site of disease that was ever present, and that the radiologic complete response cannot be treated as a pathologic complete response. I am more than a little concerned about going down the path of debulking surgery that you are proposing in this paper based on existing data and the data you present.

Closing Discussant

Dr. Mark G. Van Vledder: To address your concern and your first question, indeed, we should be concerned about these disappearing liver metastases, and I think the goal should be to completely resect or ablate all initial sites that were diagnosed prior to chemotherapy, when possible.

To address your question about the follow-up for these patients, we found that most of the disappearing lesions that were left in place recurred within 1 year, so we think it is safe to conclude most lesions that would have recurred did so within these 19 months time of follow-up.

Discussant

Dr. David Mahvi (Chicago, IL, USA): I have two questions. Do you think there's ever a liver metastasis cured with chemotherapy? Is there a size below which chemotherapy would just fix it?

Second, is there any disadvantage to not resecting a metastasis the first time? If the lesion is not visible by imaging, can you come back when it does appear and have a similar outcome?

Closing Discussant

Dr. Mark G. Van Vledder: Thank you Dr. Mahvi for your questions. Regarding whether a durable complete response

can be achieved with chemotherapy in small lesions, perhaps this can best be estimated by the frequency of complete pathologic response. We did not specifically look at this. However, one study from Memorial Sloan–Kettering Cancer Center did not find a significant correlation between lesion size the rate of pathologic complete response.

Your second question relates to the salvage rate when an undetected and untreated lesion recurs. We found that of those patients in which they only recurred at the original site, a true local only recurrence, a second procedure to resect or ablate was possible in all cases. Of course, it is likely that patients were only operated upon in our series where all original sites were in potentially treatable locations. So, we feel that while only patients who are potentially resectable or ablatable based on the number and location of all original sites, if for some reason all sites cannot be identified at the time of surgery and a blind resection is not feasible or safe, one can consider leaving them in place with an option for potential subsequent salvage therapy if they recur.

Discussant

Dr. Mukund Didolkar (Baltimore, MD, USA): I know your study related mainly CT scans, but did you study PET CT, which would be a functional scan? And did that complete disappearance or negative PET CT correlate with the histology?

Closing Discussant

Dr. Mark G. Van Vledder: Many patients in this study did indeed undergo PET imaging prior to and after chemotherapy. And in many of these patients, complete response of one or more lesions on PET imaging was observed. In fact, tumors often responded to a greater extent on PET than on CT. However, in this study, we did not use PET imaging to define complete radiological response but relied only on complete disappearance on CT. We have not looked into the relationship between PET response and pathologic response.

Discussant

Dr. Thomas Biehl (Seattle, WA, USA): I have noticed over the years that almost all of these "disappearing mets" come back. And with that observation, I usually recommend what I call a chemotherapy holiday between the time when they finish chemotherapy and the recommendation for an operation. I'm wondering how much time did you have between the completion of chemotherapy and operation? And do you ever use this to help plan your operation?

Closing Discussant

Dr. Mark G. Van Vledder: This is an interesting question. Similarly, might the wait time between a radiologic response following chemotherapy and surgery, without evidence of recurrence at that site, determine the probability of a complete pathologic response. In our study, the median time in between the last cycle of chemotherapy and surgery was 2 months, ranging from 1 month to 24 months. In only on a very limited number of patients did we actually waited for longer period of time to allow metastases to declare themselves during follow-up. Such a concept is a useful one which warrants further investigation.

Discussant

Dr. Merril T. Dayton (Buffalo, NY, USA): Your study focuses on disappearing hepatic metastases. And your message is pretty clear that even when they disappear, they should be resected.

You didn't say much, though, about how chemotherapy may change an unresectable liver met into a resectable liver met. Do you have any data on that? In other words, - - maybe the ultimate utility of the chemotherapy is in converting lesions which are unresectable into resectable ones.

Closing Discussant

Dr. Mark G. Van Vledder: For this study, we primarily focused on patients that underwent curative intent surgery, some of whom were considered initially resectable and some that were felt to have been converted to a resectable state. It is difficult for me to specifically answer your question. Our general management philosophy has been to operate on only those patients in whom we feel all original sites were potentially resectable, even if converted.

Discussant

Dr. Heriberto Medina-Franco (Mexico City, Mexico): What would be your approach in a patient that received conversion chemotherapy for bilobar disease, and disappear the lesions in only one side of the liver?

Closing Discussant

Dr. Mark G. Van Vledder: Indeed, cases such as that which you describe can be quite difficult to manage. As mentioned, at least for now, our philosophy is to operate only upon those patients in which treating all original sites of disease is feasible, and every attempt should be made to identify and treat all of these sites. In cases in which contralateral disease cannot be found and hemihepatectomy is required to resect detectable disease, one can feel comfortable leaving these sites behind, provided that contralateral recurrence occurs at these sites, a salvage operation or procedure can be performed at a later date.

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2010 SSAT PLENARY PRESENTATION

Redefining Mortality After Pancreatic Cancer Resection

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Abstract
Introduction Distinct outcome measures such as in-hospital and 30-day mortality have been used to evaluate pancreatectomy results. We posited that these measures could be compared using national data, providing more precision for evaluating published outcomes after pancreatectomy.
Methods Patients undergoing resection for pancreatic cancer were identified from the linked SEER-Medicare databases (1991–2002). Mortality was analyzed and trend tests were utilized to evaluate risk of death within ≤60 days of resection and from 60 days to 2 years post-resection. Univariate analysis assessed patient characteristics such as race, gender, marital status, socioeconomic status, hospital teaching status, and complications.
Results One thousand eight hundred forty-seven resected patients were identified: 7.7% (n=142) died within the first 30 days, 83.6% of whom died during the same hospitalization. Postoperative in-hospital mortality was 8.1% (n=150), 79% of which was within 30 days, greater than 90% of which was within 60 days. Risk of death decreased significantly over the first 60 days (P<0.0001). After 60 days, the risk did not decrease through 2 years (P=0.8533). Univariate analysis showed no difference between the two groups in terms of race, gender, marital status, and socioeconomic status, but patients dying within 60 days were more likely to have experienced a complication (41.1% vs. 17.0%, P<0.0001).
Conclusions In-hospital and 30-day mortality after resection for cancer are similar nationally; thus, comparing mortality utilizing these measures is acceptable. After a 60-day post-resection window of increased mortality, mortality risk then continues at a constant rate over 2 years, suggesting that mortality after pancreatectomy is not limited to early ("complication") and late ("cancer") phases. Determining ways to decrease perioperative mortality in the 60-day interval will be critical to improving overall survival.

Keywords Pancreatic adenocarcinoma · Outcomes · Resection · Survival · SEER-Medicare

Synopsis Mortality in pancreatic adenocarcinoma cancer care was assessed for patients receiving resection. In-hospital mortality and 30-day mortality were shown to be comparable; mortality was also assessed as a pattern of risk, with risk falling for resected patients directly following surgery for 60 days, but then remaining constant up to 2 years.

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Introduction

As the fourth leading cause of cancer death in the United States, pancreatic cancer mortality rates approach annual incidence.[1] Most patients present with locally advanced or distant disease; for those with localized tumors, tumor resection represents the only potential cure.[2] Reports describing outcomes following resection describe survival in multiple measures, including in-hospital, 30-day, and 5-year survival, making comparisons difficult when considering the aggregate single-center US experience.

Despite recent work detailing improvements in operative mortality and increasing utilization of potentially curative surgery, few conclusions have been drawn regarding the optimal means of reporting outcomes following resection

for pancreatic cancer.[3–6] Studies establishing surgical determinants of improved survival such as small tumor size and negative nodal status, for instance, do not account for long-term survival reported among patients with larger tumors and advanced nodal disease.[7] Certainly, studies with both extensive (long-term) patient follow-up and evaluation of surgically relevant prognostic factors are scarce.[8] At the other end of the spectrum, 30-day and in-hospital mortality may lack complete assessment as appropriate endpoints for surgical outcomes.[9] In fact, they may be similar and thus comparable outcome measures.

In the current work, we hypothesized that national data could be used to assess incremental postoperative mortality to determine the relationships between 30-day and in-hospital mortality. We further hypothesized that deaths following resection might be classified as early (from complications) and late (cancer-related) deaths, and sought to review the chronology of post-resection deaths in a national dataset.

Methods

Data

Patients diagnosed between 1991 and 2002 were identified from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. The SEER program is a National Cancer Institute-sponsored tumor registry that collects cancer incidence and survival data; patients with diagnoses living in 17 SEER registry areas are linked to US Medicare claims data. These registries represent approximately 26% of the US population. Each registry reports information on incident cancer cases, including patient demographics, date of diagnosis and stage, primary site, histologic type, initial cancer-directed surgery and/or radiotherapy, and date and cause of death. Through SEER's linkage with Medicare beginning in 1991, additional information on patients age 65 and older is captured about any service for which a claim may be filed, including inpatient and outpatient procedures, physician- and laboratory-generated claims, as well as home-care and hospice billings.[10]

Cohort Definition

We selected all Medicare-eligible patients, age ≥65 years at time of diagnosis, living in SEER registries between January 1, 1991 and December 31, 2002, who underwent pancreatic resection for pathologically defined pancreatic cancer (International Classification of Diseases for Oncology codes 8000, 8001, 8010, 8012, 8020, 8021, 8022, 8031, 8041, 8050, 8070, 8140, 8210, 8260, 8261, 8440, 8453, 8470, 8471, 8480, 8481, 8490, 8500, 8550, 8560). Curative-intent surgery was identified in the Medicare databases using the International Classification of Diseases, 9th Revision (ICD-9; procedure codes 52.51 to 52.53, 52.59, 52.6, and 52.7). In addition, Current Procedure Terminology codes (48140, 48145, 48146, 48150, 48152, 48153, 48154, 48155, 48160) were queried to include physician-generated procedure claims for patients undergoing resection.[11] Patients with histologies to suggest non-pancreatic primary tumors and neuroendocrine tumors, and those for whom information regarding date and stage at diagnosis was unavailable, were excluded. Patients discontinuously enrolled in Medicare Parts A and B following diagnosis were excluded. Patients were also excluded if the diagnosis was obtained only from a death certificate or autopsy, if the date of death differed by more than 2 months in the SEER and Medicare database, if the patients had additional HMO coverage, and if patients qualified for Medicare on the basis of disability or End-Stage Renal Disease claims. Patients with a second cancer (non-pancreatic) diagnosis within 12 months after the date of diagnosis with pancreatic cancer were also excluded.

Patient comorbidity was assessed using both inpatient and outpatient Medicare claims for the 13 months to 1 month prior to cancer diagnosis. The Klabunde and Deyo modifications of the Charlson comorbidity index were employed.[12,13]

Postoperative complications were comprehensively identified according to methodology previously described by our group.[14,15] General postoperative complications such as acute myocardial infarction, deep venous thrombosis, re-exploration of surgical site, and pulmonary compromise are included and are identified using ICD-9 codes associated with individual resection Medicare claims.

Survival Analyses

Survival was calculated as time from operation to death from any cause. Date of surgery was determined using Medicare claims; date of death was derived from SEER data and the National Death Index, which is maintained and updated annually by the National Centers for Health Statistics. For survivors, date of last follow-up was December 31, 2005.

Definition of Patient and Health System Characteristics

After extracting pertinent patient demographic information from SEER data, comparisons based on the following covariates were made between patients who were flagged as having died in-hospital (within the same hospital stay as resection) following their procedure and as having died within 30-days of their procedure: age group (65–70, 71–75, ≥76), sex, race, marital status, comorbidity status, tumor

stage, hospital teaching status, and postoperative complications. For purposes of comparison, logistic regression models were fit to determine the independent effect of specific covariates upon these respective outcomes, with covariates selected on the basis of univariate screening or clinical plausibility.

We then performed univariate analysis of patients who had died within 60 days of their procedure versus resected patients remaining in the cohort. Proportional hazards were used to identify significant independent predictors of survival. Covariates adjusted for in this model were also selected from univariate analysis or for clinical plausibility, and included gender, age, race, marital status, comorbidity, tumor stage, hospital teaching status, and presence of a complication. Risk of death during these two distinct timeframes was then calculated using derivatives of product limit estimates from the time of operation to death in order to characterize further post-resection mortality—this was accomplished incrementally in 10-day windows by assessing the ratio of patients having died by the number at risk in each window and then testing for trends.

This study was evaluated and determined to be exempt from review according to the University of Massachusetts Medical School Institutional Review Board.

Results

Patient Demographics

One thousand eight hundred forty-seven patients were included in the analysis. Mean age at time of diagnosis was 73.7 years for this cohort, with a median of 73.1 years and a range of 65 to 93.5 years. Men comprised 48.1% of the cohort; 87.5% were White, and 62.3% were married. The majority resided in an urban setting (93.0%). Surgery was performed in a teaching hospital for 66.5% of patients. A majority of patients had no comorbidities (65.5%, Charlson score=0) and in terms of disease stage, had a predominance of regionally advanced disease (70.4%), followed by localized/in situ (19.0%) and distant (10.6%) disease (Table 1).

Thirty-Day and In-Hospital Mortality

Of the 1,847 resected patients identified, 7.7% (n=142) died within the first 30 days (Table 2). Postoperative in-hospital mortality was 8.1% (n=150), 79% of which was within 30 days, and greater than 90% of which was within 60 days. Postoperative complications occurred in 19.9% of

Table 1 Overall patient demographics and univariate comparison of patients who died within 60 days of resection and remaining resected patients

Patient Characteristics	Overall n=1,847 (%)	Died within 60 days n=219 (%)	Remaining cohort n=1,628(%)	P value
Age Group				
65–70	653(35.4)	56(25.6)	597(36.7)	0.0008
71–75	593(32.1)	70(32.0)	523(32.1)	
≥76	601(32.5)	93(42.4)	508(31.2)	
Sex				
Female	959(51.9)	94(42.9)	865(53.1)	0.0045
Male	888(48.1)	125(57.1)	763(46.9)	
Race				
White	1,616(87.5)	187(85.4)	1,429(87.8)	0.3158
Black/Other	231(12.5)	32(14.6)	199(12.2)	
Married	1,150(62.3)	126(57.5)	1,024(62.9)	0.124
Charlson score				
0	1,209(65.5)	134(61.2)	1,075(66.0)	0.3661
1	430(23.3)	57(26.0)	373(22.9)	
≥2	208(11.2)	28(12.8)	180(11.1)	
Tumor Stage				
Localized/In situ	351(19.0)	35(16.0)	316(19.4)	0.009
Regional	1,300(70.4)	148(67.6)	1,152(70.8)	
Distant	196(10.6)	36(16.4)	160(9.8)	
In-hospital death	150(8.1)	*	*	
Teaching Hospital	1,228(66.5)	131(59.8)	1,097(67.4)	0.026
Residence in urban area	1,718(93.0)	207(94.5)	1,511(92.8)	0.352
Complication	367(19.9)	90(41.1)	277(17.0)	<0.0001

*SEER-Medicare prohibits reporting of individual cells with <11 patients; the percentage of patients with in-hospital deaths in the first 60 days is >90%

Table 2 Comparison of patient and pathological characteristics: discrete in-hospital mortality and 30-day mortality

Patient Characteristics	30-day Mortality (142 total deaths)	In-Hospital Mortality (150 total deaths)
Age Group		
65–70	39 (27.5)	40 (26.7)
71–75	43 (30.3)	49 (32.7)
≥76	60 (42.2)	61 (40.6)
Sex		
Female	65 (45.8)	65 (43.3)
Male	77 (54.2)	85 (56.7)
Race		
White	123 (86.6)	130(86.7)
Black/Other	19 (13.4)	20 (13.3)
Married	78 (54.9)	87 (58.0)
Not Married	64 (45.1)	63 (42.0)
Charlson score		
0	87 (61.3)	91 (60.7)
1	36 (25.3)	37 (24.7)
≥2	19 (13.4)	22 (14.6)
Tumor Stage		
Localized/In situ	22 (15.5)	22 (14.7)
Regional	101 (71.1)	109 (72.7)
Distant	19 (13.4)	19 (12.6)
Teaching Hospital	82 (57.8)	90 (60.0)
Complications	57 (40.1)	66 (44.0)

all patients (n=367); of those patients dying within 60 days, 41.1% were associated with a complication. Multivariable logistic regression models demonstrated similar significant covariates and odds ratios predicting death for both 30-day and in-hospital mortality, respectively, in regards to male sex (odds ratio [OR] 1.47, 95% confidence interval [CI] 1.01–2.13 vs. OR 1.57, 95% CI 1.09–2.27), age ≥76 (OR 1.66, 95% CI 1.08–2.56 vs OR 1.68, 95% CI 1.09–2.57), as well as postoperative complications (OR 2.95, 95% CI 2.05–4.23 vs. OR 3.55, 95% CI 2.50–5.04). The only predictors of death that were not congruent between 30-day mortality and in-hospital mortality were marital status and hospital teaching status, although these statistical relationships approached similar significance (Table 3).

Risk of Death

Post-resection risk of death decreased significantly over the first 60 days (P<0.0001; Fig. 1). After 60 days, the risk did not decrease through 2 years (P=0.8533; Fig. 2). Univariate analysis showed no difference between the two groups in terms of race, marital status, and comorbidity status, but patients dying within 60 days were more likely to have been male (57.1% vs. 46.9%, P=0.0045), have advanced age (age ≥76, 42.4% vs. 31.2%, P=0.0008), have advanced stage of disease (16.4% vs. 9.8%, P=0.009), and to have had experienced a complication (41.1% vs. 17.0%, P< 0.0001; Table 1). Those that died within 60 days were also less likely to have received resection in a teaching hospital (59.8% vs. 67.4%, P=0.026).

Multivariable Analysis

A Cox proportional hazards model constructed to evaluate independent predictors of overall survival following resection demonstrated that age ≥76 (hazards ratio [HR] 1.17, 95% CI 1.04–1.31, referent ages 65–70), tumor stage (regional stage HR 1.48, 95% CI 1.30–1.68; distant stage HR 2.58, 95% CI 2.15–3.11, referent localized stage), non-teaching hospital (HR 1.18, 95% CI 1.07–1.31), and post-resection complications (HR 1.42, 95% CI 1.26–1.59) negatively impact survival (Table 4).

Multivariable logistic regression performed using identical covariates as the proportional hazards model to evaluate predictors of mortality within 60 days of resection for pancreatic adenocarcinoma, demonstrated that age ≥76 (OR 1.91, 95% CI 1.33–2.75) and distant tumor involvement (OR 2.14, 95% CI 1.27–3.60) increased odds of death, as did the presence of a post-resection complication (OR 3.39, 95% CI 2.50–4.60). In addition, patients who were male (OR 1.68, 95% CI 1.23–2.30) or who were unmarried (OR 1.43, 95% CI 1.04–1.97) also had increased odds of death in this 60-day post-resection window. Lastly, having surgery performed at a non-teaching hospital increased odds of death within 60 days (OR 1.38, 95% CI 1.03–1.87; Table 5).

Discussion

In this population-based retrospective analysis, we first demonstrated that in-hospital and 30-day mortality are similar and thus comparable for patients undergoing resection for pancreatic adenocarcinoma. We then demonstrated incremental patterns of post-resection mortality risk, showing a decrease in the risk of death over the first 60 days following resection, but no significant decrease in the risk of death between 60 days and 2 years. Overall univariate analysis demonstrated that patients dying within the first 60 days more frequently were male, were older, had more advanced disease, and had increased complications compared to patients who survived past 60 days; in addition, those dying within 60 days were less frequently treated at a teaching hospital. Cox proportional hazards analysis showed that age, tumor stage, surgery at a non-teaching hospital, and complications confer a negative independent impact upon survival. Lastly, logistic regres-

Table 3 Comparison of mortality predictors: multivariable logistic regression of in-hospital mortality and 30-day mortality

Patient Characteristics	30-day Mortality OR (95% CI), *P* value	In-Hospital Mortality OR (95% CI), *P* value
Age Group		
65–70(referent)		
71–75	1.21 (0.76–1.90), 0.4228	1.37 (0.88–2.14),0.1598
≥76	1.66 (1.08–2.56), 0.0205	1.68 (1.09–2.57),0.0176
Sex		
Female (referent)		
Male	1.47 (1.01–2.13), 0.0425	1.57 (1.09–2.27),0.0155
Race		
White (referent)		
Black/Other	1.10 (0.66–1.85), 0.7101	1.12 (0.67–1.86), 0.6635
Married (referent)		
Not Married	1.53 (1.05–2.24),0.0259	1.37 (0.94–1.98),0.0986
Charlson score		
0 (referent)		
1	1.15 (0.76–1.73),0.5209	1.12 (0.74–1.68),0.5885
≥2	1.14 (0.67–1.94),0.6353	1.26 (0.76–2.09), 0.3737
Tumor Stage		
Localized/In situ(referent)		
Regional	1.32 (0.81–2.14), 0.2629	1.45 (0.89–2.35), 0.1333
Distant	1.64 (0.85–3.14), 0.1394	1.64 (0.85–3.16), 0.1382
Teaching Hosp.(No vs Yes)	1.49 (1.05–2.13),0.0274	1.34 (0.95–1.91), 0.1007
Complications(Yes vs No)	2.95 (2.05–4.23), <0.0001	3.55 (2.50–5.04), <0.0001

sion showed that postoperative complications, in addition to older age, male sex, distant stage disease, and surgery at a non-teaching hospital, independently impact 60-day mortality; complications also significantly increased odds of in-hospital death and 30-day death following resection.

Defining survival following resection for pancreatic adenocarcinoma is problematic. Bradley suggested discrepancies between reported actuarial long-term survival and actual long-term survival may cause overly optimistic projections of patient survival.[7] Other groups point to single-institution data to suggest that survival is robust in particular subsets of populations, particularly those populations with favorable tumor characteristics.[8] Khuri et al. investigated factors associated with both long-term and perioperative survival and concluded that complete assessment of survival following surgical care for major operations should include data beyond 30-day survival; he also suggested that evaluation of in-hospital mortality is lacking as a measure of quality of care.[9] Others have adopted the position that 30-day mortality may misrepresent an institu-

Fig. 1 Survival during the first 60 days, represented as risk of death following resection (ratio of patients who died by number at risk)

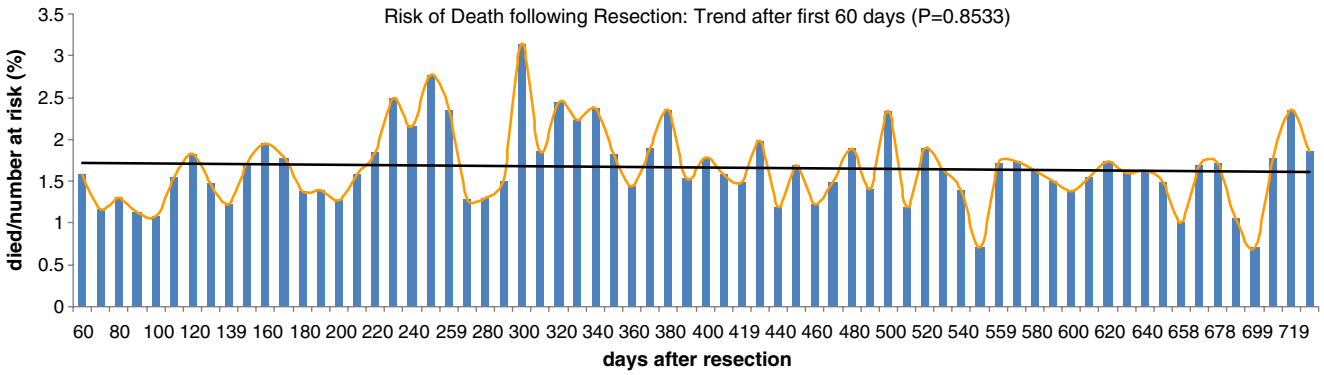

Fig. 2 Survival during 61 days through 2 years, represented as risk of death following resection (ratio of patients who died by number at risk)

tion's experience following resection for pancreatic cancer, and that mortality is best characterized with data recorded both prior to and after hospital discharge.[16]

Conclusions presented by Ferrone et al. highlight a common theme among authors investigating resection for pancreatic adenocarcinoma: despite documented advances, resection remains an inadequate treatment for most patients.[17] Favorable long-term survival may be achieved, but may seem dependent upon careful staging, patient selection, and a multidisciplinary approach toward resection and subsequent adjuvant therapy.[14] The impact of resection in this national database does seem limited: in a similar SEER-Medicare-based dataset, Reddy et al. examined hospital readmissions in resected patients and demonstrated a relationship between postoperative complications and early readmission, while also concluding that late readmissions are predominantly disease-related.[18] These findings correspond with our data related to risk of death after 60 days.

Our study confirms the expected role of complications in mortality following resection for pancreatic adenocarcinoma and also provides evidence that disease-related mortality does not occur in a discrete long-term postoperative window. Rather, the significant decrease in the first 60 days following resection suggests that operative factors, such as hospital teaching status and complications, may favorably

Table 4 Proportional hazard ratios of overall patient survival following resection

Patient Characteristics	Hazard Ratio	95% Confidence Interval	*P* value
Age Group			
65–70(referent)			
71–75	1.07	0.95–1.21	0.2492
≥76	1.17	1.04–1.31	0.0113
Sex			
Female (referent)			
Male	1.10	0.99–1.21	0.08
Race			
White (referent)			
Black/Other	1.07	0.92–1.23	0.40
Married.(No vs. Yes)	1.09	0.98–1.21	0.114
Charlson score			
0 (referent)			
1	1.12	0.996–1.256	0.058
≥2	1.18	1.01–1.37	0.04
Tumor Stage			
Localized/In situ(referent)			
Regional	1.48	1.30–1.68	<0.0001
Distant	2.58	2.15–3.11	<0.0001
Teaching Hosp.(No vs. Yes)	1.18	1.07–1.31	0.0014
Complications(Yes vs. No)	1.42	1.26–1.59	<0.0001

Table 5 Logistic regression of mortality within 60 days following resection

Patient Characteristics	Adjusted Odds Ratio	95% Confidence Interval	*P* value
Age Group			
65–70(referent)			
71–75	1.42	0.97–2.08	0.0707
≥76	1.91	1.33–2.75	0.0005
Sex			
Female (referent)			
Male	1.68	1.23–2.30	0.0012
Race			
White (referent)			
Black/Other race	1.26	0.83–1.92	0.28
Married.(No vs. Yes)	1.43	1.04–1.97	0.0271
Charlson score			
0 (referent)			
1	1.19	0.85–1.68	0.3193
≥2	1.06	0.67–1.67	0.8126
Tumor Stage			
Localized/In situ(referent)			
Regional	1.22	0.82–1.83	0.32
Distant	2.14	1.27–3.60	0.0042
Teaching Hosp.(No vs. Yes)	1.38	1.03–1.87	0.0341
Complications(Yes vs. No)	3.39	2.50–4.60	<0.0001

contribute to patient survival. However, our finding that the risk of death does not change significantly between 60 days and 2 years has more ominous implications—despite improvements in surgical intervention, disease recurrence nonetheless has a rapid, consistent impact on the majority of patients in this national dataset.

Administrative databases such as SEER-Medicare are subject to limitations. The level of clinical detail available cannot rival that found in institutional databases or extensive retrospective clinician chart reviews, both which enable analysis of specific tumor and operative characteristics, including blood loss, operative duration, and surgical margin status. With the incorporation of Medicare claims data into SEER, our study is limited to patients 65 years and older, which captures the majority, but not all pancreatic adenocarcinoma patients. Also, as a claims-based database, Medicare data will fail to reflect services for which no bill was submitted.

Despite this, SEER-Medicare represents a rich source of administrative data with both disease- and treatment-specific details, and its use in the current study imparts the analysis with several strengths including its longitudinal nature, level of detail on patient demographics, and on certain elements of patients' postoperative courses, in both the inpatient and outpatient settings. To strengthen our methods internally, strict exclusion criteria were utilized to ensure that the cohort of patients represents the desired sample. Most pancreatic cancer series published represent single-institution data and are subject to publication and selection bias. External validity is enhanced with SEER-Medicare given the broad national sample of hospitals and outpatient settings providing data. This eliminates potential bias, allowing our results to be generalized to the US population.

In conclusion, our review of a large national database demonstrates that in-hospital and 30-day mortality after resection for pancreatic adenocarcinoma are similar, making comparisons between these outcomes reasonable. After a 60-day post-resection window of increased mortality, mortality risk does not decrease through 2 years, suggesting that risk of death following resection does not conform to discrete early (postoperative) and late (cancer-related) periods. Providing more uniformity in the analysis of patient mortality and extending mortality endpoints (e.g., 60-day mortality) following resection for pancreatic cancer are reasonable goals. Doing so may positively impact clinician communication with patients regarding complex surgical treatments for a devastating disease and provide further evidence in determining optimal patient selection.

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Discussant

Dr. Thomas John Howard: James, congratulations on a nice paper. I think it's important for anyone who does pancreatic surgery to read this manuscript because it gives a nice summary of patient mortality time line, not just after you are through with your operation and for 30 or 60 days following but throughout the rest of their life.

Let me ask you several questions.

1. Could you elaborate on why you used the SEER-Medicare database rather than some other administrative database to answer your questions? And was this database the best fit, given the limitations of all administrative databases?

2. You mentioned a little bit in your manuscript how we could use some of this information to pick our patients preoperatively. I will tell you, if you took all of the elderly male patients out of my practice (your identified high risk group), I wouldn't have anything to operate on. So maybe you could give us a little bit of an explanation on how we could use this to choose patients preoperatively for pancreas cancer operations.

Closing Discussant

Dr. James Edward Carroll: I'll start with the second question first. It's difficult to think of your own individual experience at a large center and apply it directly to our study, because our study is informed so much by small outlying hospitals, hospitals that have probably far higher mortality, far higher complications, even higher readmissions as documented in other manuscripts in the same database.

But I do think that if you use this data in discussions with your patients, it's fair to say that you can look at certain factors like preoperative comorbidities and inform them as to when a procedure is most appropriate.

Regarding as to why we used SEER-Medicare—it is limited by the fact that its patients are over 65. One of the stronger aspects of the database, though, is that it represents a significant portion of the pancreatic cancer population. Also, it isn't limited to in-hospital mortality, like Nationwide Inpatient Sample and NSQIP. It certainly doesn't have as many variables as NSQIP—it doesn't have 136 variables—but we believe that it's generalizable because it does have an effect on those outlying hospitals. We can speak to the small hospital experience. In fact, we can sometimes tease out data from those hospitals and perhaps create a bridge of communication between the larger hospitals, the big centers where you observe better outcomes, and those hospitals.

Discussant

Dr. Karl Y. Bilimoria (Chicago, IL): We did something similar, and I'm trying to understand why maybe we got different results. We used NSQIP, so we had a smaller sample of hospitals than you had, but we had all ages. So I'm trying to figure out why we found that 20% to 30% of complications and deaths were missed for pancreas if you only look at the in-hospital stay as compared to 30-day outcomes. Any thoughts?

Closing Discussant

Dr. James Edward Carroll: I'm not sure how to address why we don't get a certain subset of complications, except to say that the difference is somehow inherent between SEER-Medicare and NSQIP. If you could somehow take NSQIP limitations and inform them from SEER-Medicare, and take SEER-Medicare limitations and inform them from NSQIP, you'd have a pretty good, fairly powerful database.

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2010 SSAT PLENARY PRESENTATION

Modified "Liver-Sparing" Multivisceral Transplant with Preserved Native Spleen, Pancreas, and Duodenum: Technique and Long-Term Outcome

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Abstract
Background Modification of the originally described multivisceral transplant operation was introduced at our institution 17 years ago. Donor liver was spared, and native spleen along with pancreaticoduodenal complex was preserved.
Methods Thirty-six modified multivisceral grafts that include stomach, duodenum, pancreas, and intestine were given to 30 adults and six children. Leading causes of intestinal failure were pseudo-obstruction and Gardner's syndrome. Native spleen was preserved in 24 (67%) recipients along with pancreaticoduodenal complex in 18 (50%). Immunosuppression was tacrolimus-based, and recipient preconditioning was utilized in 80% of patients.
Results Patient survival was 94% at 1 year and 75% at 5 years with graft survival of 91% and 51%; respectively. With mean follow-up of 51±35 months, full nutritional autonomy was achieved in 89% of current survivors with no single example of disease recurrence. Preservation of native spleen was associated with increased survival and reduced risk of PTLD, life-threatening infections, and GVHD with no significant impact on graft loss due to rejection. Concomitant preservation of pancreaticoduodenal complex eliminated risks of biliary complications and glucose intolerance.
Conclusion Modified multivisceral transplantation with and without preservation of native spleen, pancreas, and duodenum is a valid therapeutic option for patients with diffuse gastrointestinal disorders and preserved hepatic functions.

Keywords Modified multivisceral transplantation · Splenic preservation technique · PTLD · GVHD · Gardner's syndrome · Pseudo-obstruction · Duodenopancreatectomy

Introduction

Exactly half a century ago, the multivisceral transplant procedure was born as a result of the experimental pioneer work of Starzl et al.[1] The initially described operation "mass homotransplantation of abdominal organs in dogs" was originally designed for immunologic premises with no insight for clinical application. The original procedure included total complete excentration of the extra-renal abdominal visceral organs with replacement of all except the spleen. Twenty-three years later, the same group attempted the first human multivisceral transplantation at the University of Pittsburgh with no observation beyond the grave technical difficulties.[2] Despite worldwide sporadic attempts under cyclosporine immunosuppression, the procedure was clinically feasible soon after the advent of tacrolimus in 1989.[3,4]

Before the clinical introduction of tacrolimus and based upon preclinical data, inclusion of the liver as part of a composite visceral graft was believed to be essential to achieve successful engraftment of the intestine.[5] However, the Pittsburgh initial encouraging results with isolated intestinal transplantation under tacrolimus-based immunosuppression compounded by the increasing scarcity of cadaveric liver allografts stimulated our efforts to modify the originally described multivisceral operation with sparing of the liver in patients with preserved hepatic functions.

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The multivisceral specimen is envisioned as a grape cluster with a double central stem consisting of the celiac axis and superior mesenteric artery.[6] With preservation of the relevant axial blood supply, our surgical objectives were technically feasible by separating the donor liver from the en bloc retrieved other abdominal visceral organs. With the clinical introduction of the operation in 1993, the term "modified" multivisceral transplantation was revealed for the first time to the scientific literature.[7]

With increased practicality and prolonged survival, long-term outcome analysis identified native splenectomy as a significant risk factor for development of life-threatening post-transplant lymphoproliferative disorder (PTLD).[8] Accordingly, a new technical dimension was added to the recipient operation by preserving the native spleen with the premise to reduce risk of PTLD and improve long-term outcome.[9,10] We also hypothesized that simultaneous preservation of the pancreaticoduodenal complex, in selected patients, may further improve the procedure's technical safety and augment its long-term metabolic advantages.

This report is the first to fully address the logistics and technical details of the "modified" multivisceral transplant procedure with surgical evolution of both the donor and recipient operation. Furthermore, the conservative approach of the recipient evisceration technique is described with special reference to the underlying gastrointestinal disorders. The short- and long-term outcomes were also analyzed in the context of the primary premises of sparing donor liver and native spleen along with other abdominal visceral organs.

Materials and Methods

Case Material

Graft Between May 2, 1990 and March 1, 2010, a total of 548 consecutive visceral allografts were transplanted at the University of Pittsburgh Medical Center. Of these, 121 (22%) were multivisceral allografts with en bloc inclusion of stomach, duodenum, pancreas, and intestine. The liver was part of the multivisceral allograft "full" in 85 (70%), and the remaining 36 (30%) were "modified" with exclusion of the liver. The distribution of the 36 modified multivisceral grafts over the 20-year study period is shown in Fig. 1.

All donors were deceased with a male/female ratio of 4:1 and mean age of 23±11 years (range 0.6–50). All grafts were ABO identical with recipients, and human leukocyte antigen (HLA) match was random with 22% positive T/B cell lymphocytotoxic cross-match. Allograft immune modulation with low-dose (750 cGy) ex vivo irradiation and donor bone marrow augmentation ($3–5\times10^8$ cell/kg recipient body weight) was utilized in seven (19%) allografts. Epstein–Barr virus (EBV) and cytomegalovirus (CMV) serology was positive in 88% and 47% of the donors; respectively. The cold ischemia time was 6 to 13 h with a mean of 9±2. Follow-up ranged from 3 to 120 months with a mean of 51±35.

Patient Thirty patients were adults and six were children with a mean age of 36±13 years (range 19–71) and 15±8 years (range 1.8–17), respectively. Of these, 35 were primary recipients, and the remaining patient was a prior recipient of an isolated intestinal graft that was lost due to rejection. All patients were on home parental nutrition (HPN) with no significant hepatic dysfunction. Pseudo-obstruction ($n=19$) and Gardner's syndrome ($n=10$) were the main underlying gastrointestinal disorders (Table 1). The underlying pathology of the pseudo-obstruction syndrome was hollow visceral myopathy and/or neuropathy with extensive involvement of the gastrointestinal tract including the stomach. Of the ten Gardner's syndrome patients, six had extensive desmoid tumors that involved the main mesenteric vascular pedicle, pancreas, and duodenum with failed previous attempts of curative resection or autotransplantation. The remaining four patients had massive duodenogastric adenomatosis with strong family history of adenocarcinoma and concomitant short bowel syndrome due to prior proctocolectomy with small bowel resection ($n=3$) and mesenteric infarction after gastric bypass surgery ($n=1$). Interestingly, three of the Gardner's syndrome patients were from the same family: two siblings and an uncle.

Of the remaining seven (19%) patients, two had total gastrectomy with recalcitrant Crohn's disease, three had pancreaticoduodenectomy due to traumatic and thrombotic arterial visceral occlusion, and two had extensive abdominal adhesions with gastric dysmotility after multiple abdominal surgeries including enterectomy of an isolated intestinal graft. Full details of the recipient clinical features are summarized in Table 1.

Transplantation

A good-quality allograft with a safe recipient operation is the Achilles heel of a successful transplant procedure (Fig. 2). Of utmost importance is preservation of the arterial vascular anomalies encountered with retrieval of the donor liver or retention of the recipient organ as fully described in this report.

Donor Technique

With prior verbal approval from the donor liver surgeon, it has been our practice to retrieve the celiac trunk en bloc

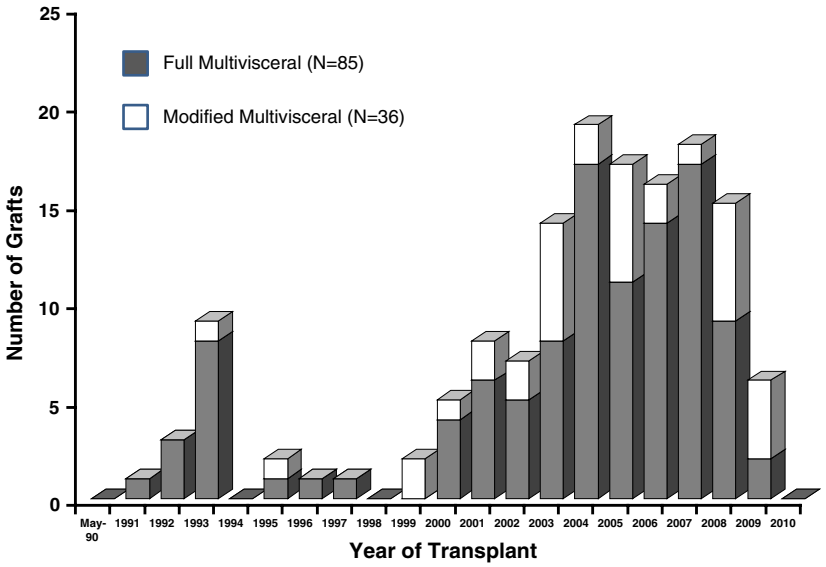

Fig. 1 The yearly distribution of the full and modified multivisceral transplant procedures over the last 20 years at the University of Pittsburgh Medical Center. Note that the first modified multivisceral transplant was performed in 1993

with the visceral organs (Fig. 3). On a few occasions, our request was denied or the procedure was aborted because of arterial vascular anomalies that could potentially compromise the quality of the isolated liver allograft. One important principle of the procedure is en bloc retrieval of the donor duodenum with the stomach and intestine to maintain continuity of the gastrointestinal tract. The pancreas, as part of the duodenopancreatic complex, must also be included to

Table 1 Clinical features of the study modified multivisceral recipients with and without preservation of the native spleen and pancreaticoduodenal complex

	Total	Without preservation	With preservation	*p* Value
No. of allografts	36	12	24	
No. of patients				
Adults	30	6	24	
Children	6	6	0	
Gender (Male/Female)	14:22	6:6	8:16	0.470
Causes of intestinal failure				0.12
Dysmotility	19	4	15	
Gardner's syndrome	10	6	4	
Other	7	2	5	
Duration of HPN (month)[a]	39±49	37±57	40±46	0.900
Prior abdominal surgeries				
Total no. (range)	1–20	1–20	2–10	
Splenectomy	2	1	1	
Total bilirubin (mg/dl)[a]	0.8±1.1	0.9±1.0	0.8±1.1	0.659
Positive T/B cell crossmatch	8 (22%)	2 (17%)	6 (25%)	0.69
Preservation solution (UW/HTK)	32/4	10/2	22/2	0.59
Preservation of native spleen	24 (67%)			
With duodenum and pancreas	18 (50%)	NA	18 (75%)	
With pancreaticoduodenectomy	6 (17%)	NA	6 (25%)	
Operative time (hour)[a]	14±3	15±3	14±3	0.304
Cold ischemia time[a]	9±2	9±2	8±2	0.114
Recipient preconditioning	29 (80%)	10 (83%)	19 (79%)	1.000
Immune modulation	7 (19%)	4 (33%)	3 (13%)	0.190
Positive EBV donor	29 (88%)	8 (67%)	21 (100%)[b]	0.006
Positive CMV donor	17 (47%)	6 (50%)	11 (46%)	0.546
Follow-up (month)[a]	51±35	65±37	44±32	0.105

HPN indicated total parenteral nutrition, *UW* University of Wisconsin, *HTK* histidine–tryptophan–ketoglutarate, *NA* not applicable, *EBV* Epstein–Barr virus, *CMV* cytomegalovirus

[a] Mean ± SD

[b] EBV serology was not available in three donors

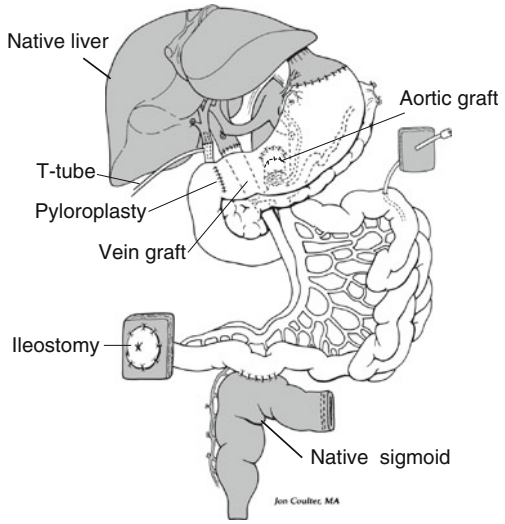

Fig. 2 Modified multivisceral transplantation. Note engraftment of the modified multivisceral graft (*unshaded organs*) after complete evisceration of the recipient left upper abdominal organs. The infrarenal aortic graft is anastomosed to the Carrel patch conduit and the interposition vein graft to the donor portal vein. With sparing of the native liver and resection of the native pancreaticoduodenal complex, the bile duct is reconstructed with a T-tube insertion. Because of inevitable organ denervation, pyloroplasty is performed for gastric drainage

maintain integrity of the axial blood supply. The three generic key phases of the operation include variable dissection of the organs with an intact donor circulation, in situ cooling by aortic infusion of the sub-diaphragmatic organs with simultaneous exsanguination, and the back-table preparation of the composite visceral allograft for transplantation. Providing there is early control of the aorta, the first phase can be terminated at any time with prompt institution of the second phase with no penalty of warm ischemia. Full details are comprehensively described elsewhere.[6,11,12]

Phase 1 With intact donor circulation, no efforts were made to modulate the graft immunologic tissue. The initial donor dissection aimed at identifying major vascular anomalies that may preclude simultaneous retrieval and utilization of both the liver and composite visceral graft for two different candidates. Because all of the significant branches that arise from the celiac axis and superior mesenteric artery and supply the liver are end arteries, anomalous branches from these sources must be retained with the hepatic graft and carefully revascularized. Therefore, the decision to proceed with visceral organ retrieval, in the presence of replaced right and/or left hepatic artery, is commonly based upon the willingness of the liver surgeon to reconstruct these vessels on the back-table with the main hepatic artery.

The in situ dissection of the visceral organs starts with mobilization of the colon, small bowel, and root of mesentery from the retroperitoneal structures. After Kocherization of the duodenum, the spleen, pancreas, and stomach are mobilized and medially rotated without compromising its blood supply. During the course of dissection, complete or partial resection of the colon is performed using a GIA stapler. The extent of the in situ hepatic hilar dissection is commonly determined by the liver surgeon.

Phase 2 The second phase of the procurement procedure starts with the in situ flushing through the aortic cannula utilizing the University of Wisconsin solution in 32 (89%) and histidine–tryptophan–ketoglutarate solution in the remaining four (11%) grafts. Concomitant in situ perfusion of the liver through a separate inferior mesenteric vein cannula is usually left up to the donor liver surgeon. The subsequent steps include: (a) completion of the en bloc dissection of the liver, stomach, pancreas, spleen, duodenum, and intestine from the diaphragm and retro-peritoneum, (b) transection of the gastrointestinal tract proximally at the abdominal esophagus and distally at the terminal ileum or descending colon, (c) transection of the vena cava above and below the liver, and (d) removal of the celiac axis and superior mesenteric artery in continuity with the descending thoracic aorta or anterior wall of the abdominal aorta. The liver graft is separated in situ or on the back-table by dissecting the hepatic hilar structures close to the superior wall of the duodenum. The bile duct is cut 5–10 mm above the duodenum to allow duct to duct reconstruction of the biliary system in recipients with pancreaticoduodenectomy. In most donors, the hepatic

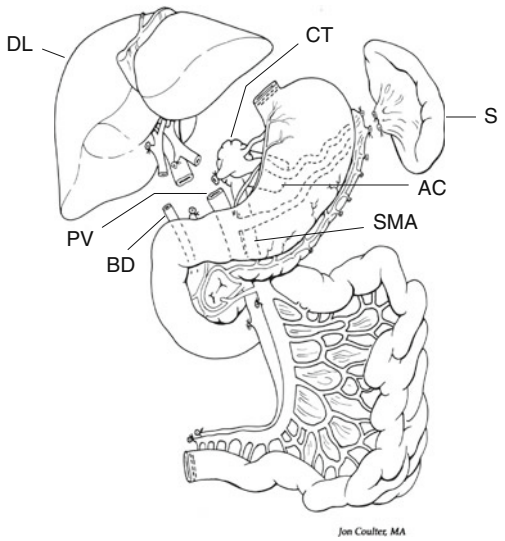

Fig. 3 "Modified" multivisceral graft with exclusion of donor liver (DL) and en bloc inclusion of stomach, duodenum, pancreas, and intestine. Splenectomy (S) was performed on the back-table and the common mouth of celiac trunk (CT) and superior mesenteric artery (SMA) was anastomosed to a segment of donor thoracic aorta as an arterial conduit (AC). The gastric blood supply was fully preserved and both portal vein (PV) and bile duct (BD) were transected 5–10 mm above superior wall of duodenum

artery is transected distal to the origin of the gastroduodenal artery or at its take off from the celiac trunk (Fig. 3). In two donors, a right replaced hepatic artery was identified and reconstructed on the back-table of the liver allograft. Finally, the portal vein is transected 5–10 mm above the confluence of the splenic and superior mesenteric veins (Fig. 3). At the end of retrieval, a large segment of the donor thoracic aorta and iliac or innominate veins are obtained for vascular reconstruction during the back-table and recipient operation.

Phase 3 The relevant steps of the back-table procedure include: (a) oversewing of the gastroesophageal stump, (b) splenectomy, and (c) placement of a thoracic aortic segment, as an arterial conduit, on the common Carrel patch of the celiac trunk and superior mesenteric artery as shown in Fig. 3. Splenectomy must be carefully performed with ligation of the vascular pedicle within the splenic hilum away from the tail of the pancreas. The arterial conduit must be of enough length and directed caudally to allow proper alignment with the infra-renal aortic graft. When the donor descending thoracic aorta is retrieved in continuity with the common mouth of the celiac trunk and superior mesenteric artery, the transected distal end of the abdominal aorta is oversewn with no need for a Carrel patch reconstruction. Detailed anatomy of the modified multivisceral graft is illustrated in Fig. 3.

Recipient Operation

The complex and lengthy operation includes: (a) removal of the diseased organs with preservation of the hepatic arterial blood supply including any major vascular anomalies, (b) establishment of the main route of arterial inflow and venous outflow to the new organs, and (c) en bloc implantation of the allograft organs with vascular, biliary, and gastrointestinal reconstruction.

With generous midline incision and left subcostal extension, recipient organs are removed en bloc or in a piece meal fashion guided by the surgical objectives of the evisceration technique and extent of the abdominal pathology. The evisceration procedure is either major including removal of the intestine, stomach, duodenum, pancreas, and spleen or conservative by retaining the spleen with or without the pancreaticoduodenal complex. The changing faces of the recipient operation are depicted in Fig. 4. With the full clinical features summarized in Table 1, both groups were similar with no significant statistical difference except for positive EBV allografts among recipients with splenic preservation.

With the major evisceration technique (Fig. 4a), the commonly utilized piece meal removal of the residual intestine, stomach, spleen, pancreas, and duodenum occurs in three steps. First, the residual small bowel and duodenum are mobilized from the retroperitoneal structures and transected at the third portion of the duodenum with high ligation and interruption of the superior mesenteric artery and vein. Second, stomach is transected proximally 5–8 cm below the gastroesophageal junction and distally beyond the pylorus after ligation of the different blood vessels close to the gastric wall with preservation of the upper terminal branch of the left gastric artery (Fig. 4). With left replaced hepatic artery, the main trunk of left gastric artery is maintained and sheared of the gastric wall. Finally, removal of the spleen, pancreas, and duodenum is accomplished after the organs are mobilized from the retroperitoneum with individual ligation and interruption of the central end of the splenic artery and vein. During the course of dissection and subsequent organ removal, great attention must be directed towards the common hepatic artery and any vascular anomalies, particularly right replaced hepatic artery with ligation and interruption of the gastroduodenal artery close to the duodenal wall. With the en bloc excision, the attached intestine, duodenum, pancreas, spleen, and stomach are removed after central ligation of the individual blood supply and transection of the gastroesophageal junction. The common bile duct is interrupted just above the superior border of the duodenum. The technique was performed in 12 patients: two were transplanted before introduction of the conservative technique and six failed the conservative approach due to extensive adhesions or desmoid tumors involving the splenic pedicle or the pancreaticoduodenal complex. The remaining four recipients were children with no attempts to apply the conservative technique.

With the splenic preserving technique including retention of the native duodenum, pancreas, and spleen, the third step is eliminated and the procedure is limited to completion enterectomy and near total gastrectomy (Fig. 4b). The retained duodenum is shortened in patients with pseudo-obstruction to avoid the potential risk of segmental dysmotility (Fig. 4b). The technique was successfully performed in a total of 18 patients: 16 with pseudo-obstruction syndrome and two had prior total gastrectomy with intestinal failure due to end-stage Crohn's disease.

The technique of splenic preservation with removal of the pancreaticoduodenal complex (Fig. 4c) starts with completion enterectomy followed by near total gastrectomy as described above. The utilized technique for the total pancreaticoduodenectomy is similar to that described with the Whipple procedure. In brief, the pancreas is transected anterior to the confluence of the portal vein and both segments with inclusion of the duodenum are removed after dissection and individual ligation of the feeding pancreatic and duodenal vessels. The procedure is accomplished in a total of six patients: two had pancreaticoduodenal fistulae due to vascular injuries and four had Gardner's syndrome with dysplastic duodenal adenomas.

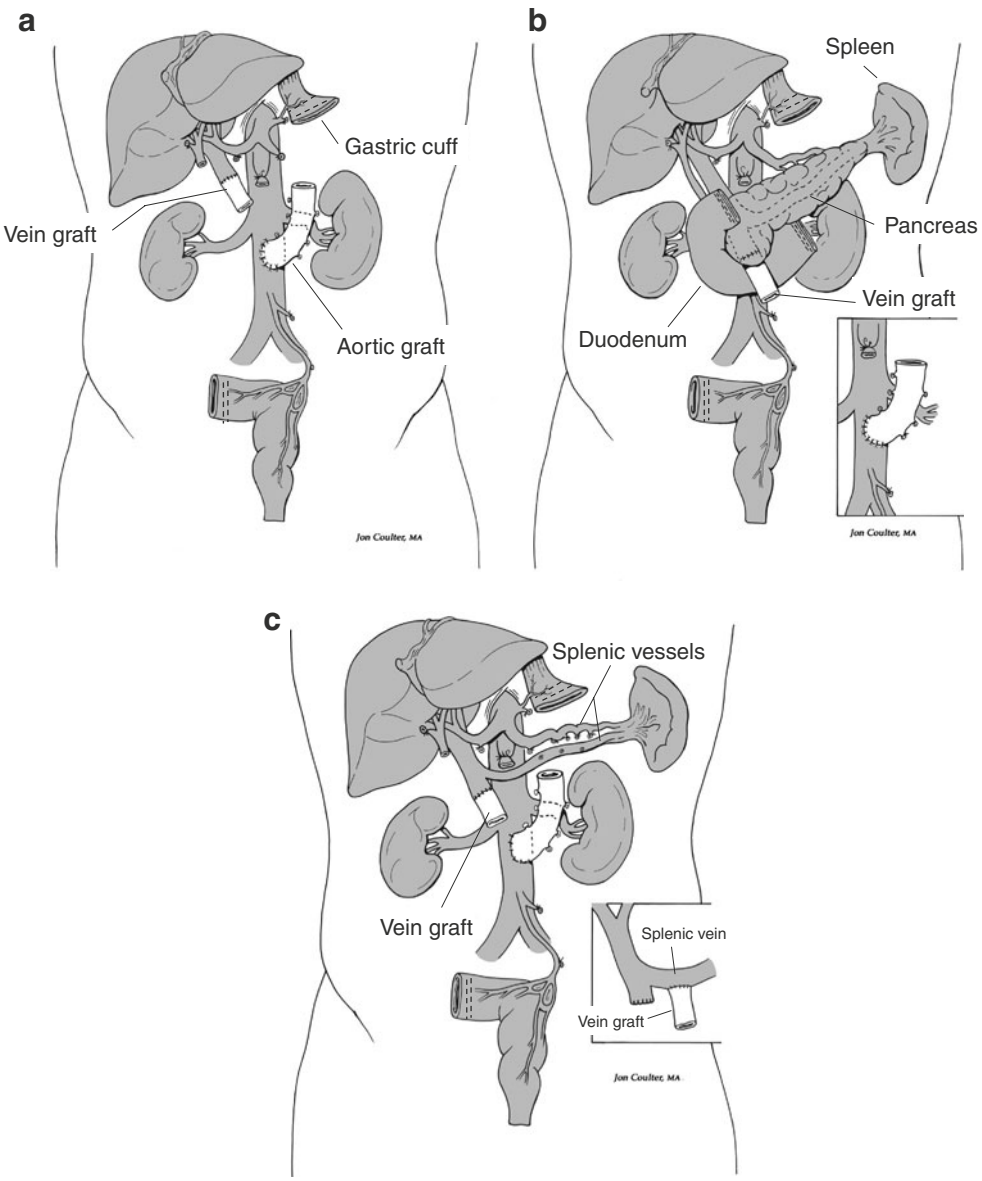

Fig. 4 The recipient operation with complete or partial removal of the native left upper abdominal organs. **a** Major evisceration with completion enterectomy and surgical excision of the native stomach, duodenum, pancreas, and spleen. **b** Preservation of the splenopancreaticoduodenal complex with completion enterectomy and near total gastrectomy. **c** Gastroenterectomy and pancreaticoduodenectomy with preservation of the splenic compartment. Note placement of an arterial conduit on the infra-renal aorta and a segment of donor vein on the portal (**a**) superior mesenteric (**b**) or splenic vein (**c**, *insert*)

Although the vascular reconstruction is similar, in principle, to that described with the original multivisceral transplant operation, a few new modifications have been introduced. Of these are early placement of an arterial and venous conduit to the recipient infrarenal aorta and portal vein or its constituent vessels; respectively (Fig. 4a–c). Such a modification avoids having to work in a confined space around the bulky visceral graft, with easier exposure and possible shortening of the warm ischemia time. It is also our recommendation to place the arterial graft prior to interruption of the splenic circulation to minimize the period of hepatic deportalization. In all cases, the arterial inflow was infrarenal (Fig. 4a–c) and the venous outflow was portal via the main portal (Fig. 4a), superior mesenteric (Fig. 4b), or splenic (Fig. 4c-insert) vein.

Biliary reconstruction by performing a duct-to-duct anastomosis (Fig. 2) is required for recipients of the major evisceration and splenic preserving pancreaticoduodenectomy techniques (Fig. 4a, c). Preservation of the native pancreaticoduodenal complex maintains continuity of the pancreaticobiliary system and gastrointestinal tract utilizing the native duodenal segment as an enteric conduit. The native and transplanted duodenums are anastomosed in a side to side (piggyback) fashion.

As shown in Fig. 2, the gastrointestinal tract is reconstructed proximally by anastomosing the anterior wall of the donor stomach to the posterior wall of the residual recipient gastric cuff or abdominal esophagus. Distally, the continuity is restored in recipients with remnant rectosigmoid segment, and a temporary vent chimney or simple

loop ileostomy is created to provide easy access for surveillance endoscopy. A pyloroplasty or pyloromyotomy of the denervated stomach is performed after reperfusion. A jejunostomy tube is inserted for immediate postoperative decompression and early feeding. In recent cases, placement of a gastrostomy tube is eliminated.

Postoperative Management

Details of recipient management including immunosuppression, immunologic monitoring, nutritional care, and infectious prophylaxis are fully described elsewhere.[12–14] Maintenance immunosuppression was tacrolimus-based for all allografts (Prograf®, Astellas Pharma, Deerfield, IL). In addition, induction therapy with cyclophosphamide or daclizumab was utilized in five patients. A minimization immunosuppressive strategy consisting of recipient pretreatment with a single 5 mg/Kg intravenous dose of rATG (Thymoglobulin, Genzyme, Cambridge, MA) or a 30-mg single infusion of alemtuzumab (Campath-1H, ILEX, Cambridge, MA) and tacrolimus monotherapy was applied to 29 (81%) patients. The distribution of patients who received the pretreatment protocol according to the evisceration technique is summarized in Table 1. Maintenance steroids were applied from the outset in all but the pretreated recipients except those who developed acute rejection or adrenal insufficiency. Anti-lymphoid preparations were used to treat steroid resistant and severe rejection episodes.

The utilized methods and criteria for diagnosing acute and chronic rejection of the transplanted organs are defined and fully described elsewhere.[15,16] The diagnosis of graft versus host disease (GVHD) was confirmed by histologic and immunocytochemical studies that allowed identification of donor leukocytes including PCR techniques, in situ hybridization using the Y-chromosome-specific probe, immunohistochemical staining of donor-specific HLA antigens, and more recently, the short tandem repeats technique.[14]

Nutritional management and evolution of protocols for prophylactic, preemptive, and active treatment of viral, bacterial, and fungal infections are fully described in recent publications.[14,17] Of particular interest is the development of the PCR assay in 1994 that allowed early detection, preemptive treatment, and serial monitoring of EBV replication in all of the study patients. Similarly, the PP-65 antigenemia test and CMV-PCR assay have been useful for early detection and treatment of viral reactivation or de novo infection. Selective gut decontamination and prophylactic systemic antimicrobial therapy were used for all donors and recipients.[12]

Statistics

With an honest broker approved by the University of Pittsburgh Institutional Review Board, the prospectively collected data (as of March 1, 2010) of all of the modified multivisceral grafts were pooled from a computerized database. Recipients were substratified according to the evisceration technique with or without preservation of the native spleen. The distribution of each subcohort over the study period is shown in Fig. 5. Continuous variables were presented as mean ± SD and categorical data as proportions. Differences in group means were tested using the standard two-sample *t* test, and differences in proportion were tested by the Pearson Chi-Square exact test.

Patient and graft survival were calculated utilizing the Kaplan–Meier method. The same method was used to calculate the cumulative risk of rejection related graft loss, PTLD, and GVHD. Group comparison was performed

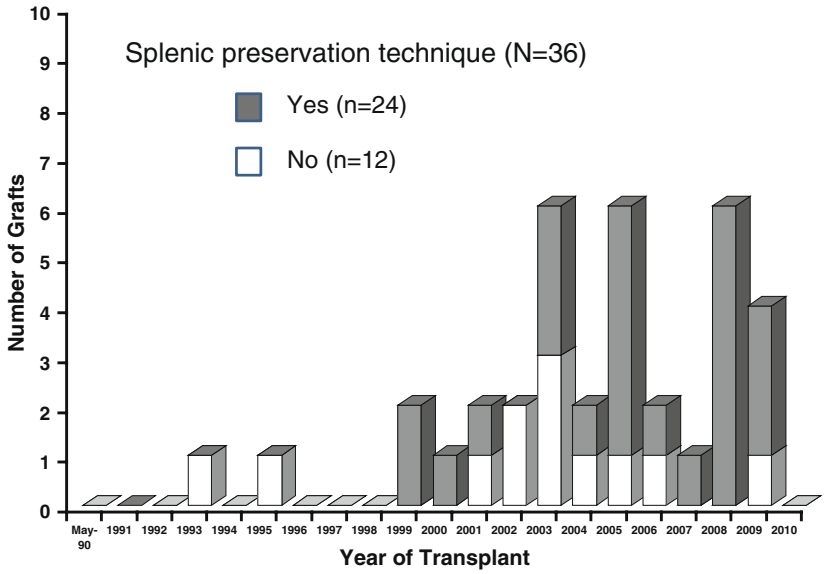

Fig. 5 The yearly distribution of the modified multivisceral grafts according to the type of the recipient operation. Note introduction of the splenic preservation techniques in 1999

using log-rank test. All analyses were performed using SPSS (SPSS, Inc., Chicago, IL).

Results

Technical and Relevant Postoperative Complications

With the major evisceration technique, none of the patients developed technical complications. Pseudoaneruysm of the Carrel patch arterial graft developed in one (6%) of the 18 recipients with preserved splenopancreaticoduodenal complex 163 days after transplantation that was successfully repaired with combined radiologic and surgical intervention. Biliary leak occurred in two of the six recipients who underwent spleen-preserving pancreaticoduodenectomy with an overall incidence of 11% among the 18 patients who required biliary reconstruction after the major evisceration and the splenic preserving pancreaticoduodenectomy. The two recipients were successfully treated with internal stenting.

Early postoperative allograft pancreatitis was observed in two (6%) recipients. Symptomatic pancreatic divisum was diagnosed early after transplantation in another two recipients that required endoscopic sphincterotomy. Interestingly, spontaneous simultaneous pancreatitis of both native and transplanted pancreas developed in one recipient 660 days after transplantation that was successfully treated with conservative measures.

Survival

With a mean follow-up of 51±35 months (range: 3–120), 27 (75%) patients are currently alive with functioning grafts. Of these, 23 are adults and four are children. The causes and time of death with special reference to the type of the recipient operation are summarized in Table 2. Interestingly, fatal infections occurred, with the intent to treat, at a higher ($p=0.6$) rate in the primary splenectomized recipients (17%) compared to those with preserved spleen (8%). In addition, one of the six patients who underwent splenectomy at the time of retransplantation with a full multivisceral graft died of overwhelming sepsis (see below and footnote of Table 2).

Retransplantation was successfully performed in a total of seven (19%) patients. In six recipients, a full multivisceral graft with replacement of the native liver was required with en bloc inclusion of the kidney in one case. Complete exenteration of the extra-renal native and transplanted abdominal visceral organs, including the spleen, was performed at the time of retransplantation. Partial retransplantation with an isolated intestinal graft was successfully performed in the remaining recipient after exfoliative allograft rejection with preferential recovery of the modified multivisceral graft. Time and causes of graft loss are summarized in Table 2.

The overall cumulative patient survival was 94% at 1 year and 73% at 5 years with a graft survival rate of 91% and 51%, respectively (Fig. 6). Comparing the primary causes of intestinal failure, pseudo-obstruction seems to have better patient (Fig. 7a) and graft (Fig. 7b) survival compared to those with Gardner's syndrome. With similar patient survival, the graft survival was better ($p=0.9$) in recipients with splenic preservation (Fig. 8).

Post-transplant Lymphoproliferative Disorder

With a total of four (11%) PTLD morbid cases, the disease was diagnosed in three of the 12 (25%) splenectomized recipients and one (4%) of the 24 who underwent splenic preservation. The cumulative risk was higher ($p=0.06$) with a 5-year rate of 30% and 4%, respectively (Fig. 9). Such a difference was observed despite the significantly ($p=0.006$) higher percentage of EBV-positive allografts given to recipients with splenic preservation. Interestingly, none of the PTLD cases in either group received donor bone marrow infusion or allograft irradiation.

The disease was polymorphic and EBV-driven in all recipients with primary involvement of the intestinal allograft. Interestingly, the malignancy was proven to be of donor origin in two cases with a single example in each group. Recipients were successfully treated with minimization of immunosuppression and aggressive antiviral therapy in all but one of the splenectomized pediatric recipients who died of the disease (Table 2).

Allograft Rejection

Within the first 90 postoperative days, a total of 22 (61%) recipients experienced acute intestinal allograft rejection: seven (58%) with the major evisceration technique and 15 (63%) with the splenic preservation procedure. The difference was not statistically significant with a p value of 0.139. Severe and steroid-resistant episodes were documented in one (14%) and nine (60%) of the rejected allografts, respectively ($p=0.057$). Interestingly, one of these allografts was rescued with isolated replacement of the intestinal component after full recovery of the allograft stomach, duodenum, and pancreas.

Acute rejection of the pancreatic allograft was clinically diagnosed in a total of six (17%) recipients with gastric allograft rejection in another four (11%). All recipients were among the splenic preservation group, and the rejection episodes occurred concomitant with or independent of the intestinal rejection episodes. All of the instances were successfully treated with steroid therapy.

Table 2 Time and cause of patient death and graft loss among the modified multivisceral recipients without and with splenic preservation including the pancreaticoduodenal complex

Graft/recipient	Age group	Date of transplant	Splenic preservation	Time (days)[a]	Cause
Patient death					
1	Pediatric	3/21/93	No	675	Post-transplant lymphoproliferative disorder
2	Pediatric	5/03/95	No	3,243	Aspiration pneumonia
3	Adult	12/09/99	Yes	1,507	Intracranial bleed-chronic rejection
4	Adult	1/21/03	No	238	Graft versus host disease-cerebral amoeba
5	Adult	8/04/03	Yes	951	Aspergillosis-chronic rejection
6	Adult	10/11/03	Yes	1,783	Aspergillosis
7	Adult	6/06/05	Yes	1,275	Aortic graft thrombosis-chronic rejection
8	Adult	7/05/06	Yes	123	Acute rejection-acute respiratory failure
Retransplantation					
1	Adult	7/02/99	Yes	2,042	Chronic rejection[b]
2	Adult	4/16/02	No	349	Aortic graft thrombosis-chronic rejection
3	Pediatric	10/16/04	No	1,125	Aortic graft thrombosis-chronic rejection
4	Adult	1/14/05	Yes	1,169	Acute rejection of intestinal component
5	Adult	4/05/05	No	689	Chronic rejection
6	Adult	8/31/05	Yes	464	Chronic rejection
7	Adult	10/12/05	Yes	566	Chronic rejection

[a] Time from transplant to death or retransplant

[b] Patient died 68 days after a full multivisceral retransplantation from acute respiratory failure and overwhelming sepsis

Chronic intestinal allograft rejection was histologically diagnosed in a total of 10 (28%) allografts: four (33%) among the splenectomized recipients and six (25%) in those with the splenic preserving technique (Table 2). Of these, six underwent retransplantation with a liver-contained multivisceral allograft and three died awaiting retransplantation. The remaining recipient is currently recovering from limited distal ileal resection. Simultaneous chronic rejection of both the stomach and pancreas was histologically documented in all of the explanted specimens.

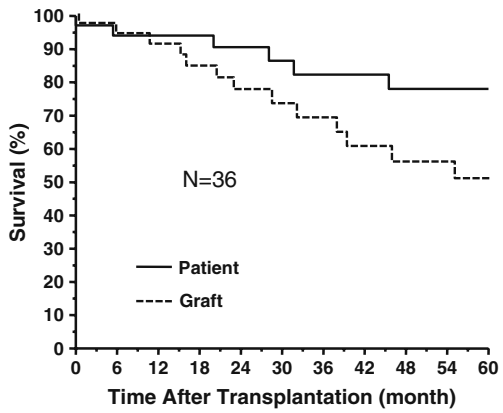

Fig. 6 The cumulative Kaplan–Meier survival curves for the 36 modified multivisceral recipients and primary transplanted allografts. Note the difference between the two curves which reflects the rescue benefits of retransplantation

The overall cumulative risk of graft loss due to both acute and chronic rejection was 4% at 1 year and 49% at 5 years with splenic preservation. With no significant (p= 0.6) difference between both cohorts, the splenectomized recipients experienced a lower cumulative risk with 12% and 38%, respectively (Fig. 10).

Graft Versus Host Disease

Graft versus host disease was clinically suspected and histologically diagnosed with molecular evidence of peripheral blood macrochimerism in three (25%) of the recipients who underwent splenectomy with the major evisceration technique. None of these patients received donor bone augmentation or allograft irradiation. There was no single (0%) example of the disease among the 24 patients with the splenic preserving procedure.

The skin was the primary site and the diagnosis was made 13 to 15 days after transplantation. All patients were treated with augmented steroid therapy that was successful in two. The third recipient died of Acanthamoeba of the brain during plasmapheresis for chronic GVHD (Table 2).

Diabetes Mellitus

None of the patients with preserved native pancreaticoduodenal complex developed biochemical evidence of disturbed blood sugar metabolism. Of the 18 patients with

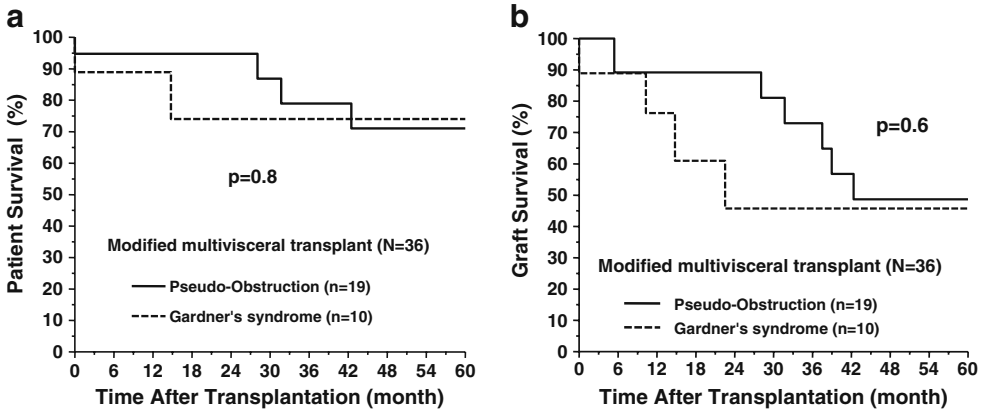

Fig. 7 Patient (**a**) and primary graft (**b**) survival according to the underlying gastrointestinal disorder. Note better survival outcome with pseudo-obstruction up to 42 months after transplantation

native pancreaticoduodenectomy, only two (11%) developed diabetes which occurred within the first year after transplantation. One patient is requiring full insulin therapy and the other is receiving glyburide, an oral hypoglycemic agent, at 10 mg three times a day with satisfactory blood sugar control. The first recipient is an adult who received a pediatric donor, and the second has become morbidly obese after transplantation.

Disease Recurrence

Post-transplant allograft dysmotility particularly of the stomach and duodenum was clinically observed in three (17%) recipients who retained their native duodenopancreatic complex. Dumping syndrome was also observed in another recipient that was successfully treated with conservative medical management. All of these patients were transplanted for pseudo-obstruction, and the postoperative dysmotility improved by the end of the first year except in two patients. One recipient underwent gastrojejunostomy and the other continued to receive intermittent HPN therapy. Interestingly, the PCR studies on the peripheral blood of these and all other recipients who were transplanted for motility disorders showed no evidence of JC viral infection. None of the Gardner's syndrome patients developed recurrent desmoid or any new neoplastic disorders in their remaining native gastric cuff or colorectum.

Rehabilitation

As of March 1, 2010, 27 of the 36 recipients were alive with their primary (n=21) or secondary (n=6) allograft. All of these recipients achieved full nutrition autonomy except three due to chronic graft dysmotility (n=1), recent ileal resection due to chronic rejection (n=1), and early transplantation (n=1).

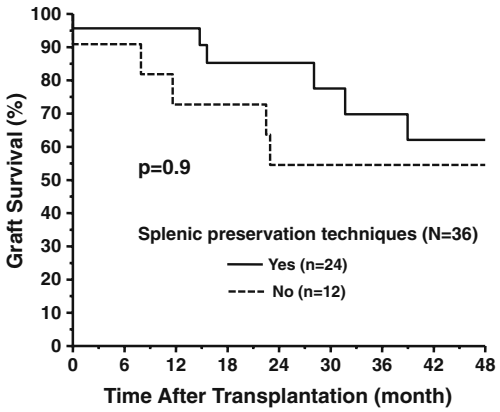

Fig. 8 Kaplan–Meier graft survival according to the type of the recipient operation. The *curves* are showing better short- and long-term survival with the splenic preservation techniques

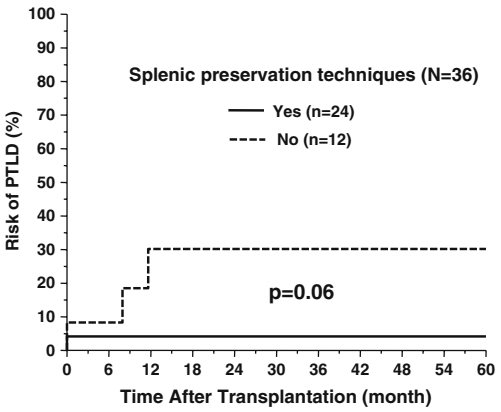

Fig. 9 Cumulative risk of post-transplant lymphoproliferative disorders (PTLD) in patients with and without preservation of the native spleen. Note the lower risk of PTLD with splenic preservation and absence of disease development beyond the very early postoperative period. The single PTLD that occurred with splenic preservation was diagnosed on a single random endoscopic mucosal biopsy with no clinical symptoms or any further documentations close to the time of diagnosis or thereafter

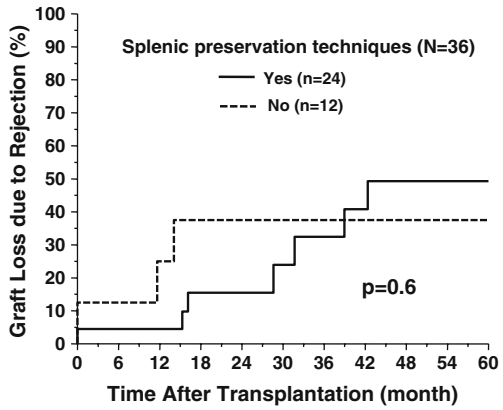

Fig. 10 Cumulative risk of graft loss due to rejection according to the type of the recipient operation. Note *crossing of the curves* with higher long-term cumulative risk of graft loss due to rejection, mostly chronic, among recipients with the splenic preserving techniques

Discussion

Over the last two decades, different innovative surgical techniques have been introduced to the field of intestinal and multivisceral transplantation to increase practicality and improve long-term outcome.[8,18,19] The technical feasibility of these surgical objectives is primarily due to better understanding with proper utilization of the anatomic axial blood supply of the different abdominal visceral organs. The described herein modifications of both the donor and recipient operation highlights the evolution of the procedure reflecting the innovative techniques introduced by the same surgeon (senior author) over the last 20 years. The technical details, applicability, and long-term outcome of these modifications in the context of the underlying gastrointestinal disease and original premises have been fully addressed.

Despite current disputes, the multivisceral graft originally described by Starzl et al. was defined by en bloc inclusion of the stomach, duodenum, pancreas, intestine, and liver.[2,10,20] By sparing the liver, we introduced the nomenclature "modified" multivisceral graft to the scientific literature after performing the first successful case in 1993.[7,12] The initial efforts have stemmed primarily from the early encouraging results with isolated intestinal transplantation under the tacrolimus-based immunosuppression and further fueled by the increasing demand for isolated cadaveric liver grafts to rescue patients with end-stage hepatic failure. This report fully describes the technical details of the donor operation and back-table procedure with simultaneous separate retrieval of the liver and the en bloc modified multivisceral graft.

With preserved hepatic functions and in the absence of portal hypertension, the modified multivisceral graft can be safely offered to patients with diffuse gastrointestinal disorders that primarily involve the hollow viscera including the stomach, duodenum, and intestine. Of these are patients with pseudo-obstruction and Gardner's syndrome. En bloc inclusion of the pancreas with the visceral graft, despite preserved structural and functional integrity of the native gland, is often necessary to maintain integrity of the axial blood supply to the contained organs particularly the duodenum. The overall predominance of adults in this study may reflect more vulnerability of the pediatric liver to HPN and/or underlying gut disorder with the development of liver failure and subsequent need for spontaneous hepatic replacement as part of a full multivisceral graft.

Controversies still exist concerning the type of visceral allograft that should be given to patients with pseudo-obstruction. After our initial experience in a few patients with poor functional outcome after receiving an isolated intestine with or without subtotal gastric resection, it has been our practice to transplant these patients with a modified multivisceral graft with replacement of the diseased stomach. To the best of our knowledge, there has been no outcome data in the current scientific literature reflecting the claim of other transplant centers of offering the pseudo-obstruction syndrome patients intestine-only allograft with concomitant gastric resection.

Modification of the recipient operation with conservative surgical resections limited to the diseased organs was applied for the first time in 1999 after the proven detrimental effect of native splenectomy on risk of PTLD and survival outcome.[8,9] With the primary premise of reducing risk of PTLD, simultaneous preservation of the pancreaticoduodenal complex carries additional technical and metabolic advantages to the expected immunologic privileges of the preserved spleen.

The conservative techniques of the recipient operation seem to be more applicable to the pseudo-obstruction patients than those with Gardner's syndrome. In this report, the procedure was durable in 79% of the pseudo-obstruction and only 40% of the Gardner's syndrome patients. The limited applicability of the procedure in the Gardner's syndrome patients is commonly due to delayed referral, after exhaustion of all conventional medical and surgical options, with subsequent involvement of the splenic hilum and pancreaticoduodenal complex with desmoid tumors. In addition, the presence of extensive duodenal adenomatosis dictates the need for pancreaticoduodenectomy with possible splenic preservation. Regardless of the primary disease, prior splenectomy does not preclude preservation of the pancreaticoduodenal complex. Nonetheless, the described herein conservative techniques are not warranted in patients with portomesenteric and splenic venous thrombosis and those with duodenopancreatic malignancy.

Preservation of the native or donor spleen has been the center of attention in recent years.[9,10,21,22] The presented herein data proves our initial premise by confirming the protective effect of our innovative techniques of preserving the native spleen on risk of PTLD. The study has also revealed

other significant immunologic advantages including protection against GVHD and life-threatening infections without significant increase in the acute and chronic risk of host versus graft reaction. On the contrary, preservation of the donor spleen, as part of the multivisceral graft that has been recently advocated by the Miami group, was associated with increased risk of GVHD and other serious hematologic disorders.[21,22] The documented herein therapeutic advantages of preserving the native spleen could be partially explained by a favorable net state of competent immune system, immune surveillance, and T/B cell repertoire. On the other hand, the unwanted effects of the transplanted spleen is possibly the result of creating a state of immune imbalance with increased number of harmful donor lymphocytes in a milieu of suppressed recipient immune system. Further experimental and immunologic studies, however, are required to properly dissect the exact underlying mechanisms of these clinical observations.

The concomitant preservation of the native pancreaticoduodenal complex has several technical and metabolic advantages. Of these are elimination of the need for biliary reconstruction and augmentation of the islet cell mass. As shown in this study, none of the recipients with preserved pancreaticoduodenal complex experienced primary biliary complications or post-transplant diabetes. It remains to be seen if these recipients with double pancreaticoduodenal complex will continue to maintain these metabolic benefits or experience organ specific disorders with further long-term follow-up.

In conclusion, modified multivisceral transplantation is a valuable therapeutic option for patients with diffuse gastrointestinal diseases and preserved hepatic functions. The concomitant preservation of the native spleen along with the pancreaticoduodenal complex further improves the therapeutic efficacy of this unique and complex procedure due to the associated technical, metabolic, and immunologic advantages. Such a modification may be of superior therapeutic benefits for the pediatric population because of the expected technical challenges and inborn naïve immune system.

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Discussant

DR. JEAN-NICOLAS VAUTHEY (Houston, TX): This is an impressive and well presented series, representing the state of the art in multivisceral transplantation. The data reflect a more economical

approach over the years in visceral transplantation and suggest a benefit in the preservation of the spleen. Although the analysis is limited by the small numbers, there seem to be less GVHD and less post-transplantation lymphoproliferative disorders, and this occurs without an increase in rejection.

I have two questions for you.

The first is regarding the indication for Gardner's syndrome. I think this is a controversial indication. There is only a small subset of patients with Gardner's syndrome that truly benefits from transplantation. We have observed and not resected many patients with desmoid tumors, and we are also using an economical approach in terms of oncologic procedures in these patients. So when and why would you transplant these patients? The second question is regarding the mechanism underlying the protective effect of the spleen and the reason for the lower rate of GVHD and post-transplant lymphoproliferative disorders. What is the pathophysiology underlying this protective effect?

Discussant

DR. RUY CRUZ, JR.: Thank you Dr. Vauthey for agreeing to discuss our manuscript, and we greatly appreciate your nice comment. Your first question is a valid one reflecting, similar to other organ transplantation, the evolution of the indication for our described herein new technique. With being the second common indication, the procedure is utilized as the ultimate rescue therapy for patients with extensive desmoid tumors that could not be resected without evisceration of the native left upper abdominal organs. In a subset of patients, the coexistence of short gut syndrome with irreversible intestinal failure precluded a conservative surgical resection of high-grade duodenal adenomas without worsening of the intestinal failure. Before referral, all of the ten recipients underwent comprehensive medical and surgical management including chemotherapy, irradiation, and multiple abdominal explorations without successful outcome. Most of these patients underwent a final surgical exploration at our institution to assess resectability with the aim for conservative surgical treatment including autotransplantation. Such a conservative approach continued to be adopted with allotransplantation and the native spleen was preserved in 67% of these unique patients.

Your second question concerning the protective effect of the preserved native spleen on post-transplant lymphoproliferative disorders (PTLD) and graft versus host disease (GVHD) is a very interesting one. As we all know, the spleen is an important immunologic organ that we all need. The results did not surprise us and our academic interest trying to dissect the underlying mechanism is currently under investigation. Our hypothetical explanation is a protective immune surveillance effect and a favorable net balance state between the recipient and donor immune complex.

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2010 SSAT PLENARY PRESENTATION

Patients Admitted with Acute Abdominal Conditions are at High Risk for Venous Thromboembolism but Often Fail to Receive Adequate Prophylaxis

Emily A. Pearsall · Ujash Sheth · Darlene S. Fenech · Margaret E. McKenzie · J. Charles Victor · Robin S. McLeod

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Abstract
Introduction The aim was to determine the frequency with which thromboprophylaxis is prescribed, factors predicting its prescription, and the frequency of symptomatic venous thromboembolism in patients admitted with acute abdominal conditions.
Methods Charts of patients admitted with acute abdominal conditions that did not have surgery for at least 24 h following admission were audited to identify if thromboprophylaxis was prescribed, if it was prescribed appropriately, factors affecting its prescription, and the rate of symptomatic venous thromboembolism.
Results Of 350 patients (176 females, mean age 64.9±18.6), 194 (55.4%) were admitted for bowel obstruction, 113 (32.3%) for biliary conditions, 14 (4.0%) for diverticulitis, 8 (2.3%) for pancreatitis, and 21 (6.0%) for other conditions. One hundred forty-two (40.6%) underwent surgery. Two hundred fifty-two (72.0%, 95% CI 67.3–76.7%) received thromboprophylaxis although only 199 (56.9%, 95% CI 51.7–62.1%) received adequate thromboprophylaxis. Hospital site and having surgery were associated with prescription of thromboprophylaxis. Twelve patients (3.4%, 95% CI 1.5–4.3%) developed symptomatic venous thromboembolism (nine deep venous thrombosis, three pulmonary embolism).

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Conclusions Despite patients admitted with acute abdominal conditions being at high risk for development of symptomatic venous thromboembolism, many do not receive adequate thromboprophylaxis. Further work is required to decrease this gap in care.

Keywords Thromboprophylaxis · VTE risk · Surgery · Knowledge transfer

Introduction

Pulmonary embolism is the most frequent preventable cause of death in both surgical and medically ill hospitalized patients, accounting for approximately 10% of in-hospital deaths.[1–5] Approximately 75% of these thromboembolic-related deaths occur in non-surgical patients.[1–5] On surgical wards, patients with acute diverticulitis, pancreatitis, small and large bowel obstructions, intra-abdominal abscesses or phlegmons secondary to appendicitis, inflammatory bowel disease (IBD), and acute biliary tract disease including cholecystitis and cholangitis are frequently treated non-operatively or are observed initially before undergoing emergent or urgent surgery. These patients appear to be a high risk group of patients because of their disease processes and associated comorbidities.

There is Level I evidence supporting the use of prophylaxis in patients admitted emergently with acute medical conditions.[5] In a recent meta-analysis, Mismetti et al. reported that the risk of symptomatic VTE was reduced by approximately 50% in this cohort of patients.[5] While there are no trials which have specifically included patients admitted to surgical wards, many surgical patients are admitted emergently with similar conditions and comorbidities as those admitted acutely to medical wards, and thus likely, the results of these trials are generalizable to patients admitted to surgical wards.

While there is now great awareness about the importance of prescribing thromboprophylaxis to patients having elective surgery, there appears to be less awareness of the need for prophylaxis in patients admitted emergently to surgical wards. Thus, the primary objective of the study was to determine the proportion of patients admitted to surgical wards with acute abdominal conditions who were treated non-operatively for at least the first 24 h after admission and who received adequate thromboprophylaxis at the seven University of Toronto adult teaching hospitals. The second objective was to assess factors predicting prescription of thromboprophylaxis. Third, the proportion of patients who developed symptomatic VTE in patients was documented.

Methods

Patients

The charts of patients who were admitted to surgical wards with acute abdominal conditions and were treated non-operatively for at least 24 h following admission were audited at seven adult teaching hospitals at the University of Toronto (Mount Sinai Hospital, St. Joseph's Health Centre, St. Michael's Hospital, Sunnybrook Health Sciences Centre, Toronto East General Hospital, Toronto General Hospital, Toronto Western Hospital). The Medical Records Department at each site generated a list of patients based on predetermined diagnostic codes (Table 1). Consecutive charts of patients fitting these criteria who were admitted before May 2009 were audited until 50 charts, which fit the inclusion criteria at each site, were included.

Demographic information as well as information on risk factors for VTE, diagnosis, and operative procedure was collected. In addition, details regarding thromboprophylaxis and whether a patient developed a symptomatic VTE were recorded.

Data extraction forms were developed to collect information in order to ascertain whether thromboprophylaxis was administered appropriately in accordance with previously published guidelines. They were pilot tested. The data were extracted from the charts using information from operative reports, pre-admission assessments, clinic notes, doctors'

Table 1 ICD-10 Codes used to identify patients

Condition	Codes
Bowel obstruction	K56.5, K56.6, K91.3, K56.3, K56.0, K56.2
Acute cholecystitis	K81.0, K80.00, K80.01, K80.40, K80.41
Cholangitis	K83.0, K80.30, K80.31, K80.40, K80.41
Biliary colic	K80.50, K80.51
Acute diverticulitis	K57.0, K57.2, K57.4, K57.4, K57.8
Pancreatitis	K85.0, K85.1, K85.2, K85.3, K85.8, K85.9, K86.0, K86.1, B25.2

orders, and discharge notes by a medical student (US) and reviewed by one of the senior authors (RM). All data were entered into an Access database.

Outcomes

Patients were considered to have received thromboprophylaxis if they received oral prophylaxis (coumadin), low molecular weight heparin (LMWH), or low dose unfractionated heparin (LDUH) subcutaneously or intravenously at any time during admission. Patients were considered to have received appropriate thromboprophylaxis if the agent was ordered at the correct dose on admission and continued until discharge.

The diagnosis of symptomatic VTE was based on documentation in the chart. In all cases, there was either a diagnostic test which confirmed a pulmonary embolism or deep venous thrombosis or the patient had received a course of therapeutic anticoagulation.

Sample Size

It was estimated that appropriate thromboprophylaxis would be administered in approximately 40–70% of patients. With a sample size of 350 patients, we could be 95% certain that the true rate would be within 5% of the observed rate. Furthermore, in order to assess factors predictive of patients receiving thromboprophylaxis, assuming a baseline event rate of 50%, 350 participants would provide 80% power to identify an odds ratio of 1.85 as statistically significant at alpha=0.05 assuming that there were seven binary covariates in the model, and the average odds ratio of covariates was approximately 1.25.

Data Analysis

All data are presented as proportions or means and standard deviation. Student's *t* test was used to compare differences in means and chi-square test to test for differences in proportions. To determine which factors impact on the likelihood of whether patients received thromboprophylaxis, the following variables were included in logistic regression models of receipt of thromboprophylaxis: age, gender, hospital, diagnosis, whether the patient had surgery, IBD, cancer, and history of VTE. Body mass index (BMI) was not included in the model because these data were only available in 99 (28.3%) patients. None of the patients were pregnant or had protein C deficiency so neither of these were included despite them being risk factors for the development of VTE.

The study was approved by the Research Ethics Board at all hospitals.

Results

The demographic and clinical information of the 350 patients included in the audit is shown in Table 2. One hundred ninety-four (55.4%) patients were admitted for bowel obstruction (large bowel obstruction, small bowel obstruction, or volvulus), 113 (32.3%) for biliary conditions (acute cholecystitis, cholangitis, or biliary colic), 14 (4.0%) for acute diverticulitis, 8 (2.3%) for pancreatitis, and 21 (6.0%) for other conditions. Eighty (22.9%) patients had cancer present at the time of admission while 61 (17.4%) had a history of cancer. Twenty-three (6.6%) patients had inflammatory bowel disease. Fourteen (4.0%) had a history of VTE.

One hundred forty-two (40.6%) patients underwent surgery (mean time 5.4 days, ±5.3, range 1 to 31 following admission). Surgical procedures included laparotomy and lysis of adhesions or creation of stoma (48), cholecystectomy (38), large bowel resection (21), small bowel resection or bypass (14), ileocolic resection (10), colostomy or ileostomy only (8), appendectomy (1), gastric procedure (1), and inguinal hernia repair (1).

Administration of Thromboprophylaxis

A total of 252 (72.0%, 95% CI 67.3–76.7%) patients received some type of thromboprophylaxis. In 27 of these patients, thromboprophylaxis was begun after admission (mean time 8.2±9.4 days after admission, range 1–38). In the other 225 patients, thromboprophylaxis was started on admission but in 20 patients, thromboprophylaxis was

Table 2 Baseline characteristics

Age (mean)	64.9, ±18.6
BMI (mean)	27.04, ±5.9
Gender (*n*/%)	
Male	174 (49.7%)
Female	176 (51.3%)
Diagnosis (*n*/%)	
Bowel obstruction	194 (55.4%)
Biliary tract	113 (32.3%)
Diverticulitis	14 (4.0%)
Pancreatitis	8 (2.3%)
Other	21 (6.0%)
Risk factors (*n*/%)	
Inflammatory bowel disease	23 (6.6%)
Immobility prior to admission	4 (1.1%)
Cancer	80 (22.9%)
Age ≥75	112 (32.0%)
Pregnancy	0 (0%)
Protein C deficiency	0 (0%)

discontinued before discharge and one patient received only one dose of unfractionated heparin and five received LDUH once daily. Therefore, in total, 199 (56.9%, 95% CI 51.7–62.1%) patients received appropriate thromboprophylaxis.

One hundred sixty-eight (66.7%) patients received LDUH while 66 (26.2%) received LMWH. Eighteen patients (7.1%) received other types of prophylaxis which included more than one type of heparin (11), coumadin only (4), therapeutic intravenous heparin (2), and danaparoid (1). Of the 168 patients who received LDUH, 128 received it twice daily, 23 received it three times daily while one patient received it once daily, and 16 patients received one dose only. Of the patients who received LMWH, 26 received enoxaparine, 38 received dalteparin, and 2 received tinzaparin.

There were 142 (40.6%) patients who underwent surgery after admission of whom 114 (80.3%) received some type of prophylaxis. However, prophylaxis was considered to be appropriate in only 84 (59.2%) of the patients who had surgery. Seven other patients received prophylaxis after admission but prior to undergoing surgery (mean time 7.4±5.5 days after admission, range 1 to 16 days).

Factors Affecting Prescription of Prophylaxis

Eight factors were included in a model to assess factors predictive of patients receiving any thromboprophylaxis as well as appropriate thromboprophylaxis. These included gender, age, diagnosis, IBD/no IBD, cancer/no cancer, history of VTE, surgery/no surgery and hospital (Tables 3 and 4). In the best performing hospitals, 42 patients (84.0%) received prophylaxis whereas at the two lowest performing hospitals, the rate of thromboprophylaxis administration was significantly lower (62.0%, OR 0.26, 95% CI 0.1, 0.7, p=0.008 and 52.0%, OR 0.21, 95% CI 0.08, 0.56, p= 0.002). As well, patients having surgery were significantly more likely to receive thromboprophylaxis (80.3% vs 66.3%, OR 2.08, 1.11, 3.89, p=0.022; Table 3).

With regards to whether patients received appropriate thromboprophylaxis, only hospital site was a significant factor: 37 (74.0%) of patients at the best performing hospital received appropriate prophylaxis whereas three hospitals had significantly poorer rates of administration (50.0%, OR 0.36, 95% CI 0.15, 0.87, p=0.22; 56.0%, OR 0.42, 95% CI 0.17, 1.00 and 40.0%, OR 0.26, 0.11,0.64, p=0.003). There was no difference in the rate of appropriate prophylaxis

Table 3 Factors predicting administration of any thromboprophylaxis

	Yes	Adjusted odds ratio (95% CI)	p
Male	122/174 (70.1%)	1.00 (Ref)	0.934
Female	130/176 (73.9%)	1.02 (0.61, 1.71)	
Age <75	171/238 (71.8%)	1.00 (Ref)	0.887
Age ≥75	81/112 (72.3%)	1.04 (0.59, 1.84)	
Diagnosis			
Bowel obstruction	146/194 (75.3%)	1.00 (Ref)	
Biliary tract	76/113 (67.3%)	0.74 (0.41, 1.33)	0.317
Diverticulitis	8/14 (57.1%)	0.4 (0.11, 1.38)	0.145
Pancreatitis	7/8 (87.5%)	1.73 (0.19, 16.14)	0.629
Other	15/21 (71.4%)	0.88 (0.28, 2.79)	0.828
No inflammatory bowel disease	237/327 (72.5%)	1.00 (Ref)	0.218
Inflammatory bowel disease	15/23 (65.2%)	0.51 (0.18, 1.48)	
No cancer	191/270 (70.7%)	1.00 (Ref)	0.812
Cancer	61/80 (76.3%)	1.08 (0.56, 2.11)	
History of VTE[a]	14/14 (100.0%)	–	–
No history of VTE	238/336 (70.8%)		
No surgery performed	138/208 (66.3%)	1.00 (Ref)	0.022
Surgery performed	114/142 (80.3%)	2.08 (1.11, 3.89)	
Hospital			
A	42/50 (84.0%)	1.00 (Ref)	
B	42/50 (84.0%)	1.04 (0.35, 3.12)	0.943
C	41/50 (82.0%)	0.83 (0.24, 2.88)	0.769
D	37/50 (74.0%)	0.57 (0.21, 1.59)	0.286
E	33/50 (66.0%)	0.4 (0.15, 1.07)	0.067
F	31/50 (62.0%)	0.26 (0.1, 0.7)	0.008
G	26/50 (52.0%)	0.21 (0.08, 0.56)	0.002

[a] History of VTE was omitted from the regression model due to small cell sizes (i.e., 0% of those with a history of VTE were administered thromboprophylaxis)

Table 4 Factors predicting appropriate administration of thromboprophylaxis

	Yes	Odds ratio (95% CI)	*p*
Male	98/174 (56.3%)	1.00 (Ref)	0.747
Female	101/176 (57.4%)	0.93 (0.59, 1.46)	
Age <75	135/238 (56.7%)	1.00 (Ref)	2.0
Age ≥75	64/112 (57.1%)	0.9 (0.54, 1.49)	0.68
Diagnosis			
Bowel Obstruction	115/194 (59.3%)	1.00 (Ref)	
Biliary Tract	60/113 (53.1%)	0.61 (0.36, 1.05)	0.075
Diverticulitis	7/14 (50.0%)	0.58 (0.19, 1.84)	0.358
Pancreatitis	6/8 (75.0%)	1.31 (0.23, 7.41)	0.759
Other	11/21 (52.4%)	0.79 (0.29, 2.16)	0.651
No Inflammatory Bowel Disease	189/327 (57.8%)	1.00 (Ref)	0.193
Inflammatory Bowel Disease	10/23 (43.5%)	0.53 (0.21, 1.38)	
No Cancer	159/270 (58.9%)	1.00 (Ref)	0.052
Cancer	40/80 (50.0%)	0.57 (0.32, 1.00)	
History of VTE[a]	187/336 (55.7%)	–	–
No history of VTE	12/14 (85.7%)		
No surgery performed	115/208 (55.3%)	1.00 (Ref)	0.265
Surgery performed	84/142 (59.2%)	1.36 (0.79, 2.35)	
Hospital			
A	37/50 (74.0%)	1.00 (Ref)	
B	34/50 (68.0%)	0.84 (0.34, 2.05)	0.701
C	25/50 (50.0%)	0.36 (0.14, 0.96)	0.040
D	30/50 (60.0%)	0.62 (0.26, 1.51)	0.293
E	25/50 (50.0%)	0.36 (0.15, 0.87)	0.022
F	28/50 (56.0%)	0.42 (0.17, 1.00)	0.050
G	20/50 (40.0%)	0.26 (0.11, 0.64)	0.003

[a] History of VTE was omitted from the regression model due to small cell sizes

received by patients undergoing surgery versus those who did not (59.2% vs. 55.3%, OR=1.36, 95% CI 0.79–2.35, p=0.265). For both analyses, other factors were not predictive of patients receiving thromboprophylaxis.

Development of Symptomatic VTE

Twelve patients (3.4%, 95% CI 1.5–5.3%) developed symptomatic VTE: three suffered a pulmonary embolism while nine suffered a deep venous thrombosis. The mean time to development of a VTE was 14.1±14.8 days (range 1 to 49) after admission. Two patients (16.7%) had a prior history of VTE. Seven (58.3%) patients were admitted with a bowel obstruction and two (16.7%) with acute cholecystitis or cholangitis. Five (41.7%) patients had cancer and another three (25.0%) had IBD. Six (50.0%) underwent surgery on this admission. Although 11 patients had received thromboprophylaxis, only seven (58.3%) patients received appropriate prophylaxis (LDUH in seven, LMWH in three, both LDUH and LMWH in one). One (8.3%) patient in this group died of acute renal failure, sepsis, and multi-organ failure.

Overall, 6 of the 142 patients (4.2%) who had surgery developed a symptomatic VTE compared with 6 of the 208 (2.9%) patients who did not undergo surgery during this admission (p=0.499).

Discussion

While many patients admitted emergently to surgical wards undergo immediate surgery, there are others who are admitted for medical management of their disease or are initially observed before undergoing surgery. These patients may be admitted with an array of benign and malignant conditions including appendicitis, bowel obstruction, acute cholecystitis, pancreatitis, and diverticulitis. There are limited data on the risk of VTE in this cohort of patients. On the other hand, it is generally accepted that patients admitted to hospital with acute medical conditions are at moderate risk for the development of symptomatic VTE. Reported rates vary depending on the disease process, risk factors present, as well as whether symptomatic or asymptomatic VTE rates are reported. Furthermore, the

rates may vary depending on what test is used to diagnose asymptomatic DVT. Zakai and colleagues reported that 1.3% of patients admitted to medical wards develop symptomatic VTE.[6] The reported rate of asymptomatic VTE is much higher. In medical patients randomized to the control group of three large randomized controlled trials assessing the effectiveness of thromboprophylaxis, venous thromboembolism was detected in 5.0–14.9% of subjects.[7–9] In these studies, bilateral venography[7,8] or compression ultrasonography[9] were used to detect VTE. The authors of the MEDENOX Study also reported that an acute infectious disease, age older than 75 years, cancer, and a history of VTE were significantly associated with increased VTE risk in acutely ill general medical patients.[10]

While a large proportion of patients in medical studies are admitted with cardiac conditions, patients with inflammatory bowel disease, cancer, and infectious processes such as pneumonia are also often included in these cohorts. Thus, it is probable that general surgical patients who are admitted emergently with acute abdominal conditions are at similar if not higher risk of developing a VTE since not infrequently they have underlying cancer or inflammatory bowel disease or are admitted with acute inflammatory or infectious conditions such as diverticulitis, pancreatitis, cholecystitis, and appendicitis. In addition, intra-abdominal sepsis is a frequent complication in surgical patients. Finally, patients admitted to surgical wards often have the same risk factors found in medical patients including obesity, history of VTE, immobility, and older age.

While there are no trials assessing the effectiveness of thromboprophylaxis in general surgical patients admitted with acute abdominal conditions, there is evidence from several large randomized controlled trials that both unfractionated and low molecular weight heparins are effective in decreasing the risk of VTE in patients admitted with acute medical conditions. Mismetti and colleagues performed a meta-analysis which included seven randomized controlled trials with over 15,000 patients assessing the effectiveness of LDUH and LMWH in patients admitted to general internal medicine wards.[5] Patients with acute myocardial infarction and stroke were excluded. They found a 56% and 58% decrease, respectively, in the risk of DVT and PE in the treatment groups. In a meta-analysis of nine trials comparing LDUH to LMWH, there was no significant difference in the rates of DVT and PE.[5] Based on these data, the American College of Chest Physicians (ACCP) Guidelines recommend that acutely ill medical patients who are admitted with congestive heart failure, severe respiratory disease, and who are confined to bed and have one or more additional risk factors (including previous VTE, cancer, sepsis, or inflammatory bowel disease) should receive prophylaxis with LDUH or LMWH.[1]

In the present study, the observed rate of symptomatic VTE was 3.4% which is higher than that reported in either medical patients admitted acutely or general surgery patients undergoing elective surgery where rates of 1–2% have been reported.[11–13] Using prospectively collected data from the Patient Safety Study, Rogers et al. reported symptomatic DVT rates of 0.5% and PE rates of 0.3% following elective surgery. Patients having hysterectomies, total knee, and hip replacements as well as general surgical procedures were included in this sample.[11] The @RISTOS Project was a prospective observational study which included patients undergoing general, urologic, or gynecologic cancer surgery in 31 units in Italy. In the 688 patients who had a general surgical procedure, the observed VTE rate was 2.8%.[12] Finally, using administrative data, Qadan and colleagues reported that 0.4% patients developed a DVT and 0.3% developed a PE.[13]

It is not surprising that the rate of VTE is higher in this cohort of patients since many individuals had multiple known risk factors as well as having intra-abdominal sepsis and inflammatory or infectious conditions. Interestingly, 7 of the 12 patients who developed a VTE were considered to have received appropriate prophylaxis. However, as shown in Table 5, this subgroup of patients were at much higher risk for developing a VTE than those who did not receive appropriate prophylaxis being older and more likely to have a history of VTE, had surgery or had cancer. Furthermore, the mean time to development of VTE was 14 days, highlighting the need for thromboprophylaxis until discharge.

The purpose of this study was to determine the frequency with which thromboprophylaxis is prescribed in

Table 5 Frequency of risk factors for symptomatic VTE in patients who did or did not receive appropriate thromboprophylaxis

	Appropriate thromboprophylaxis (n=199)	Other patients (n=151)	p
Age ≥75	81 (40.7%)	31 (20.5%)	$p<0.001$
History of VTE	14 (100%)	0 (0%)	$p<0.001$
IBD	15 (7.5%)	8 (5.2%)	$p>0.25$
Immobility	3 (1.5%)	1 (0.7%)	$p>0.25$
Cancer	61 (30.6%)	19 (12.6%)	$p<0.001$
Surgery	114 (57.3%)	28 (18.5%)	$p<0.001$

patients admitted with acute surgical conditions and were treated for at least 24 h non-operatively. Overall 72.0% of patients received some type of prophylaxis for variable durations although only 56.9% received appropriate prophylaxis. The latter proportion is of greater importance because those receiving some but inadequate thromboprophylaxis are probably at the same risk for thromboembolic complications as those who do not receive any prophylaxis. The proportion of patients who received adequate prophylaxis in this study is much lower than the results of a previous audit at the University of Toronto which showed that approximately 90.0% of patients having elective surgery for colorectal procedures received appropriate prophylaxis (unpublished data, 2007). Among patients having major general surgery procedures at 57 hospitals in Canada 79.0% received appropriate thromboprophylaxis.[14] On the other hand, the results of this study are similar to other reports of patients admitted to medical wards with acute conditions. Bergman and colleagues reported that only 49.6% of patients with gastrointestinal or hepatobiliary conditions treated medically received prophylaxis and 41.5% received prophylaxis according to ACCP guidelines.[15]

Because this is a retrospective study, there are some limitations. First of all, it was not possible to determine whether prophylaxis was withheld in some patients because of contraindications such as bleeding. Second, although we based the appropriateness of prophylaxis on the ACCP guideline recommendations, we ultimately decided that we would consider patients to have received appropriate prophylaxis if it was ordered at admission and continued until discharge of the patient. As well, we considered prophylaxis with coumadin, unfractionated, and low molecular weight heparin to be adequate prophylaxis. None of the hospitals use compression devices so that was not a consideration. Third, there were incomplete data on BMI, and likely, there was incomplete recording of some other risk factors as well. We did not collect data on whether patients were on anticoagulation before being admitted to hospital and if so, for what reason.

Not only did this study show that there is a gap in the appropriate administration of thromboprophylaxis, it also showed that there is significant variation amongst the hospitals, even though all hospitals are part of the University of Toronto teaching system. This was particularly surprising since the residents in our program rotate through all of these hospitals and for emergency admissions, thromboprophylaxis is almost always prescribed by residents. Not surprisingly, patients who underwent surgery were more likely to receive prophylaxis although it was disappointing to observe that the rate of appropriate thromboprophylaxis was not significantly higher.

This audit was performed as part of the Best Practice in General Surgery initiative at the University of Toronto. This project was started several years ago with the intention of standardizing practice in the general surgery divisions of the seven adult teaching hospitals based on best evidence. For each initiative taken by the group, we have performed an initial audit to understand the current situation, followed by development and implementation of a guideline. While the guidelines are based on best evidence, we have ensured that there is consensus with the recommendations amongst general surgeons and residents as well as other key stakeholders such as physicians from other clinical disciplines, nurses, and administrators. We have then used various strategies to increase compliance with the guidelines including talks at surgical conferences, resident teaching sessions and publication of guidelines on the websites of the University of Toronto Division of General Surgery and the individual hospitals. We have placed posters in key areas of the hospital and distributed laminated cards that can be placed in laboratory coat pockets to increase awareness of the guideline. This strategy has been successful in increasing compliance with a Bowel Preparation for Colon Surgery Guideline as well as a SSI Prevention Guideline.[16,17]

For thromboprophylaxis, we have already developed a guideline based on the ACCP guideline which has been tailored to the local hospitals (www.bpigs.ca). At each hospital, there are general surgery champions who are involved in the Best Practice in General Surgery initiative who work with hospital stakeholders and administrators at their hospitals to implement change.

In the knowledge translation literature, electronic reminders and pre-printed orders have been shown to be effective in increasing adherence with guidelines and these strategies have been adopted at some of the hospitals involved.[18] However, none have pre-printed orders for patients admitted through the emergency room and this may be an effective strategy for increasing the proportion of patients receiving thromboprophylaxis and decreasing the variation amongst hospitals. It is also noteworthy that while 252 patients were prescribed thromboprophylaxis, in 53 patients, it was inadequate either because of inadequate dosing schedule or duration of administration. Stinnet and colleagues reported on a strategy which included audit and feedback, development of standard admission order forms based on patient risk and educational sessions which was successful in increasing compliance with VTE prophylaxis prescription from 43.0% to 72.0% in patients admitted to medical wards.[19]

In conclusion, this study shows that patients admitted with acute abdominal conditions are a high risk group for the development of symptomatic VTE having, in many instances, multiple risk factors. Despite strong evidence to support thromboprophylaxis in patients admitted with acute medical conditions, only 56.9% received what was consid-

ered to be appropriate thromboprophylaxis. Given the volume of patients that are admitted through the emergency rooms with acute abdominal conditions, there is significant need for improvement. This audit is the first step to determine the current status of practice but multiple strategies are needed to increase compliance with current guidelines for thromboprophylaxis. Collaborative initiatives involving all physicians, residents, and other allied personnel and administrators are required.

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Discussant

Dr. Michael S. Nussbaum (Jacksonville, FL): Emily, that was an excellent presentation. This paper addresses a very important and timely issue related to VTE prophylaxis in surgical patients, and you have demonstrated that the approach to prophylaxis is quite variable, even when you looked at multiple hospitals in a single system.

As everyone knows, VTE prophylaxis is a Surgical Care Improvement Project (SCIP) measure, and it specifically measures our compliance with the application of VTE measures. The specific requirements are VTE prophylaxis within 24 h preoperatively and up to 24 h postoperatively. You used much stricter criteria for your definition of appropriate VTE prophylaxis in this study, requiring measures on admission and until discharge.

Why did you choose to use the stricter approach? Would the patients that you deemed as not meeting your criteria have met the more lax SCIP criteria?

As you pointed out, 12 patients had VTE complications, and these were in a higher risk category. Eleven of the 12 who suffered VTE received some form of prophylaxis but four of these patients did not receive appropriate prophylaxis by your criteria but would they have met the SCIP measures?

Why didn't you use sequential compression devices (SCDs)at any of your hospitals? Was that a financial issue? I was surprised that SCDs were not an option for VTE prophylaxis.

What is your rationale for continuing VTE prophylaxis once a postoperative patient is ambulatory? You required that they remain on prophylaxis until they were discharged from the hospital. What justification do you have for this approach in ambulatory patients?

As a final comment, I agree with you that not having BMI information on these patients is a weak point of the paper, because morbidly obese patients are going to be at higher risk for developing VTE, and also you were not able to determine if appropriate dosing was used in such patients.

Closing Discussant

Dr. Robin S. McLeod: To answer your first question about adequate prophylaxis, I think the SCIP measures criteria are used as really for quality indicators for pay for to assess hospital performance. But if you look at what you need for the evidence for optimal patient care, that's when the evidence is clear that patients require prophylaxis for the entire duration of their hospital stay, and no one refutes it that patients should have prophylaxis until discharge.

And, in fact, in some situations, in some particular cancer operations, that there is some evidence that perhaps it should be continued after surgery discharge. So this is really looking at a quality improvement initiative for patients, not looking at it as an indicator for paid-for assessing hospital performance. So that would be the big difference.

I think just to go on to maybe with regards to your third question, in our study, there were 11 of 12 patients who developed a VTE, patients that got/received some type of prophylaxis. Four of them got what we called inappropriate prophylaxis. However, all of these patients were high risk patients and had multiple risk factors, and they got a DVT. So it's what is appropriate.

I guess the last thing I could say about that is that if you look at the Chest guidelines, the Chest guidelines' recommendations are that prophylaxis should be given until discharge.

With respect to the use of the sequential compression devices, I think that is a difference, sort of a cultural difference between Canada and the United States. I suspect that the reason the cultural difference is there is because in Canada at McMaster University, they were probably doing some of the early pharmacological trials in DVT prophylaxis. We have a real history of that. And I think there was a big influence there.

Sequential compression devices are not used at any hospitals in Toronto even though they are an accepted method of prophylaxis. But if you look at it, I think that the evidence in support of pharmacological prophylaxis is much stronger, stronger for pharmacological prophylaxis. And the other point is that compression devices, the compliance with compression devices is overall low. So I think that people are moving probably towards pharmacological rather than away from it.

And the BMI, I think it would just make our point even stronger that you need to give it prophylaxis in this group of patients. We realize that it is a limitation of this study in terms of looking at risk factors.

Discussant

Dr. Kimberly Brown (Kansas City, KS): Did you notice any system differences that may explain some of the variations in compliance, such as whether any of your hospitals have computerized physician order entry, where you're prompted to enter medication orders for VTE prophylaxis?

The other question I had was, did any of these patients undergo laparoscopic procedures? Because the application of the Chest guidelines to laparoscopic procedures allows some room for interpretation among our different surgeons, and we are not required to monitor and report VTE prophylaxis measures for laparoscopic procedures for our SCIP.

Closing Discussant

Dr. Robin S. McLeod: I think that's a really interesting question; it is really interesting, your first one, and that is the variation in the seven hospitals.

Just to back up, our Best Practice in General Surgery initiatives is one of the reasons why we have was undertaken it, to minimize variation amongst the because there is a differences amongst the seven hospitals, and it really has sort of gained momentum and there is support to try to standardize things.

None of the seven hospitals have pre-printed orders forms for patients admitted through the ER—these are all patients who were admitted through the emergency room. We do have pre-printed orders for elective patients but not through the emergency room. And the variation in use of VTE prophylaxis is it's very surprising, actually, because I would suspect that probably 99.9% of orders that are written in emergency patients are written by residents, and our residents rotate around the seven hospitals. So even with probably the same people, or same group of people ordering them, that there is there was quite a big difference, a lot of variation. Other than that, we can't say why.

Again, I have to emphasize, this is a group of emergency patients that were admitted through the emergency department, only 140 out of the 350 actually went to surgery. So some of them were treated non-operatively. So I think the some of the patients had laparoscopic issue, procedures but we did not look at its effect. We did collect that data. But I have to say we haven't analyzed it.

But I think that however, this group of patients have so many risk factors, in addition to just the surgical procedure, that they probably all should have prophylaxis. In fact, sort of one of the things in this area in terms of improving one of the main trends in order to increase compliance with VTE prophylaxis is to make it simple. And our recommendations are all patients now who come to a general surgery ward, with a couple of exceptions, that is, outpatient surgery, anorectal procedures, that they should get receive prophylaxis. And we may over treat a few, but if people get it in their mind if it becomes a habit, then those that would benefit prophylaxis won't be forgotten.

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2010 SSAT PLENARY PRESENTATION

Alcohol Exposure as a Risk Factor for Adverse Outcomes in Elective Surgery

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Abstract
Background and Aims Alcohol consumption is a well-documented determinant of adverse perioperative outcome. We sought to determine the effect of active alcohol consumption following elective surgery.
Methods We queried discharge records from the American College of Surgeons' National Surgical Quality Improvement Program (NSQIP, 2005–2007) for all elective adult admissions. The 7,631 (2.5%) patients with documented alcohol use (active alcohol use of at least two drinks per day within 2 weeks of surgery; ETOH use) underwent elective surgery; 301,994 (97.5%) patients denied ETOH use. Multivariate analysis was performed with adjustments for demographic and comorbid factors. Primary outcome measures included length of stay (LOS), postoperative complications, and death.
Results ETOH use associated with elective surgery decreased over the course of the study ($p<0.0001$). ETOH use was an independent predictor of pneumonia (OR 1.98, 95% CI 1.84–2.13), sepsis (OR 1.19, 95% CI 1.03–1.37), superficial surgical site infection (SSI; OR 1.15, 95% CI 1.02–1.31), wound disruption (OR 1.41, 95% CI 1.11–1.80), and prolonged LOS (OR 1.17, 95% CI 1.08–1.26). Except for SSI, these complications were independent risk factors for postoperative mortality. ETOH use was associated with earlier time to wound disruption (9 vs. 11 days; $p=0.04$), longer median hospital stays (5 vs. 3 days; $p<0.0001$), and longer LOS after operation (4 vs. 3 days; $p<0.0001$).
Conclusions Active alcohol consumption is a significant determinant of adverse outcomes in elective surgery; patients with ETOH use who are scheduled to undergo elective surgery should be appropriately educated and counseled.

Keywords NSQIP · Alcohol use · Elective surgery

Introduction

Alcohol abuse represents a major disease burden on the US population, with 12-month prevalence of alcohol abuse and alcohol dependence approaching 5% and 4%, respectively, of the population.[1] The economic costs of alcohol abuse in the USA is difficult to quantify, but has been recently estimated in a World Health Organization report as exceeding $180 billion dollars annually.[2] Alcohol abuse is over-represented in hospital admissions. One report following all admissions to a major urban academic medical center found that the prevalence of screen-positive alcoholism ranged from 12.5% (in patients admitted to obstetrics/gynecology) to 30% (in patients admitted to psychiatry.) In that study, the prevalence of patients with screen-positive alcohol dependence among patients admitted to surgery was approximately 23%.[3] Another study reported that while 7.4% of admitted patients had a primary or secondary

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alcohol-related diagnosis, up to 23% of patients were screen-positive for alcohol abuse, suggesting that the true incidence of alcohol abuse in inpatient settings is frequently underestimated.[4]

Chronic alcohol has been associated with immunosuppression via multiple mechanisms.[5] Whereas acute alcohol exposure has been reported to have anti-inflammatory effects, chronic ethanol exposure can increase the response to pathogenic bacterial products such as lipopolysaccharide, exacerbating tissue injury in conditions such as hepatitis and pancreatitis.[6] Additionally, chronic alcohol abuse negatively impacts the function of antigen-presenting cells, including monocytes, macrophages, and dendritic cells, and suppresses the activation of T cells in the cell-mediated immune response.[7]

Given the effects of chronic alcohol on immunity, as well as the data from earlier studies, we hypothesized that active alcohol exposure would be associated with increased postoperative morbidity and mortality. Since operations performed on an emergent basis have higher risks of complications, and because the clinician cannot control the timing of surgery in these cases, our analysis was restricted to elective operations. Using a national prospective database of all elective surgeries, we aimed to determine the effect of active alcohol exposure on elective surgery outcomes.

Methods

Data was collected from the National Surgical Quality Improvement Program (NSQIP) database from the American College of Surgeons during the years 2005 to 2007. The NSQIP database has been previously described and is among the first nationally validated programs for measuring risk-adjusted surgical morbidity and mortality.[8] Briefly, the database was initiated under the Veterans Administration as a prospective, multicenter registry with the purpose of improving quality measures in surgical outcomes. The program collects, from medical records and personal communication with patients, comprehensive clinical data about patient demographics, preoperative risk factors and laboratory values, operative information, and perioperative and postoperative outcomes within 30 days of the index operation. Since then, it has grown to include 186 participating centers, and collects de-identified information on over 130 measures from patients who have provided informed consent.[9]

From the 363,987 patients in the 2005–2007 NSQIP database, we identified all adult cases (18 years and older) that were coded with the alcohol use (ETOH) code. This code identifies patients who report consuming at least two drinks per day in the 2 weeks prior to operation. Specifically, 'Yes' was entered if the patient admits to drinking >2 oz of hard liquor or more than two 12-oz cans of beer or less than two 6-oz glasses of wine per day in the 2 weeks prior to admission. If the patient is a binge drinker, the number of drinks during the binge is divided by 7 days and then the definition is applied. A total of 9,511 patients carried the ETOH code, which included patients who underwent emergency as well as elective operation. When we restricted analysis to non-emergency cases to reduce confounding effects of variables associated with emergency admissions, we found 7,631 patients with alcohol exposure. The control population consisted of 301,994 patients who did not have active alcohol exposure at the time of elective surgery. The status of the operation was determined as emergency or non-emergency by the surgeon or anesthesiologist. Emergency operations were generally performed no later than 12 h after the patient's admission or onset of related symptoms.

We further identified the number of cases by year, to determine the trend of operations performed on patients with alcohol exposure over time. Current Procedural Terminology (CPT) codes were used to categorize surgical procedures. Demographic and clinical variables were examined including patient age, sex, ethnicity, smoking status, inpatient status, and history of comorbidities including diabetes mellitus, congestive heart failure, myocardial infarction, ascites, esophageal varices, coma, pneumonia, acute renal failure, dialysis, steroid use, chemotherapy, or radiotherapy. Preoperative weight loss was defined as loss >10% weight in the previous 6 months.

The effect of alcohol exposure on postsurgical outcomes, specifically 30-day morbidity and mortality, was the primary endpoint. We selected nine available complications in the database, including death, pneumonia, sepsis, septic shock, superficial surgical site infection, organ space surgical site infection, deep incisional surgical site infection (SSI), urinary tract infection (UTI), and wound disruption. Superficial site infection (NSQIP code SUPINFEC) includes patients who have an infection involving only skin or subcutaneous tissue in the incision within 30 days of surgery, and does not include stitch abscess or infected burn wounds. Wound disruption (NSQIP code WNDINFD) identifies deep soft-tissue infections occurring 30 days from the time of surgery as identified by clinical or radiographic criteria. Organ space infection (NSQIP code ORGSPCSSI) identifies organ infection other than skin or soft tissues that were manipulated during the surgery, occur 30 days from the time of surgery, and are identified clinical or radiographic evidence. Wound disruption (NSQIP code DEHIS) denotes separation of the layers of a surgical wound with disruption of the fascia within 30 days of surgery. Sepsis (NSQIP code OTHSYSEP) refers to patients with sepsis as follows: temperature >38°C or <36°C; heart rate>90 beats

per minute; respiratory rate>20 beats per minute; PaCO2< 32 mmHG; WBC>12,000 or more than 10% band forms, as well as a documented source of infection. Septic shock (NSQIP code OTHSESHOCK) identifies patients with septic shock by the following clinical criteria: sepsis associated with organ or circulatory dysfunction, including clinical symptoms of SIRS or sepsis as delineated above, and oliguria, acute alteration in mental status, acute respiratory distress, hypotension, requirement for pressors, or inotropic agents. Patients that had preoperative sepsis with worsening status postoperatively are also captured under this code.

A crude odds ratio (OR) for patients with alcohol exposure versus patients without alcohol exposure was calculated. Then an adjusted odds ratio was determined that compared the alcohol group to a cohort from the control group matched in terms of patient demographics and all comorbidities identified in the patient characterization.

Statistical Methods

Statistical analyses were performed using the statistical package SAS® 9.1.3 (SAS Institute Inc. Cary, NC). Results for continuous variables in this study are reported as median/fifth and 95th percentile. The Wilcoxon rank-sum test was used for comparison between groups as groups were not normally distributed. Categorical variables were tested for statistical significance with chi-square analysis. Continuous variables were tested using the *t* test. Temporal trends were assessed using the Cochrane-Armitage trend test. All tests were two-sided and a *P* value less than 0.05 were considered significant.

The multivariable logistic model was introduced by including all demographic factors with the difference between presurgery alcohol exposure and non-alcohol exposure, and was assessed for independent association with each postsurgery complication with entry and retention in the model set at a significance level of 0.25 and 0.05, respectively. A final model was then constructed by enforcing age, gender, and other factors that were generally considered as complication-relevant. Receiver operator characteristic curves were used to define optimal cutoff point for days of hospital stay and days from operation to discharge with regarding to presurgery alcohol exposure. Maximized Youden index was adopted in determining the optimal cutoff point. Results of multivariate model are presented as OR with 95% confidence interval (95% CI).

Results

From the period 2005–2007, the frequency of active alcohol exposure in patients undergoing elective surgery trended downward, from 2.9% in 2005 to 2.4% in 2007 ($p<0.0001$). However, the total number of cases reported in the NSQIP database increased during the same period as the database grew in volume, from 819 patients in 2005 to 4,315 patients in 2007 (Fig. 1). The top three elective procedures performed from 2005 to 2007 in the NSQIP database were laparoscopic cholecystectomy, inguinal hernia repair, and gastric bypass. The top elective operations with active alcohol exposure were inguinal hernia repair, thromboendarterectomy, and laparoscopic cholecystectomy (Table 1).

Table 2 displays the demographics of the two groups: patients with active alcohol use ($n=7,631$; 2.5%) at the time of elective surgery and patients who did not have active use ($n=301,994$; 97.5%). Patients with active alcohol exposure were more likely to be male (76.5% vs. 40.3%, $p<0.0001$) or current smokers (47.7% vs. 19.9%, $p<0.0001$). There were also racial differences between the groups ($p<0.0001$). Additionally, patients with active alcohol exposure were more likely to have preoperative comorbidities such as a history of congestive heart failure (1.0% vs. 0.8%, $p<0.05$), myocardial infarction (0.8% vs. 0.6%, $p<0.01$), ascites (1.6% vs. 0.8%, $p<0.0001$), pneumonia (0.9% vs. 0.3%, $p<0.0001$), or acute renal failure (0.5% vs. 0.3%, $p<0.01$). Patients with active alcohol use were more likely to be malnourished with an albumin <3.5 mg/kg (3.1% vs. 2.4%, $p<0.0001$) or have weight loss (3.5% vs. 2.4%, $p<0.0001$) in the previous 6 months. On the other hand, patients with active alcohol exposure were less likely to have diabetes mellitus (8.5% vs. 14.5%, $p<0.0001$) or to have current steroid use (2.5% vs. 3.2%, $p=0.01$).

Preoperative active alcohol exposure was then examined as a risk factor for postoperative complications (Table 3). In the unadjusted analysis, active alcohol exposure was a risk factor for death, pneumonia, sepsis, septic shock, superficial SSI, deep incisional SSI, and wound disruption ($p<$

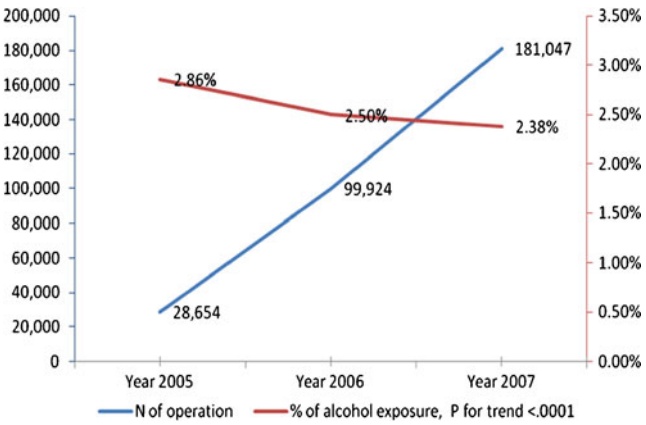

Fig. 1 Total number of elective operations and percent of patients with and without active alcohol exposure, NSQIP 2005–2007 ($p<0.0001$)

Table 1 Most frequent elective operations in patients with alcohol exposure and control population

Rank	CPT	Count (%)	Name of surgical procedure
Patients without alcohol exposure			
1	47,562	29,245 (9.4)	Laparoscopic cholecystectomy
2	44,970	16,544 (5.3)	Laparoscopic appendectomy
3	49,505	15,952 (5.2)	Repair initial inguinal hernia
4	47,563	10,943 (3.5)	Laparoscopic cholecystectomy with cholangiogram
5	43,644	10,704 (3.5)	Laparoscopic gastric restrictive procedure, with bypass and Roux-en-Y gastroenterostomy
6	35,301	10,423 (3.4)	Thromboendarterectomy, carotid by neck incision
7	49,560	8,533 (2.8)	Repair initial incisional or ventral hernia, reducible
8	19,125	143 (1.9)	Excision breast lesion identified by preoperative radiological marker
9	44,140	7,323 (2.4)	Colectomy, partial with anastomosis
10	19,120	6,717 (2.2)	Excision breast mass
Patients without alcohol exposure			
1	49,505	539 (7.1)	Repair initial inguinal hernia, age 5 or older
2	35,301	415 (5.4)	Thromboendarterectomy, carotid by neck incision
3	47,562	361 (4.7)	Laparoscopic cholecystectomy
4	44,140	215 (2.8)	Colectomy, partial with anastomosis
5	49,585	193 (2.5)	Hernia Repair, umbilical
6	49,560	184 (2.4)	Repair initial incisional or ventral hernia, reducible
7	44,204	167 (2.2)	Laparoscopic colectomy with anastomosis
8	49,650	143 (1.9)	Laparoscopic inguinal herniorrhaphy
9	47,563	142 (1.9)	Laparoscopic cholecystectomy with cholangiogram
10	44,145	104 (1.4)	Colectomy, partial with coloproctostomy

0.0001). In the multivariable regression analysis, active alcohol use was a significant risk factor for pneumonia (OR 1.98, 95% CI 1.84–2.13; $p<0.0001$), sepsis (OR 1.19, 1.03–1.37; $p=0.03$), septic shock (OR 1.40, 95% CI 1.17–1.68; $p<0.0001$), superficial SSI (OR 1.15, 95% CI 1.02–1.31; $p<0.0001$), and wound disruption (OR 1.41, 95% CI 1.11–1.80; $p<0.0001$). Additionally, active alcohol exposure was associated with significantly increased days of hospital stay (OR 1.34, 95% CI 1.31–1.37; $p<0.0001$) and days from operation to discharge (OR 1.24, 95% CI 1.17–1.30; $p<0.0001$).

Because of the greater likelihood of increased length of stay in patients with active alcohol exposure before elective surgery, the timing of development of postoperative complications was examined (Table 4). Active alcohol exposure decreased the median time to development of sepsis (7 vs. 8 days; $p<0.05$) and wound disruption (9 vs. 11 days; $p<0.05$). There was increased likelihood of longer hospital stays in patients with alcohol exposure with median stays of 2 days for patients with active alcohol exposure versus 1 day for patients without alcohol exposure ($p<0.0001$). Since this measure includes both inpatient procedures and outpatient procedures, the differences among inpatients were examined separately. In inpatients, the median length of hospital stay was 5 days in patients with active alcohol exposure, versus only 3 days in those patients without alcohol exposure ($p<0.0001$). Additionally, since these measures do not account for delays in operation from the time of admission, the time from operation to discharge for inpatients was examined. Active alcohol exposure was associated with a similarly increased median number of days from operation to discharge (4 vs. 3 days; $p<0.0001$).

An estimate of the likelihood for mortality from infectious complications in active alcohol-exposed patients was then determined in a multivariate logistic regression model (Table 5). Death was predicted by the occurrence of pneumonia (OR 8.89, 95% CI 7.92–9.95; $p<0.0001$), sepsis (OR 1.64, 95% CI 1.42–1.91; $p<0.0001$), septic shock (OR 20.27, 95% CI 18.0–22.8; $p<0.0001$), UTI (OR 1.32, 95% CI 1.10–1.60; $p=0.004$), and wound disruption (OR 1.74, 95% CI 1.31–2.30; $p<0.0001$). A sensitivity analysis was then performed to determine whether there was an effect of alcohol exposure on mortality. Each complication examined (pneumonia, sepsis, septic shock, superficial, deep, and organ space SSI, UTI, and wound disruption) was removed and then differences in mortality between patients with and without alcohol exposure were reviewed. Although no effect of alcohol on mortality was observed in the entire patient population, a significant effect on mortality appeared in the unadjusted analysis only when sepsis ($p=0.003$), superficial SSI ($p=0.0008$), organ space SSI ($p=0.006$), deep incisional SSI ($p=0.002$) UTI ($p=0.002$), or wound disruption ($p=0.002$) were separately examined. Since the patients with acute alcohol exposure also appeared to be more malnourished and this may account for the potential complications after elective surgery, the multivariate analyses were repeated with and without these variables (albumin<3.5 mg/kg and weight loss). The effect of alcohol as a risk factor for postoperative complications persisted despite controlling for nutritional factors (data not shown).

Discussion

Active alcohol consumption is a significant determinant of adverse outcomes in elective surgery; patients who regu-

Table 2 Characteristics of 309,625 patients who underwent elective surgery grouped by active alcohol exposure status in NSQIP 2005–2007

	All patients (n=309,625)	Patients without alcohol exposure (n=301,994)	Patients with alcohol exposure (n=7,631)	P value
Age group (n, %)				
16–30	27,727 (9.0)	27,450 (9.1)	277 (3.6)	<0.0001
31–45	63,915 (20.6)	62,803 (20.8)	1,112 (14.6)	
46–60	98,861 (31.9)	95,943 (31.8)	2,918 (38.2)	
61–75	80,569 (26.0)	78,000 (25.8)	2,569 (33.7)	
>75	38,553 (12.4)	37,798 (12.5)	755 (9.9)	
Gender (male; n, %)	127,603 (41.2)	121,769 (40.3)	5,834 (76.5)	<0.0001
Race (n, %)				
White	220,835 (78.5)	214,964 (78.4)	5,871 (84.2)	<0.0001
African American	30,091 (10.7)	29,433 (10.7)	658 (9.4)	
Hispanic	22,360 (8.0)	22,048 (8.0)	312 (4.5)	
Asian and Pacific	5,368 (1.9)	5,324 (1.9)	44 (0.6)	
American Indian or Alaska	2,636 (0.9)	2,252 (0.9)	84 (1.2)	
Current smoker (n, %)	63,842 (20.6)	60,200 (19.9)	3,642 (47.7)	<0.0001
Diabetes mellitus (n, %)	44,573 (14.4)	43,921 (14.5)	652 (8.5)	<0.0001
Weight loss	7,631 (2.5)	7,368 (2.4)	263 (3.5)	<0.0001
Albumin<3.5 mg/kg	4,124 (2.6)	3,116 (2.4)	1,008 (3.1)	<0.0001
History of congestive heart failure (n, %)	2,607(0.8)	2,527 (0.8)	80 (1.0)	0.05
History of myocardial infarction (n, %)	1,781 (0.6)	1,717 (0.6)	64 (0.8)	0.002
Ascites (n, %)	2,530 (0.8)	2,411 (0.8)	119 (1.6)	<0.0001
Esophageal varices (n, %)	392 (0.1)	368 (0.1)	24 (0.3)	<0.0001
Coma (n, %)	64 (0.02)	59 (0.02)	5 (0.00)	0.02
Pneumonia	1,065 (0.3)	994 (0.3)	71 (0.9)	<0.0001
Acute renal failure (n, %)	1,054 (0.3)	1,015 (0.3)	39 (0.5)	0.01
Dialysis (n, %)	6,605 (2.1)	6,550 (2.2)	55 (0.7)	<0.0001
Steroid use (n, %)	9,802 (3.2)	9,610 (3.2)	192 (2.5)	0.001
Chemotherapy (n, %)	2,555 (0.8)	2,501 (0.8)	54 (0.7)	0.2
Radiotherapy (n, %)	2,286 (0.7)	2,195 (0.7)	91 (1.2)	<0.0001
Patient source (n, %)				
Inpatient	186,869 (60.4)	181,688 (60.2)	5,181(67.9)	<0.0001
Outpatient	122,756 (39.6)	120,306 (39.8)	2,450 (32.1)	

larly consume alcohol and who are scheduled to undergo elective surgery should be appropriately educated and counseled. Elective surgery performed under optimal conditions of limited alcohol consumption or abstinence may reduce postoperative complications, length of stay, and hospital costs. In our analysis, we restricted our search to elective cases within the NSQIP database in order to minimize the effect of complications that might be expected with emergency cases. Although there was not a direct independent effect of active alcohol use before elective surgery for postoperative mortality, our results reveal that active alcohol use directly results in major complications after elective surgery which are surrogates for death. Examples include pneumonia, sepsis and shock, urinary tract infections, and wound disruptions.

Active alcohol exposure was associated with a significant risk of multiple adverse outcomes in the postoperative setting after elective general and vascular surgery. These results correlate well with earlier smaller studies that looked at alcoholism as a risk factor for postoperative morbidity.[10–16] Other studies, including one study that examined 106 patients undergoing shoulder arthroplasty, failed to identify alcohol as a significant contributor to negative postoperative outcomes.[17] Our study is unique in that these effects were examined in a large nationwide sample of patients, whereas earlier reports tended to report the outcomes from smaller cohorts from a single center which may lead to regional- and center-specific bias from varying patient populations and care. The NSQIP database specifically tracks the use of active alcohol exposure prior to surgery which is a very

Table 3 Presurgical alcohol exposure as predictor for postsurgical complications and other parameters, NSQIP 2005–2007

	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Death	1.38 (1.12, 1.70)	0.002	1.10 (0.87, 1.39)	0.42
Pneumonia	2.17 (1.19, 2.49)	<0.0001	1.98 (1.84, 2.13)	<0.0001
Sepsis	1.55 (1.35, 1.77)	<0.0001	1.19 (1.03,1.38)	0.021
Septic shock	1.93 (1.64, 2.27)	<0.0001	1.40 (1.17,1.68)	0.0002
Superficial SSI	1.34 (1.19, 1.51)	<0.0001	1.15 (1.02,1.31)	0.021
Organ space SSI	1.10 (0.89, 1.36)	0.37	0.86 (0.69,1.08)	0.21
Deep incisional SSI	1.50 (1.21, 1.87)	0.0002	1.21 (0.96,1.52)	0.098
Urinary tract infection	0.94 (0.77, 1.13)	0.49	0.94 (0.77,1.16)	0.59
Wound disruption	1.94 (1.54, 2.45)	<0.0001	1.41 (1.11,1.80)	0.005
Days of hospital stay for all patients	1.44 (1.38, 1.51)	<0.0001	1.34 (1.31,1.37)	<0.0001
Days of hospital stay for inpatients	1.35 (1.26, 1.45)	<0.0001	1.17 (1.08,1.26)	<0.0001
Days from operation to discharge for all patients	1.41 (1.35, 1.48)	<0.0001	1.236 (1.17,1.30)	<0.0001
Days from operation to discharge for inpatients	1.28 (1.20, 1.37)	<0.0001	1.11 (1.03,1.20)	0.005

unique feature of the database. We were unable to assess the chronicity of the alcohol use and its impact, but these results emphasize the importance of active alcohol use at the very least. We found that active alcohol exposure in patients led to longer hospital stays and higher median length of stay. This was the case regardless of whether we timed those stays as total hospital stay or days from operation to discharge. This is an important risk qualifier for analyzing hospital trends and cost analysis as active alcohol use alone can increase hospital costs by increasing length of stay from surgery and increase the risk of many possible life-threatening complications.

The incidence of chronic alcohol abuse has significant consequences for all health care providers, but of particular concern to surgeons are reports that chronic alcohol exposure is a risk factor for postoperative morbidity.[10–16, 18] One group identified 213 patients with tumors of the upper aerodigestive tract, of which 121 were identified as chronic alcoholics. Following surgical resection, chronic alcoholic patients had higher rates of mortality and prolonged ICU stay, with increased incidence of sepsis and pneumonia.[10] It is difficult to draw definitive conclusions from this study, as the study population is relatively small, and alcohol as an etiological agent of aerodigestive tract cancers may complicate the interpretation of mortality data. Furthermore, the relationship of this study to operations that do not involve the upper aerodigestive tract (i.e., that do not involve a pathway of inoculation of the lung) is unknown. Other studies reported

Table 4 Time difference of postsurgical complications between patients with presurgical alcohol exposure and those without alcohol exposure

	Alcohol exposure Median (5th, 95th percentile)/*n*	Non-alcohol exposure Median (5th, 95th percentile)/*n*	*P* value[a]
Days from operation to death	11 (1, 27)/94	12 (1, 28)/2,698	0.72
Days from operation until pneumonia	5 (1, 25)/219	5 (1, 23)/4,061	0.53
Days from operation until sepsis	7 (1, 23)/230	8 (1, 25)/5,947	0.05
Days from operation until septic shock	5 (0, 24)/155	5 (0, 23)/3,211	0.68
Days from operation until superficial incisional SSI	11.5 (3, 27)/296	11 (3, 27)/8,817	0.26
Days from operation until organ space SSI	10 (4, 24)/89	11 (3, 27)/3,201	0.16
Days from operation until deep incisional SSI	14 (4, 28)/86	13 (3, 28)/2,270	0.64
Days from operation until wound disruption	9 (1, 25)/77	11 (2, 27)/1,576	0.04
Days of hospital stay for all patients	2 (0, 22)/7,631	1 (0, 15)/301,994	<0.0001
Days of hospital stay for inpatients	5 (1, 28)/5,181	3 (1, 20)/181,687	<0.0001
Days from operation to discharge for all patients	2 (0, 16)/7,031	1 (0, 11)/301,994	<0.0001
Days from operation to discharge for inpatients	4 (1, 21)/5,181	3 (1, 15)/181,688	<0.0001

[a] Wilcoxon rank-sum test

Table 5 Infectious complications as predictor of mortality

Complication:	Crude OR	*P* value	Adjusted OR	*P* value
Pneumonia	22.60 (20.53, 24.87)	<0.0001	8.88 (7.92, 9.95)	<0.0001
Sepsis	7.05 (6.27, 7.92)	<0.0001	1.64 (1.42, 1.91)	<0.0001
Septic shock	68.76 (62.85, 74.88)	<0.0001	20.27 (18.02,22.80)	<0.0001
Superficial SSI	1.46 (1.21, 1.76)	<0.0001	0.83 (0.67, 1.03)	0.096
Organ space SSI	5.33 (4.50, 6.32)	<0.0001	2.16 (1.75, 2.68)	<0.0001
Deep incisional SSI	2.66 (2.03, 3.48)	<0.0001	0.94 (0.70, 1.28)	0.71
Urinary tract infection	4.45 (3.81, 5.50)	<0.0001	1.32 (1.10, 1.60)	0.004
Wound disruption	5.57 (4.42, 7.01)	<0.0001	1.736 (1.31, 2.30)	<0.0001

OR Odds Ratio, *SSI* Superficial Site Infection

increased risk of complications in alcoholic patients after colon and rectal surgery, hysterectomy, and resection of lung cancer, but were also performed with small cohorts of patients and controls.[19–21] Collectively, these studies suggest that immunosuppressive effects of chronic alcohol may negatively impact the development of postsurgical complications. In our study, alcohol also appeared to accelerate the appearance of two adverse outcomes, namely, sepsis and wound disruption. The earlier appearance of wound disruption and sepsis in alcohol-exposed patients may represent a pathophysiological manifestation of alterations in the inflammatory response that have been well documented in animal models[5, 6, 22] and correlate with earlier findings demonstrating altered levels of proinflammatory mediators in the serum of chronic alcoholics after trauma[18] or who underwent resection of aerodigestive tract tumors.[12]

Each of the complications for which we found an association with active perioperative alcohol exposure was independently associated with a higher risk of mortality in the adjusted analysis. When we sought to determine the overall effect of active alcohol use on mortality, we did not find that alcohol conferred an increased risk of mortality in elective surgeries. When we restricted our analysis by excluding any single complication, we found that active alcohol use was significantly associated with an increased risk of mortality in the crude odds ratio, but not in the adjusted odds ratio. Further analysis is needed to assess the true effect of alcohol on these complications and removing all potential confounding effects such as disparities in care, provider bias, and variation in management of diseases.

A strength of our study is the discovery of a significant effect of ethanol exposure using a large nationwide database. This database was not designed with the intent of stratifying patients based on alcohol consumption, and one limitation of the study is that we cannot discriminate between patients who consumed greater or lesser quantities of alcohol beyond the two drinks per day threshold of the database. Another limitation is that the method of reporting alcohol exposure may significantly underestimate the true incidence of active alcohol exposure in the sample. For example, one study found that up to 23% of patients admitted to a general surgery service were screen-positive for alcohol dependence, and other studies have shown that the method of data gathering affects the observable prevalence of alcohol dependence.[3, 4] The number of patients undergoing elective surgery who were also positive for alcohol dependence was quite low in this study (<3% of the total sample size). The incidence of alcohol use in the NSQIP patient population may be significantly less, and this in turn would be expected to have some effect on the analysis of our data. Additionally, there are other factors that may influence postoperative complications that are not captured in our study. Recent investigations have demonstrated adverse outcomes for patients with cirrhosis undergoing elective surgery.[23] Additionally, other studies have demonstrated a clear dependence on surgeon volume for pancreatic resection, suggesting an operator-dependent effect that is not captured by our study.[24]

Another consideration is that the types of elective cases differed somewhat between the patients undergoing elective surgery in the alcohol-exposed and the non-alcohol-exposed groups. Notably, breast cases were two of the top ten elective cases among all patients in the NSQIP database, whereas breast cases were not among the top ten cases in the alcohol-exposed group. The remainder of the cases in the top ten among alcohol-exposed and non-alcohol-exposed patients were very similar, further suggesting that case selection played a minor, if any, role in the observed differences between the groups.

To our knowledge, this is the first study that has demonstrated a negative effect of active alcohol use on the development of postsurgical complications using a large population-based patient sample. Our study did not find an increased risk of death in patients who had alcohol exposure prior to surgery versus matched controls. However, each of the postoperative complications associated with alcohol was independently associated with a significantly increased risk of mortality in the adjusted analysis. Patients undergoing elective surgery may be unaware of the added risk posed by ethanol consumption, and education of patients to avoid alcohol in the weeks preceding surgery may result in decreased complication rates and decreased costs associated with hospital stays and days to discharge.

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Discussant

Dr. Craig P. Fischer (Houston, TX): Dr. Nath, and the group at UMass have established a fantastic outcomes research unit which has examined surgical outcomes and have been interested in nomograms that might predict surgical outcomes based upon readily available clinical data.

I have two simple questions.

The first is, your data set tries to look at elective patients, yet I would imagine that most surgeons, if they knew their patient had been drinking alcohol recently, might not operate.

So my question is how good is NSQIP at distinguishing urgent, emergent, and completely elective operations? It's a fine lie between urgent and emergent—and to be useful—this information regarding alcohol consumption must be available prior to a planned operation, with enough time to modify the risk factor.

One of the reasons I liked your abstract was the word in your title, "modifiable."

So tell me about that. You apparently are interested in finding a way to modify this risk factor. So given this information, this is new, what can you do to now try to find these folks and then limit this risk factor?

Closing Discussant

Dr. Bharath Nath: I'll begin by addressing the first question, which I understood to be how good NSQIP is at distinguishing urgent versus emergent conditions. The code in the database identifies emergent procedures as those that occur within 12 h of admission. So this actually leads to some cases that might be thought of as acute falling into the elective category.

However, our concern in really separating out emergency and elective cases was to discern which patients had been scheduled with enough time for appropriate planning for surgery, and which ones were taken straight to the OR, without time to compensate for other preoperative factors that may predispose to complications.

From that perspective, the difference between emergent and elective codes in NSQIP is sound. Now, that said, it

still has the disadvantage of being a binary variable. If time to surgery could be coded as a continuous variable, I think that there might be opportunities to ask some interesting questions for future studies.

Now, to address the second question, namely, if alcohol is a modifiable risk factor, what are the means by which we may modify this factor? Notably, few if any recent discussions on risk factors include alcohol. So I would hope that, on the basis of these data that we've presented today, surgeons would feel comfortable discussing alcohol intake with their patients, and suggest that as long as patients are actively drinking, there's a likelihood that they will have more complications. So from a practice perspective, that's the approach that we would suggest.

Then there's the question, of course, of a hospital process. And I think that as these data become more widely disseminated, it's reasonable to think that a process of identifying these patients on admission and counseling them and making surgeons aware would be useful.

Discussant

Dr. Timothy Pawlik (Baltimore, MD): I want to echo Dr. Fischer's comments about your group at UMass. Really some excellent work.

My comment specifically regards a statistical issue. You showed that the alcohol consumption group and the group that didn't consume alcohol are very disparate. Although you use multivariable logistic regression to control for some of that, I'm sure your group is well aware that this does not suffice when the groups are so different. In fact, causal inferences from that type of modeling, when the groups so different, can be misleading.

Did you use other statistical modeling, like a propensity index, which I think may have worked nicely with this data set? And did you find similar results, if indeed you did use that other modeling?

Closing Discussant

Dr. Bharath Nath: That's a great point. In terms of the work that we presented here today, we did not. However, that is exactly the direction that we are working on right now. So we hope to present those data in the near future.

Discussant

Dr. Steven Demeester (Los Angeles, CA): You know, I'll just follow up on that and say that in the types of complications you presented, I wouldn't have anticipated from an alcohol type thing; they struck me more as smoking things, pneumonia, sepsis, respiratory, well-known problems with smoking.

A simple thing to do is take your people that are drinking alcohol, divide them by those that are active or former smokers versus those that are nonsmokers, and see if your differences really hold up in that alcohol-only group. That would be a quick test to see if you are really onto something or whether you are being confounded by the smoking issue.

Closing Discussant

Dr. Bharath Nath: Absolutely. I think that's also a great point. A synergistic effect between smoking and alcohol would be a very intriguing one to uncover. Now that said, I came to the study after completing my Ph.D. work in the area of alcohol and its effects on pathogenesis of liver disease.

One of the things that becomes clear is that chronic alcohol use tends to predispose to hyperresponsive macrophage activation, particularly when macrophages are challenged with immunogenic particles such as the gram-negative cell wall product lipopolysaccharide. So from that perspective, there is a rationale to think that pneumonia and sepsis could indeed be worsened by chronic alcohol exposure quite independently of smoking.

But I absolutely agree that it would be intriguing to validate that observation, made in the laboratory, with a study that stratified the effect of smoking and ethanol on surgical outcomes.

Discussant

Dr. Gerard V. Aranha (Maywood, IL): In your alcohol group, what percentage of patients had ascites or varices? If you are operating upon Child C group patients, wouldn't you have a higher mortality and morbidity?

Closing Discussant

Dr. Bharath Nath: That's a good point. The prevalence of ascites in the alcohol-exposed gruop was 1.6%, whereas in the non-alcohol-exposed group it was 0.8%. These differences were indeed statistically significant between the two groups. However, ascites was one of the preoperative patient characteristics that we considered when performing our adjusted analysis. Within the limits of performing an adjusted analysis, differences in the prevalence of ascites did not affect our findings.

Discussant

Dr. John Bowen (New Orleans, LA): I don't doubt your correlations; I do question one word you use, which is "determination." In other words, you correlate these factors with alcoholism, but is it not possible that alcoholism is simply an indicator of a type of personality or person that's coming in and continuing to drink prior to surgery, rather than a specific kind of physiological defect because of the alcohol?

The only way I could see you could unravel this is to identify these people before you operate, not operate on them, have them stay off the alcohol for a couple of weeks, and then operate on them and see if you had a difference, if you really did have all these complications.

It's my feeling that this is more of a proxy for a group of patients that are acting badly, for whatever reason, and it's having a bad effect on them physiologically, emotionally, or whatever. And I would be very interested to see that part of it unraveled.

Closing Discussant

Dr. Bharath Nath: I think that's a great comment as well. I would be very interested to see some sort of clinical trial that compared patients in those two arms. That said, whether it's a physiological process or whether it's an indicator of bad habits, minimizing those may still have the same effect. And so, knowing this data as we do, I would feel that counseling a patient to avoid alcohol might still be in the best interests of the patient.

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2010 SSAT POSTER PRESENTATION

Postprandial Proximal Gastric Acid Pocket in Patients after Roux-En-Y Gastric Bypass

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Abstract
Introduction An unbuffered postprandial proximal gastric acid pocket (PPGAP) has been noticed in normal individuals and patients with gastroesophageal reflux disease (GERD). The role of gastric anatomy in the physiology of the PPGAP remains unclear. It is also unclear whether operations that control GERD, such as Roux-en-Y gastric bypass (RYGB) and Nissen fundoplication, change the PPGAP.
Aims This study aims to analyze the presence of PPGAP in patients submitted to RYGB.
Methods Fifteen patients who had a RYGB for morbid obesity (mean age 53 years, 14 females, mean time from operation 3 years) were studied. All patients were free of foregut symptoms. Patients underwent a high-resolution manometry to identify the location of the lower border of the lower esophageal sphincter (LBLES). A station pull-through pH monitoring was performed from 5 cm below the LBLES to the LBLES in increments of 1 cm in a fasting state and 10 min after a standardized fatty meal (40 g of chocolate, 50% fat).
Results Acidity was not detected in the stomach of four patients before meal. After meal, PPGAP was not found in eight patients. In three patients, a PPGAP was noted with an extension of 1 to 3 cm.
Conclusion PPGAP is present in a minority of patients after RYGB; this finding may explain part of the GERD control after RYGB and that the gastric fundus may play a role in the genesis of the PPGAP.

Keywords Gastroesophageal reflux · Roux-en-Y gastric bypass · Acid pocket

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Introduction

An unbuffered postprandial proximal gastric acid pocket (PPGAP) has been noticed in normal individuals and patients with gastroesophageal reflux disease (GERD).[1–3] However, the role of gastric anatomy in the physiology of the PPGAP remains unclear. It is also elusive whether operations that control GERD, such as Roux-en-Y gastric bypass (RYGB) and Nissen fundoplication, may change the PPGAP.

This study aims to analyze the presence of PPGAP in patients submitted to RYGB.

Methods

Population

Fifteen individuals submitted to RYGB for morbid obesity (mean age 52.7±4.6 (range 44–63) years, 14 females, mean time from operation 3.3±2.9 (range 0.3–7) years) were

studied. Body mass index was 46.1±9.9 (range 34–68) Kg/m^2 and 32.3±5.8 (range 23–46) Kg/m^2 before operation and at the time of the study, respectively. All operations were done via laparotomy by the same surgeon. The gastric pouch was constructed measuring 5 cm of length and 30 ml of volume and calibrated by a 12-mm endoluminal bougie.

All individuals were free of foregut symptoms. Upper digestive endoscopy was routinely performed before operation, and no patient presented with hiatal hernia. Postoperative endoscopy was not performed since patients were asymptomatic. No individual was in use of antacid medication or drugs that may affect digestive motility. Patients were excluded in case of: (a) foregut surgery other than the RYGB, (b) denial to participate in the study, and (c) operation less than 3 months before the study.

Esophageal Tests

The subjects were fasting for at least 6 h before testing. All individuals underwent a high-resolution manometry (Sierra Instruments, Los Angeles, CA, USA) to assess esophageal body motility and to identify the lower border of the lower esophageal sphincter (LBLES). Patients were offered ten swallows of water in horizontal decubitus. Data acquisition and analyses were accomplished with the dedicated software (ManoScan and Manoview, Sierra Instruments, Los Angeles, CA, USA).

A station pull-through pH monitoring (Alacer biomedica, São Paulo, SP, Brazil) was performed in a sitting position from 5 cm below the LBLES up to the LBLE. Correct positioning of the catheter was confirmed by acid reading or giving the subject orange juice to confirm acid detection in the proximal sensor prior to the proximal sensor. Radiography was not obtained due to the use of radiation for ethical reasons since all individuals were volunteers. The catheter was withdrawn in increments of 1 cm every 1 min, signaled by pushing the event bottom of the hardware.

The pH catheter was replaced 5 cm bellow the LBLES and the pull-through repeated 10 min after a standardized fatty meal (Nescau bar, Nestle Brasil, 40 g of chocolate, 50% fat).

PPGAP Assessment

PPGAP was defined by the presence of acid reading (pH<4) in a segment of the stomach above a non-acid segment and followed by a step-up in pH at the level of the LES (Fig. 1). PPGAP extent was recorded.

Ethics

The protocol was approved by local ethics committee. Informed consent was obtained from all individuals.

Results

High-resolution manometry analysis showed that all patients had normal esophageal peristalsis. Esophageal

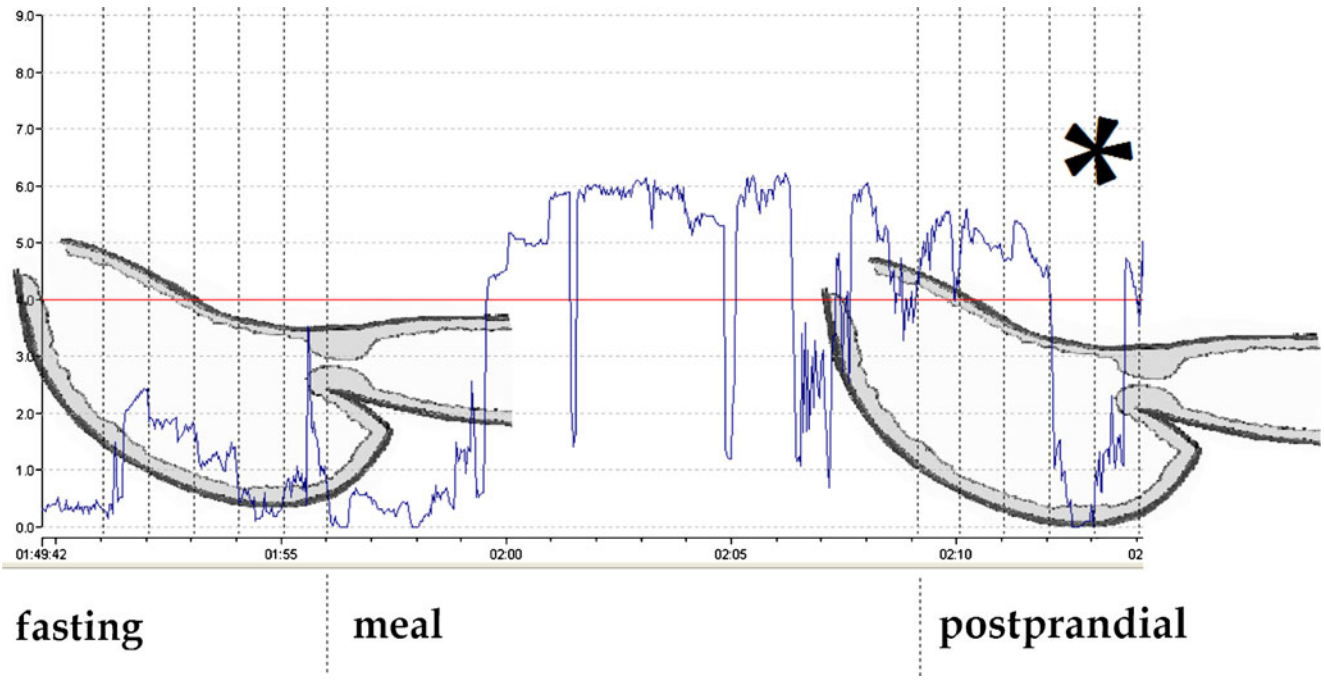

Fig. 1 Postprandial proximal gastric acid pocket detected during pH monitoring pull-through (*asterisk*)

amplitude at 3 cm above LES was 77.5±30.9 (range 25–119) mmHg.

Acidity was not detected in the gastric pouch of four (27%) individuals in the fasting state. A meal was not offered to these subjects, and the experiment ended at this point.

After meal, PPGAP was not found in eight (53%) patients. In three (20% of total) patients, a PPGAP was noticed. The extensions of the PPGAP were 1, 2, and 3 cm.

Discussion

Our results show that PPGA is present in 20% of the patients submitted to RYGP.

PPGAP

Fletcher et al.[1] described in 2001 while performing dual gastric and esophageal pH monitoring the presence of an unbuffered layer of acid just below the gastroesophageal junction that escapes the buffering effect of the meal, remaining highly acidic compared with the body of the stomach that floats above ingested food in the proximal stomach. Different studies with similar results followed this initial description.[2–6] This phenomenon explains the fact that acid reflux occurs frequently after meals[7] when intuitive thinking would suppose that gastric acid are mixed up with ingested food and not available to reflux.[2] It correlates with severe GERD[3] although asymptomatic volunteers also commonly present with a PPGAP. Also, Barrett's esophagus genesis may be linked to this constant presence of acid close to the gastroesophageal junction.

Apparently, PPGAP is a common finding in individuals with an intact stomach with or without GERD, since different studies reported a prevalence of 100%.[1,2,4,5] There are no series studying PPGAP in the obese population to date. Our series demonstrated PPGAP in only 20% of the individuals after RYGP.

Acid Pocket and Gastric Anatomy

Intragastric pH monitoring shows that stomach pH is not homogeneous after a meal.[8] Also, a PPGAP is present independent of body position[2] showing that this finding is not based on a simple gravitational or physical issue of acid floating above a lipidic layer of food.

There are no previous studies evaluating PPGP in the postoperative period. We studied RYGP patients as an experimental model to the absence of the gastric fundus. Currently, our group is also studying patients submitted to Nissen fundoplication and distal gastrectomy. Unfortunately, our subjects were not studied before operation for a matter of comparison; however, low prevalence of PPGAP found compared to literature data leads to the hypothesis that the gastric fundus plays a role in the genesis of PPGAP.

Roux-en-Y gastric Bypass and Gastroesophageal Reflux Disease

RYGB is considered an effective treatment for GERD.[9,10] The small size of the gastric pouch and the lack of stimulus to the antrum may lead to the assumption that acid production is extremely reduced or absent in this pouch. In our series, gastric acidity was indeed absent in one quarter of the cases. However, GERD control cannot be explained solely by this theory since pH monitoring studies clearly demonstrated the presence of acid in the gastric pouch of these patients.[11,12] The suppression of the PPGAP after surgery may also be a putative factor for GERD control after RYGB.

Conclusions

In conclusion, PPGAP is present in a minority of patients after RYGB. This finding may explain part of the GERD control after RYGB and that the gastric fundus may play a role in the genesis of the PPGAP.

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2010 SSAT POSTER PRESENTATION

Clinical Presentation and Diagnosis of Intestinal Adenocarcinoma in Crohn's Disease: Analysis of Clinical Predictors and of the Life-Time Risk

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Abstract
Background Late diagnosis of cancer in CD often occurs, and the prognosis is poor. The primary aim of this study was to assess the relationship between clinical presentation and diagnosis of intestinal adenocarcinoma in CD; the secondary aim was to evaluate the timing of cancer occurrence in CD patients.
Patients and methods Medical records of 12 consecutive patients with intestinal adenocarcinoma in CD and of 79 consecutive CD patients undergoing bowel surgery were reviewed. Presentation symptoms were analyzed as possible predictors. Timing of intestinal adenocarcinoma occurrence in patients with CD was analyzed including all the 347 consecutive patients that had undergone surgery for CD in our institute from January 1984 to June 2008. Life table analysis and uni/multivariate analyses were performed.
Results Ten men and two women underwent surgery for intestinal cancer in CD with a median age of 50 years (31–68). Carcinomas were localized in the terminal ileum in four cases, right colon in three, transverse colon in one, sigmoid colon in one, rectum in two, and an anorectal fistula in one. Only three patients were pre-operatively diagnosed with cancer. At multivariate analysis only age (OR 1.057 (95% CI 0.999–1.107), p=0.05) and obstruction (OR 6.530 (95% CI 1.533–27.806), p=0.01) significantly predicted cancer diagnosis. The risk rate (RR) for cancer occurrence started to rise at the end of the third decade of life (RR=0.005). The analysis of risk rate for cancer occurrence during overt CD showed that it is initially high at onset (RR=0.001) and after two other peaks at 150 months from onset, it began to rise again. The presence of Crohn's colitis was associated to a significant risk of cancer (HR=4.790, p=0.009) while the use of 5-ASA resulted to be a protective factor against cancer occurrence (HR=0.122, p=0.013).

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In memory of Prof. Attilio Cecchetto

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Discussion In CD, rectal bleeding, the most common alarm symptom for intestinal cancer, is not useful for an early diagnosis. CD patients presenting with an older age and obstruction should be thoroughly investigated to rule out neoplastic lesions. There is probably no safe interval of CD where surveillance for intestinal cancer can be omitted. In the meantime, even in absence of active disease, all CD patients should undergo therapy with 5-ASA.

Keywords Crohn's disease · Adenocarcinoma · Endoscopic surveillance

Introduction

Crohn's disease (CD) is an inflammatory bowel disease (IBD) associated with an increased risk to develop intestinal cancer compared to the general population.[1] In CD, although several studies reported a 2- to 20-fold increase for large bowel cancer[2] and an increased rate of small bowel cancer,[3] discussion of cancer risk still remains controversial. A meta-analysis, based on population-based studies only, revealed an overall increased risk of both small and large bowel cancer among patients with CD.[4]

Moreover, risk factors associated with the development of carcinoma in CD are not well defined. In literature, long disease duration and more extensive colon involvement have been indicated to contribute to the development of cancer in CD.[5,6] Furthermore, primary sclerosing cholangitis has been shown to be a possible risk factor for colorectal carcinoma in CD as well as in ulcerative colitis (UC). Colorectal cancers arising in patients with CD have different distinguishing characteristics compared with non-inflammatory colorectal tumors. The former arise in individuals at a younger age, typically progress from flat nonpolypoid dysplasia; they also have a higher rate of mucinous and signet ring cell histology and probability of finding synchronous tumors.[7] Moreover, clinical presentation of colorectal cancer arising in CD patients is often confounding, and it is not clearly described yet. Therefore, misdiagnosis due to overlapping symptoms that are often typical of active CD is frequent and delayed diagnosis results in a poor prognosis.[8]

A substantial increase in the number of new cancer cases in CD has been reported,[9] and a recent survey[10] revealed that the time interval between the first symptoms of Crohn's colitis and cancer diagnosis was very short in many patients. But differently from UC, surveillance recommendations for CD are lacking, and the current proposals are less uniform and are focused on long-standing disease.[11,12] Therefore, timing of colorectal cancer occurrence in CD patients is still controversial.

The primary aim of this study was to assess the relationship between clinical presentation and diagnosis of intestinal adenocarcinoma in CD; the secondary aim was to evaluate the timing of cancer occurrence in CD patients. This information could be useful to plan a surveillance program.

Patients and Methods

Study Design

Records of all the consecutive patients who underwent intestinal surgery for CD in the department of Surgical and Gastroenterological Sciences, University of Padova from 1984 until 2005 were reviewed as well as details of outpatient's clinic follow-up. Patients were recruited in the study if they had a confirmed diagnosis of intestinal adenocarcinoma in CD. All types of intestinal adenocarcinoma irrespectively from their origin site were included. Patients who presented other histopathological types of cancer (i.e., intestinal lymphoma or anal squamous cell carcinoma) associated to CD were excluded from this study. In this retrospective setting, diagnosis of intestinal adenocarcinoma in CD was double checked with histological revision of the slides obtained from the surgical specimens performed by a dedicated pathologist with special interest in gastroenterology (A.C.). This revision confirmed the simultaneous presence either of CD or adenocarcinoma.

The analysis of clinical presentation of patients with CD and cancer was carried on comparing the data of these patients to those of 79 consecutive patients that underwent intestinal surgery for CD in our institute from January 2004 to June 2008. In this group of patients, detailed data about clinical presentation had been prospectively collected. Their median age at operation was 39 (interquartile range (IQR) 31–48) years, and 44 of them were males. The disease duration before the operation was 60 (IQR 13–156) months. CD phenotype was "stenosing" in 57 and "fistulizing" in 22 patients. CD was localized in the terminal ileum in 41 patients, in other tracts of the small bowel in eight patients, in the perineum in four patients, and in the colon in 26 patients.

The analysis of timing of intestinal adenocarcinoma occurrence in patients with CD was carried on analyzing all the consecutive patients that had undergone intestinal surgery for CD in our institute from January 1984 to June 2008. In this time frame, 347 consecutive patients underwent intestinal surgery for CD in our institute. Their median age at operation was 36 (IQR 28–45) years, and 200 of them were males. The disease duration before the operation was 72 (IQR 17–143) months. CD phenotype was "stenosing" in 243 and "fistulizing" in 104 patients. CD was localized in the terminal ileum in 246 patients, in other tracts of the small bowel in 37 patients, in the perineum in five patients, and in the colon in 57 patients. The characteristics of all the three groups are resumed in Table 1.

Table 1 Patients' Characteristics

	CD and cancer		CD (2004–2008)		CD (1984–2008)	
	Median	IQR/%	Median	IQR/%	Median	IQR/%
Anthropometrical data						
Patients number	12		79		347	
Age at operation	50	(37–57)	39	(31–48)	36	(28–45)
Disease duration	84	(18–140)	60	(13–156)	72	(17–143)
Gender (M/F)	10/2		44/35		200/147	
Disease phenotype						
Stenosing phenotype	10	83%	57	72%	243	70%
Fistulizing phenotype	2	17%	22	28%	104	29%
Disease site						
Jejunum-Proximal ileum	–	–	8	10%	37	11%
Terminal ileum	4	33.3%	8	52%	246	71%
Colonic	7	58.3%	26	33%	57	17%
Perianal	1	8.3%	4	5%	5	1%

Statistical Analysis

The statistical analysis was performed using both Microsoft Excel and STATISTICA 7.1 software (Statsoft, Inc.). Data were expressed as median and IQR unless otherwise specified. Comparisons were carried out with Fisher exact test when analyzing dichotomous variables and with Mann–Whitney *U* test when analyzing continuous ones. Bonferroni adjustment was used where appropriate. Univariate logistic regression was used to assess the risk of colorectal cancer occurrence according the different clinical presentation. All the variables significant at the univariate analysis were included in a step-forward logistic regression model to identify independent predictors.

Life table analysis was performed to assess the risk rate and the timing of the colorectal cancer occurrence. Survival intervals used for life table calculation were set at 5 years for the analysis of the whole life of patients and 2 years for the analysis during overt CD. Survival analysis for colorectal cancer occurrence included as independent predictors gender, age at CD onset, CD affected site, familiarity for colorectal cancer, CD phenotype, and CD therapy. Cancer-free survival was calculated using Kaplan–Meier method with duration of disease or duration of life (time at risk) beginning at birth or at CD onset, respectively, and ending at the first recognition of neoplastic occurrence. Data were considered as complete when intestinal adenocarcinoma occurred. Cumulative cancer occurrence rates were compared using log rank test according to dichotomous or dichotomized variables. Multiple variable Cox proportional hazards model were used to determine independent predictors of cancer occurrence. All the variables that resulted to be significant at the univariate analysis were included in these models. A level of $p<0.05$ was considered significant in all the analyses.

Results

Patients

Ten men and two women underwent surgery for intestinal cancer in CD with a median age of 50 years (31–68). Carcinomas were localized in the terminal ileum in four cases, right colon in three, transverse colon in one, sigmoid colon in one, rectum in two, and an anorectal fistula in one. Only three patients were preoperatively diagnosed with cancer, while in the other cases, it was an intraoperative finding. At diagnosis, only three (25%) patients (one terminal ileum, one anorectal fistula, one colonic) presented with AJCC stage II cancer while four (33%; two terminal ileum, two colonic) presented with stage III, and five (42%; one terminal ileum, four colonic) with stage IV. Detailed patients characteristics are shown in Table 1.

Clinical Presentation of Cancer in CD

Clinical presentations in patients with intestinal adenocarcinoma and CD and in 79 consecutive patients operated on for CD are shown in Table 2. Obstruction and vomiting resulted to be significantly more frequent in patients with CD and cancer while diarrhea resulted significantly more frequent in control patients. Obstructive clinical presentation (nine pts) occurred in all patients with cancer of the terminal ileum and in five patients with colon cancer at advanced stages. Rectal bleeding (OR 0.385 (95% CI 0.077–1.926), $p=0.20$) and weight loss (OR 0.667 (95% CI 0.313–1.418), $p=0.17$) were unrelated to cancer diagnosis. At univariate analysis age at surgery, fever, obstruction, diarrhea, and vomiting resulted to be significantly associated to cancer diagnosis. At multivariate analysis only age at surgery (OR 1.057 (95% CI 0.999–

Table 2 Clinical Presentation of Patients with CD and Cancer and of Those with CD Undergoing Surgery Between 2004 and 2008

Patients number	CD and cancer 12	CD (2004–2008) 79	*p* Value
Clinical presentation			
Weight loss	6 (50%)	31 (54%)	0.53
Rectal bleeding	2 (17%)	27 (34%)	0.32
Mucorrhea	3 (25%)	18 (23%)	0.99
Urgency	2 (17%)	9 (11%)	0.62
Abdominal pain	10 (83%)	68 (86%)	0.66
Fever	2 (17%)	34 (43%)	0.11
Obstruction	9 (75%)	25 (32%)	0.007
Diarrhea	2 (17%)	46 (60%)	0.01
Vomiting	6 (50%)	10 (13%)	0.006
Abdominal mass	0 (0%)	6 (8%)	0.59
Urinary symptoms	0 (0%)	3 (4%)	0.99

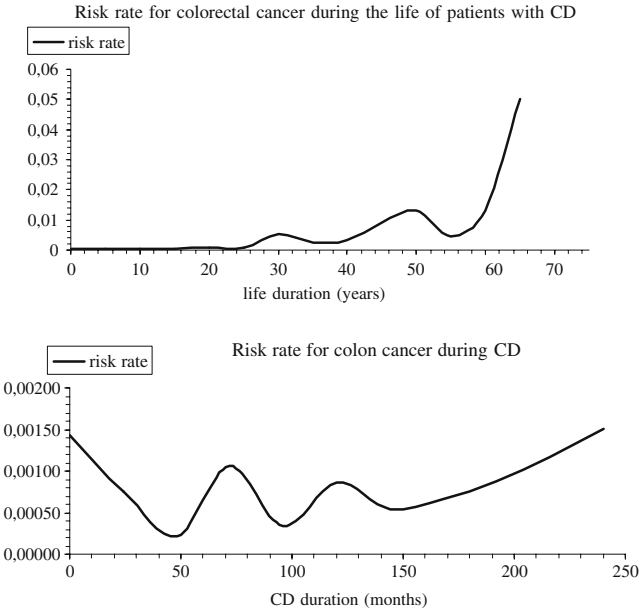

Fig. 1 Risk rate of cancer occurence in CD.

1.107), p=0.05) and obstruction (OR 6.530 (95% CI 1.533–27.806), p=0.01) significantly predicted cancer diagnosis. Significant clinical predictors of cancer occurrence in CD are shown in Table 3.

Timing of Cancer Occurrence

As shown in Fig. 1a, the risk rate (RR) for cancer occurrence started to rise at the end of the third decade of life (RR=0.005) with a second peak when the patients were of 50 years of age (R=0.013) and finally, it rose after the sixth decade (RR=0.05). The analysis of RR for cancer occurrence during overt CD showed that it is initially high at onset (RR=0.001) and then, it showed two other peaks at 72 and 120 months, respectively (RR=0.001 and 0.0009, respectively). As shown in Fig. 1b, at about 150 months from onset, the risk rate curve begins to rise again. Our data did not permit any further analysis of the following period due to the small sample size of the group of patients who was operated on for the first time. The presence of Crohn's colitis was associated to a significant risk of cancer (hazard ratio [HR]=4.790, p=0.009) while the use of 5-ASA resulted to be a protective factor against cancer occurrence (HR=0.122, p=0.013). Significant clinical predictors of cancer occurrence in CD are shown in Table 4.

Discussion

The incidence of intestinal cancer in CD disease is increasing,[9] and its diagnosis is often delayed due to the presence of symptoms that are also typical of active CD.[8] Moreover, a recent survey[10] revealed that the time interval between the first symptoms of Crohn's colitis and cancer diagnosis was very short in many patients. Nevertheless, surveillance recommendations for CD are lacking or confusing, and the current proposals are mainly focused on long-standing disease.[11,12] The aims of this study were to assess clinical presentation and timing of diagnosis of intestinal adenocarcinoma in CD.

Table 3 Clinical Presentation Symptoms as Predictors of Adenocarcinoma in CD

	Univariate				Multivariate (step forward)			
	Odds ratio	−95% CL	+95% CL	*p* Level	Odds ratio	−95% CL	+95% CL	*p* Level
Age at operation	1.050	1.001	1.102	0.044	1.052	0.999	1.107	0.051
Fever	0.265	0.053	1.316	0.100				
Obstruction	6.480	1.583	26.520	0.008	6.530	1.533	27.806	0.010
Diarrhea	0.139	0.028	0.693	0.015				
Vomiting	6.800	1.798	25.717	0.004				

Univariate and multivariate logistic regression analysis

Table 4 Significant Clinical Predictors of Cancer Occurrence in CD

Predictors	Cumulative cancer rate after 20 years	Cumulative cancer rate after 20 years	Log-rank *p* value	Hazard ratio	*P* value
CD site	Colon	All other sites			
	25.17	5.13	0.007	4.790	0.009
CD therapy	5-ASA	no 5-ASA			
	2.16	22.06	0.005	0.123	0.013

Univariate and multivariate logistic regression analysis

In our series, only three CD patients had a preoperative diagnosis of intestinal cancer. This dramatic data reflects on two aspects. First, there is a relevant delay in cancer diagnosis (75% of our patients were diagnosed at an advanced stage); second, in a standard surgical CD procedure, radical lymphoadenectomy is not mandatory. Therefore, it could result to be oncologically inadequate.[13] Moreover, these patients continue their immunosuppressive therapy until cancer diagnosis and this probably affects immunosurveillance mechanisms leading to an aggressive cancer behavior.[10]

No previous study about intestinal cancer in CD analyzed the clinical presentation and its peculiarities.[14] In our series, rectal bleeding and weight loss were unrelated to cancer diagnosis; therefore, the main symptoms for non-inflammatory colorectal cancer are invalid for the diagnosis of intestinal cancer in CD. Nowadays, the first step of all surveillance programs for non inflammatory colorectal cancer is based on occult rectal bleeding. This clinical feature is typical of active CD and it cannot be used for screening. The same could be said about weight loss which cannot be considered an alarm symptom. On the contrary, need of surgery at a young age and overt obstructive presentation significantly predicted cancer diagnosis at the multivariate analysis. Unfortunately, both of these features are typical of advanced neoplastic disease and could scarcely be useful for an early diagnosis. In fact, patients with cancer of the small bowel developed a bowel obstruction secondary to a fixed lesion which failed to resolve with medical therapy as usually occurs in patients with CD without cancer. On the other hand, more often the obstruction was secondary to a locally advanced colonic cancer or even to an overt carcinomatosis. In these cases, the initial, undefined obstructive symptoms were interpreted as common CD manifestation until it was too late.

The presence of Crohn's colitis resulted to be associated to a significant risk of cancer. Greenstein and colleagues[15] reported a relative risk of colorectal cancer of 6.9 in patients who had Crohn's colitis, Ekbom et al.[2] assessed a relative risk of 5.6 in Crohn's colitis alone and of 3.2 in Crohn's ileitis and colitis, while Gillen and colleagues[16] found an 18.2 excess risk in patients who had extensive colitis. All of this evidence suggests that the target population for an endoscopic surveillance program should be patients with colonic CD.

The use of 5-ASA resulted to be a protective factor against cancer occurrence. A large epidemiological study revealed that regular 5-ASA use is associated with some reduction in the risk of developing colorectal cancer in UC.[17] Similarly, in a systematic review, Velayos et al.[18] found a pooled ratio of 51% for the development of cancer in patients who regularly used 5-ASA medications in UC. Therefore, in spite of new therapeutic trends (up–down therapy), the use of 5-ASA, even in absence of active disease, could be justified to prevent carcinogenesis in CD.

Previous studies included long history of CD as a risk factor for intestinal cancers, often considering 20 years of disease as a cut-off before cancer development.[19] Therefore, the secondary aim of this study was to evaluate the timing of cancer occurrence in CD patients. The risk rate for cancer occurrence started to rise at the end of the third decade of life, in correspondence of CD onset, with a second peak when the patients were of 50 years of age and, finally, it rose after the sixth decade. Ekbom et al. found that young age of onset of disease increased the risk for colon cancer in CD.[2] Probably, early onset of CD could be a marker of aggressive disease leading to a long exposition of free radical and subsequent carcinogenesis.[20] In fact, in a recent study on the relationship between IBD clinical parameters and colorectal cancer interval, disease activity seemed to have an effect on the colitis-colorectal cancer interval.[21]

Moreover, Jess and colleagues in a meta-analysis that included six papers (some of the available data were several decades old) observed a linear rising trend of cumulative incidence of colorectal cancer until 25 years after CD diagnosis.[4] On the contrary, in our series, the risk rate for cancer occurrence was initially high at CD onset, and then it showed an irregular trend until 150 months when the risk rate curve begins to rise again. These data warn that during overt inflammatory disease there might be no specific risk period; therefore, there could be no safe interval of CD where surveillance could be omitted.

Conclusions

In CD, rectal bleeding, the most common alarm symptom for intestinal cancer, is not useful for an early diagnosis. CD

patients presenting with an older age and obstruction should be thoroughly investigated to rule out neoplastic lesions. Early diagnosis of intestinal cancer remains a clinical challenge in CD. There is probably no safe interval of CD where surveillance for intestinal cancer can be omitted. In the meantime, even in absence of active disease, all CD patients should undergo therapy with 5-ASA.

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2010 SSAT POSTER PRESENTATION

Ethnicity Influences Lymph Node Resection in Colon Cancer

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Abstract The purpose of this study is to determine the association between ethnicity and lymph node retrieval after colon cancer resection. Using the Surveillance Epidemiology and End Results (SEER)–Medicare database, patients who underwent colon cancer resection from 2000–2003 were evaluated. Subjects were classified as having <12 (N=20,605) or ≥12 (N=12,358) lymph nodes examined. Multivariate models were used to analyze the relationship between lymph nodes resected and independent variables. Out of a total of 32,936 patients, 62.5% had fewer than 12 lymph nodes resected. In multivariate analysis, Hispanic ethnicity was associated with a significantly lower chance of having ≥12 lymph nodes than the Caucasian population (OR=0.61; CI, 0.50–0.74). Despite this, there was no understaging: the proportion of stage II and III diagnoses was the same. Both groups received the same rate of cancer-directed surgery and survival was equivalent. During this study period, a majority of colon cancer resections were inadequate based on the current standard of ≥12 nodes. Hispanic patients were less likely to have an adequate node resection when compared to Caucasians. Despite fewer lymph nodes harvested, they had equivalent staging and survival. These results suggest that ethnicity influences the lymph node count.

Keywords Ethnicity · Lymph node · Colon cancer

Introduction

In March of 2007, the National Quality Forum endorsed the performance measure that at least 12 regional lymph nodes should be removed and pathologically examined for resected colon cancer.[1] Compliance with this benchmark has been used to evaluate hospitals,[2] select surgical providers for insurance plans, and may eventually affect reimbursement.[3] The recent focus on lymph nodes as a quality measure is due mostly to several retrospective studies that showed increased numbers of lymph nodes were associated with improved survival.[4] Whether the association is causative is not universally accepted.[3,5] However, more extensive lymph node evaluations might provide improved staging accuracy[2] and better locoregional cancer control.[6] Lymph node count is an appealing candidate for a quality indicator since it is easily measured and quantifiable, allowing for direct comparison of data and creation of a target.

Despite the established benchmark of 12 nodes, there are still a large number of resections that fall below this number. Swanson et al. found an average of nine lymph nodes resected per person[7] and Baxter et al. reported that only 37% of patients undergoing resections for cancer are actually having 12 or more lymph nodes evaluated.[8] Achieving a higher lymph node total depends on surgeon factors including the extent of resection, pathologist factors including processing techniques, and patient factors. There are a few specific patient groups that tend to have lower

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lymph node numbers, including the elderly or obese.[9–11] Other patient factors, such as ethnicity, have been shown to influence outcomes from colon cancer,[12,13] but the extent that ethnicity influences the actual number of nodes harvested is still unknown.

The aim of this study is to determine the association between ethnicity and lymph node retrieval after colon cancer resection using a large national database.

Methods

Patients

Data was taken from the Surveillance Epidemiology and End Results (SEER)–Medicare database which is a cohort of anonymized data. This database is the only comprehensive source of population-based information in the United States that includes stage of cancer at the time of diagnosis and patient survival data.[14] Beginning in late 2003, the actual lymph node number was no longer recorded as a data point. Thus, for the present study, we examined the years immediately preceding: 2000 to mid 2003. Because the database is tied to Medicare, all patients included were ≥65 years old. We selected for those with stage I–III colon cancer and those with complete lymph node data. Any patient with missing information, including race, gender, income, location, lymph node number, and tumor stage, were eliminated. This resulted in 32,963 patients with complete data information. The number of lymph nodes was then partitioned into two categories: <12 and ≥12.

Statistical Analysis

Frequencies were calculated for categorical variables of interest that included: lymph node category, race, income category, age group (broken up into groups of 65–74, 75–79, 80–84, 85–89, and ≥90 years), cancer stage, gender, Charlson comorbidity score, and population size. Cross tabulations were examined for each independent and outcome variable. Differences between the proportions were determined with the Chi-squared statistic.

Univariate logistic regression models were used to evaluate the outcomes of lymph nodes examined during surgery and cancer-directed (curative intent) surgery. All variables with a p value of 0.10 or lower were considered a variable of interest for model building.

Based on the variables extracted from the univariate regression, multiple regression analysis was performed to evaluate associations and adjust for covariates and confounders. Using a stepwise approach, all variables were entered into a model and eliminated one by one beginning with the least significant until all remaining variables were significant ($p<0.05$).

Overall survival time was measured in months after diagnosis of colon cancer to death. Patients with a cause of death not attributable to colon cancer were censored to allow us to examine cancer specific survival rates only. Univariate analysis of survival was performed using Kaplan–Meier estimates. Adjusted hazard ratios were estimated using Cox proportional hazards regression.

Results

Of the 32,963 patients included in our analysis, 54.8% were female, most were Caucasian (84.6%) and lived in a large metropolitan area (61.5%). Table 1 provides demographics of the entire group and demographics for the Caucasian and Hispanic populations. When compared to the Caucasian group, the Hispanic population was younger, had fewer females, lived in more populated areas, and had a lower annual income.

Overall, 62.5% of resections for colon cancer had fewer than 12 lymph nodes examined. The number of lymph nodes harvested was then inspected among five ethnicities: Caucasian, Black, Asian, Hispanic, and Native American. Hispanic patients had a much higher rate of inadequate resection (<12 nodes). In the multivariate model, the Hispanic group had an odds ratio of 1.64 (confidence interval (CI) 1.35–2.00) predicting a lymph node harvest of <12 (Table 2). The lymph node ratio (number of positive nodes ÷ total nodes) for Hispanics was 0.11 and for Caucasians was 0.091.

Using Caucasian as a reference group, the Hispanic population was then compared with respect to cancer-directed surgery. Overall, the rate of cancer-directed surgery was very similar between these two ethnicities: Caucasian (96.6%) and Hispanic (96.7%). This was further analyzed in a multivariate model where their odds ratios for receiving cancer-directed surgery remained the same (Caucasian, referent; Hispanic, OR 1.07, CI 0.75–1.53; Table 3). The Hispanic and Caucasian populations were then compared by cancer staging. This revealed a nearly equivalent breakdown of stage I–III tumors in these two groups. When compared to the Caucasian group and adjusted for covariates, overall survival was not influenced by Hispanic ethnicity (Table 4).

Discussion

The benchmark for lymph node harvest from a colon cancer resection has been set at 12,[1] yet this standardized goal remains difficult to consistently attain.[15] There are many

Table 1 Demographics

Characteristic	All, % (*N*=32,963)	Caucasian, % (*N*=27,884)	Hispanic, % (*N*=540)
Age			
65–69	18	17.2	13.2
70–74	21.9	21.5	29.8
75–79	24.1	24.2	27.2
80–84	19.3	19.6	16.7
85–89	11.8	12.5	10.3
90+	4.9	5	2.8
Lymph nodes			
0–11	62.5	62	73
≥12	37.5	38	27
Urban vs. rural			
Big metropolitan	61.5	59.7	70.2
Metropolitan	26.4	27.1	25.7
Urban	4.7	4.9	2.2
Less urban	6.2	6.9	1.7
Rural	1.2	1.4	0.2
Female gender	54.8	55	50
Stage			
I	31.1	31	31
II	39.5	40	40
III	29.4	29	29
Income category			
0–36,999	28.7	25.4	39.6
37,000–45,999	20.4	21	24.3
46,000–60,999	26.6	27.8	18.9
61,000+	20.9	22.4	11.9
Unknown	3.4	3.3	5.3
Total comorbidity score			
0	73.4	73.5	70.7
1	16.2	16.3	17.4
2	6.1	6.1	6.3
3+	4.3	4.1	5.6

factors that influence the number of nodes counted, including surgeon, pathologist, and patient. In this study, we showed that ethnicity, specifically Hispanic ethnicity, may be a specific patient factor associated with diminished lymph node count.

Major demographic shifts occurring in the US population include aging[16] and changes in the ethnic make-up. It is projected that by 2050, 25% of the US population will be Hispanic, almost double by what it is today.[17] Unfortunately, ethnic minorities are consistently underrepresented and underreported in medical research.[18] There have been studies describing ethnicity's influence on outcomes from various cancers,[19,20] but no study has looked at ethnicity's influence on lymph node numbers in colon cancer resection. While patient factors alone are not the only influence on lymph node count, based on our findings, some patient groups may have fewer nodes evaluated without leading to understaging, undertreatment, or decreased survival. This suggests that creating a numerical benchmark without factoring in patient characteristics might be an inappropriate measure of quality.

Most studies do show an association between increased number of lymph nodes retrieved and improved survival.[4,6,21,22] However, it is difficult to show that this association is causative. Our study adds to the list of unmodifiable biologic factors that should be considered when evaluating a fixed numerical lymph node minimum. Others include increasing age, stage of disease, and primary site. As lymphoid tissue ages, it atrophies and involutes.[23] Bilimoria et al. showed that with increasing age, the number of lymph nodes harvested decreases.[10] Earlier stage of disease is also associated with fewer lymph nodes as is

Table 2 Multivariate analysis of the probability of having fewer than 12 lymph nodes recorded

Variable		Odds ratio	95% CI	*p* value
Age category	Main effects			0.196
Race	White	Referent		<0.0001
	Hispanic	1.64	(1.35–2.00)	
	Black	1.16	(1.06–1.27)	
	Other	0.90	(0.76–1.05)	
	Asian	1.14	(1.01–1.30)	
	Native American	1.06	(0.66–1.72)	
Urban/rural	Large Metro	Referent		<0.0001
	Metropolitan	1.02	(0.97–1.08)	
	Urban	1.34	(1.19–1.51)	
	Less urban	0.89	(0.80–0.99)	
	Rural	0.98	(0.79–1.22)	
Gender	Main effects			<0.0001
Cancer stage	I	Referent		<0.0001
	II	0.42	(0.40–0.45)	
	III	0.33	(0.31–0.35)	
Income category	>36,999	Referent		<0.0001
	37,000–45,999	0.95	(0.88–1.02)	
	46,000–60,999	0.82	(0.76–0.87)	
	61,000+	0.77	(0.72–0.83)	
Total comorbidity category	0	Referent		<0.0001
	1	1.01	(0.94–1.07)	
	2	1.15	(1.04–1.26)	
	3+	1.32	(1.17–1.49)	

Table 3 Multivariate analysis for receiving cancer-directed (curative intent) surgery

Variable		Odds ratio	95% CI	*p* value
Age category	Main effects			<0.0001
Race	White	Referent		<0.0001
	Hispanic	1.07	(0.75–1.53)	
	Black	0.57	(0.50–0.66)	
	Other	0.91	(0.67–1.24)	
	Asian	1.27	(0.96–1.69)	
	Native American	0.53	(0.25–1.13)	
Urban/rural	Large metro	Referent		<0.0001
	Metropolitan	1.24	(1.11–1.39)	
	Urban	0.90	(0.74–1.10)	
	Less urban	1.15	(0.94–1.40)	
	Rural	2.41	(1.38–4.23)	
Gender	Main effects			<0.0001
Cancer stage	Main effects			<0.0001
Income category	>36,999	Referent		0.0194
	37,000–45,999	1.14	(0.99–1.30)	
	46,000–60,999	1.18	(1.03–1.34)	
	61,000+	1.13	(0.98–1.30)	
Total comorbidity category	0	Referent		<0.0001
	1	0.93	(0.83–1.05)	
	2	0.79	(0.67–0.93)	
	3+	0.66	(0.55–0.78)	

Table 4 Multivariate analysis for survival

Variable		Hazard ratio	95% CI	*p* value
Age group	65–69	Referent		<0.001
	70–74	1.21	(1.19–1.30)	
	75–79	1.51	(1.41–1.63)	
	80–84	2.17	(2.02–2.33)	
	85–89	2.98	(2.76–3.22)	
	90+	4.43	(4.05–4.84)	
Race	White	Referent		<0.001
	Hispanic	1.09	(0.94–1.26)	
	Black	1.17	(1.09–1.23)	
	Other	0.83	(0.71–0.96)	
	Asian	0.82	(0.73–0.92)	
	Native American	1.16	(0.79–1.25)	
Urban/rural	Large Metropolitan	Referent		0.019
	Metropolitan	0.94	(0.89–0.99)	
	Urban	0.96	(0.87–1.06)	
	Less Urban	0.89	(0.81–0.97)	
	Rural	0.98	(0.82–1.15)	
Gender	Male	Referent		0.518
	Female	0.98	(0.94–1.02)	
Cancer stage	I	Referent		<0.001
	II	2.23	(2.08–2.38)	
	III	5.71	(5.37–6.08)	
Income category	0–36,999	Referent		<0.001
	37,000–45,999	0.93	(0.88–0.99)	
	46,000–60,999	0.87	(0.82–0.92)	
	61,000+	0.83	(0.78–0.89)	
Comorbidity score	0	Referent		<0.001
	1	1.21	(1.14–1.27)	
	2	1.37	(1.27–1.48)	
	3+	1.83	(1.09–1.26)	

the primary site, with fewer nodes in the distal colon.[24,25] Our study shows that Hispanic ethnicity is associated with a lower lymph node count. By current quality indicators, this would suggest that these patients are inadequately staged and therefore, undertreated.[26,27] However, a recent study by Baxter et al. found that when controlling for confounding variables, staging was not affected by any node count greater than seven. This is similar to our finding that despite a larger portion of Hispanic patients with fewer than 12 lymph nodes retrieved, the staging was equal to the Caucasian group. Furthermore, we demonstrated that survival between the Hispanic and Caucasian populations was the same despite the discrepancy in lymph node harvest, suggesting these patients were not undertreated.

Reasons for this difference in Hispanic patient's lymph node counts are unclear. As previously mentioned, lymph node numbers may vary by the segment of colon resected, but the most common sites for colon cancer seem to be similar in Hispanic and Caucasian patients. Gomez et al. stated that the tumor distribution was in the left colon in 69% of Caucasians, and Chattar-Cora et al. quoted a 69% left colon tumor rate in Hispanics.[28,29] Lymph node ratio has also been a recent focus of interest for predicting prognosis from colon cancer,[30] but in our study, the Hispanic and Caucasian patients had very similar ratios.

The SEER–Medicare database allows for examination of a large patient population and long-term follow-up. Limitations to this study include possible selection bias, which is difficult to eliminate without randomization. There also may be unrecorded variables that are unaccounted for and act as confounding factors. Furthermore, the accuracy of staging in the Hispanic population with fewer nodes resected cannot be directly verified. However, we used survival as the ultimate test of staging, and this was equivalent between the two ethnicities leading us to believe that the staging was reliable. We report information for those ≥65 years old, so while we are only accounting for this subset of the population, it is the subset with the highest rates of colon cancer.

Conclusion

While most colon cancer resections have fewer than 12 lymph nodes harvested, we found that even fewer Hispanic patients met this benchmark. This difference did not translate into understaging, undertreatment, or decreased survival when compared to the Caucasian population. This suggests that ethnicity is a variable that affects lymph node number and that use of lymph nodes as a quality indicator may need to be modified depending on ethnicity.

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2010 SSAT QUICK SHOT PRESENTATION

Obstetric and Cryptoglandular Rectovaginal Fistulas: Long-term Surgical Outcome; Quality of Life; and Sexual Function

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Abstract
Purpose Rectovaginal fistula (RVF) repair can be challenging. Additionally, women may experience sexual dysfunction and psychosocial ramifications even after a successful repair. The aim of this study was to investigate variables looking for predictors of healing/failure and examine long-term quality-of-life (QOL) and sexual function in women with low RVF from obstetrical or cryptoglandular etiology
Methods From June 1997–2009, 268 women underwent RVF repair. Of those, 100 with obstetric or cryptoglandular etiology agreed to participate in this study. Healing, type of procedure, use of seton or stoma, number of previous procedures, smoking, age, body mass index (BMI), dyspareunia, QOL using SF-12, FIQL, IBS-QOL, and female sexual function index was obtained from our prospective database and telephone contact. Fisher's exact test, chi-square test, and multivariable-logistic-regression model were used to identify the variables associated with healing/failure.
Results Mean follow-up was 45.8±39.2 months; mean age 42.8±10.5 years; and BMI was 28.8±7.6. Sixty (60%) fistulas were obstetric and 40 (40%) cryptoglandular and 68/100 patients (68%) healed. On multivariate analysis, treatment failure was related to a heavier BMI ($p=0.001$) and number of repairs ($p=0.02$). Looking at each type of repair, episioproctotomy had significant healing compared to the other choices (but was not significant on multivariate analysis). Forty-seven women were sexually active at follow-up and 12/47 (25.5%) reported dyspareunia. Fecal incontinence was reported preoperatively in 42 women, more often in those with obstetric-related RVF (76% vs. 24% $p<0.05$). Healing was not affected by age, smoking, co-morbidities, preoperative seton, or stoma use. Fecal and sexual function and QOL were comparable between women with healed and unhealed RVF.
Conclusion Patients with higher BMI and more repairs had a decreased healing rate following RVF repair. Despite surgical outcome, QOL and sexual function were surprisingly similar regardless of fistula healing.

Keywords BMI · Rectovaginal fistula · RVF · Obstetric · Cryptoglandular

Introduction

Ano-recto-vaginal fistula (RVF) is defined as an abnormal epithelial-lined communication between the anterior wall of the rectum and the posterior wall of the vagina, but fistula originating in the anal canal and those extending into the perineal area are also included. Common symptoms include chronic vaginal discharge, dysparuenia, and the passage of flatus or stool through the vagina. Women affected by RVF may have significant psychosocial and sexual dysfunction as a result of both the fistula and surgical repairs undertaken for cure. RVF may be a major cause for morbidity and a

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source of considerable social embarrassment for the women involved. Successful surgical management of RVF can be challenging. Deficient or absent anterior muscle and fecal incontinence (FI) are issues that influence surgical consideration.

The main etiology of RVF is obstetrical trauma which may be unrecognized at the time of forceps delivery or precipitate vaginal delivery.[1–3] However, only 0.1% of vaginal deliveries results in a fistula.[3,4] Other benign etiologies are local infection, postoperative surgical complication, inflammatory disease, and trauma.

RVF are classified according to cause, location, and size.[5–7] Unfortunately, there is no uniform classification system making comparison of treatment results difficult.[6] Surgical techniques for repair include local repair (by transanal, vaginal, or perineal approach), several tissue transposition procedures (which use tissue such as omentum, gracilis muscle, or labial fat), and trans-abdominal repair.[6]

This study was undertaken to examine the success rate of surgical treatment of RVF in our institution from cryptogladular or obstetrical etiology. We attempted to identify factors that influence the rate of healing on this selective group of women. Additionally, the effect of surgery on quality-of-life (QOL), fecal continence, and sexual function at long-term follow-up was studied.

Methods

All women with cryptoglandular or obstetric-related RVF who underwent surgical repair between June 1997–2009 were contacted for long-term follow-up. Variables assessed were age, body mass index (BMI), smoking, type of procedure, use of seton or stoma, number of previous procedures, time interval between last repair and current repair, dyspareunia, QOL using SF-12 Health Survey Scoring,[8] The Irritable Bowel Disease Quality of Life Instrument (IBS-QOL),[9] and Fecal Incontinence Quality of Life Scale (FIQL).[10] Telephone contact by a research nurse using a four-question phone script regarding RVF recurrence symptoms and dysparuenia was administered. Then, a validated, standardized questionnaire that assessed quality of life, bowel symptoms, and sexual function was mailed to the patients.

Sexual function was evaluated using the Female Sexual Function Index (FSFI), a validated questionnaire assessing domains of sexual functioning like sexual arousal, orgasm, satisfaction, and pain. This provides a domain score range of 0–36; zero indicates no sexual activity and 36 being the best sexual function.[11]

Data were collected from an IRB approved database for pelvic floor disorders, review of medical records, patient administered questionnaires, and a telephone call. The entire study was IRB approved. Patients were excluded if the surgical procedure was not intended to close the RVF. This study also excluded all patients with pouch-vaginal fistula, Crohn's fistula, colovaginal, and iatrogenic or post-radiation fistulas. Because this study examined the results from 12 surgeons, the technical aspect are somewhat individualized. The critical part of the procedure, however, is performed in a similar fashion and has been reported elsewhere.[12,13] Various methods of repair were used and grouped as follows: episioproctotomy which essentially is a fistulotomy with overlapping sphincter repair; transanal rectal or sleeve advancement flap; Turnbull–Cutait pull through which is an abdominal proctectomy with colonic pull-through and delayed coloanal anastomosis (coloanal anastomosis); fibrin sealant instillation with oversewing of the internal bowel opening (other). Patients without a diverting stoma underwent bowel preparation with oral lavage before operation. Patients with a diverting stoma received preoperative enemas to eliminate any rectal mucus. All patients received perioperative intravenous antibiotics. We examined the overall rate of surgical success of RVF and then performed analysis on various parameters we felt could have impact on outcome. Failure was defined by passing stool, discharge, or gas per vagina with anoscopic evidence of a recurrent internal opening.

Logistic regression models were used to identify variables associated with failure. Univariable models were employed, in addition to a multivariable model to assess selected covariate-adjusted associations with outcome. Healed and unhealed groups are presented for descriptive purposes with respect to quantitative variables, which are summarized as "mean ± standard deviation" within groups. One author (JH) has a master's degree in statistical analysis and performed the statistical studies.

Results

Between 1997 and 2009, 268 women were identified with RVF. Of these, 100 women with obstetric and cryptoglandular RVF were contacted by telephone and agreed to participate in this study. The average age was 42.8± 10.5 years and BMI was 28.8±7.6. The etiology of fistulas was obstetrical injury in 60 (60%) patients and cryptoglandular in 40 (40%) patients (Table 1). The most common complaints were vaginal drainage (79%), gas per vagina (65%), and stool per vagina (52%). The mean follow-up was 45.8±39.2 months. Of these patients, 68 (68%) eventually healed after a median of two operations. Twenty-two patients (32.4%) were successfully treated after only one repair. Of the remaining healed patients, 12 underwent two repairs, 14 patients had three repairs, and 20 patients had >3 repairs. Thirty-two patients (32%) failed

Table 1 Demographic and Patient's Characteristics

Variables		Overall n=100	Healed 68 (68%)	Unhealed 32 (32%)	p Value	Odds ratio (95% CI)
Age		42.8±10.5	43.2±11.1	41.9±9.2	0.6	
BMI		28.8±7.6	26.1±5.4	34.2±8.7	0.001	2.3 (1.5–3.3)
Smoking	No	73 (73%)	51 (69.9%)	22 (30.1%)	0.5	
	Yes	27 (27%)	17(63%)	10(37%)		
Etiology	Obstetric	60 (60%)	41 (68.3%)	19 (31.7%)	0.9	1.0 (0.4–2.3)
	Cryptoglandular	40 (40%)	27 (67.5%)	13 (32.5%)		
Ethnic group	Caucasian	89 (89.0%)	63 (70.8%)	26 (29.2%)	0.046	
	African American	6 (6.0%)	3 (50.0%)	3 (50.0%)		
	Others	5(5.2%)	2(40%)	3(60%)		
Follow-up time months (mean)		45.8±39.2	48.7±39.6	39.9±38.8	0.4	
Improvement in fecal incontinence		29/42 (69%)	22/28(78.6%)	7/14(50%)	0.3	
Vaginal delivery		65 (65%)	45 (69.2%)	20 (30.8%)	0.6	
Episiotomy/tears		50(59.5%)	33(66%)	17(34%)	0.7	
ASA (mean±SD)		2±0.7	2±0.7	2±0.7	1.0	
Comorbidity	Diabetes	8 (8%)	7 (87.5%)	1 (12.5%)	0.4	
	Pulmonary	5 (5%)	2 (40%)	3 (60%)	0.3	
	Cardiovascular	10 (10%)	8 (80%)	2 (20%)	0.7	
	Irritable bowel syndrome	10 (10%)	6 (60%)	4 (40%)	0.7	

treatment after a median of four operations. Of 32 patients in whom repairs were repeatedly unsuccessful, the etiology in 19 patients was an obstetric injury and 13 patients had a cryptoglandular fistula. There were no deaths or major morbidities. Twenty-nine (29%) had one or more loose draining setons in situ before surgical repair, and 62 patients (62%) had a stoma at the time of repair (Table 2).

Preoperative fecal incontinence was reported in 42 (42%) women, more often in the obstetric RVF (76% vs. 24%, p<0.05). Of fifty patients (50%) in this cohort who underwent episioproctotomy, fecal incontinence was reported preoperatively in 25 (50%). After repair the number of patients with fecal incontinence decreased to only four patients (8%; p<0.001). However, there was no significant change in postoperative FI in patients that underwent other repairs (p=0.4).

There was no significant affect of age, etiology, smoking, co-morbidity, ASA, preoperative seton, or stoma

Table 2 Preoperative and Operative Details

Variables		Healed 68 (68%)	Unhealed 32 (32%)	p value	Odds ratio (95% CI)
Seton	Yes	18 (62.1%)	11 (37.9%)	0.4	
	No	49 (70.0%)	21 (30.0%)		
Stoma	Yes	43 (69.4%)	19 (30.6%)	0.9	
	No	24 (70.6%)	10 (29.4%)		
Type of current repair	Episioproctotomy	39 (78%)	11 (22%)	**0.04**	
	Advancement flap	23 (62.2%)	14 (37.8%)	0.3	
	Colo-anal anastomosis	3 (50%)	3 (50%)	0.4	
	Others	3 (42.9%)	4 (57.1%)	0.3	
Number of repairs median (range)		2 (1–5)	4 (1–8)	0.007	1.5 (1.1–2.0)
Interval from last repair to current (months)[a]		7.5 (4.8–12)	8.3 (5.1–13.1)	0.9	
Interval from seton to current repair (months)[a]		3.5 (2–6.8)	2.2 (1.2–2.7)	0.06	
Interval from stoma to current repair (months)[a]		5.1 (1–11.4)	4.8 (0–13.5)	0.5	

[a] Median interquartiles (IQR)

on healing rates (Table 1). Episioproctotomy was the only significant type of repair associated with a better healing rate (p=0.04). There was no significant difference in duration of time from the prior repair to the current repair (p=0.9) and the duration from stoma creation to the current repair (p=0.5) between successfully healed and failed repairs. The healed group had a longer duration between insertion of seton and the current repair than the unhealed group (p=0.06; Table 2).

Quality of Life and Sexual Function

Sixty-seven (67%) women (45 healed and 22 unhealed) agreed to complete the QOL questionnaire. There was no significant difference in the mean FIQL scores between healed and unhealed patients (p=0.5) in all areas: lifestyle (p=0.2), coping behavior (p=0.1), depression and self-perception (p=0.1), and embarrassment (p=0.7). Additionally, the IBS-QOL and SF-12 were comparable between healed and unhealed patients (Table 3).

Forty-seven women (47%) were sexually active at follow-up and of those, 12 women (25.5%) complained of dyspareunia; however, there was no significant difference between healed and unhealed patients regarding dyspareunia (p=1.0; Table 3). Thirty-four (72.3%) patients completed the sexual function questionnaire using FSFI. There was no significant difference between healed and unhealed patients (p=0.7) in all domains; desire (p=1.0), arousal (p=0.7), lubrication (p=0.2), orgasm (p=0.9), satisfaction (p=0.9), and pain (p=0.4; Table 4).

On multivariate analysis, healing was found to be related to BMI and number of repairs. Patient with a higher BMI did poorer (p=0.001). A greater number of repairs was associated with unhealed fistula (p=0.02; Table 5).

Table 3 Patient's Quality of Life

Variables		Healed 45 (67.2%)	Unhealed 22 (32.8%)	p Value
FIQL		11.3±3.8	10.8±2.9	0.5
	Life style	3.2±1.1	2.8±0.9	0.2
	Coping	2.8±1.1	2.4±0.8	0.1
	Depression	2.6±0.8	2.2±0.7	0.1
	Embarrassment	2.7±1.1	2.6±0.8	0.7
SF-12	Physical health	47.0±10.0	45.4±9.6	0.6
	Mental health	44.5±12.7	43.8±10.5	0.8
Sexual activity		31 (66.0%)	16 (34.0%)	0.08
Dyspareunia	Yes	8 (65.0%)	4 (35.0%)	1.0
	No	23 (70.0%)	12 (30.0%)	
IBS QOL score		59.4±31.3	55.2±28.1	0.6

Total numbers represent patients with this data

Table 4 Female Sexual Function Index (FSFI)

Variables		Healed n=19 (55.9%)	Unhealed n=15 (44.1%)	p Value
FSFI	Desire	3.0±1.1	3.0±1.2	0.1
	Arousal	3.0±1.9	3.2±1.8	0.7
	Lubrication	3.1±2.2	3.7±2.0	0.2
	Orgasm	2.8±2.1	2.9±1.8	0.9
	Satisfaction	3.2±2.1	3.2±1.6	0.9
	Pain	3.5±2.5	2.7±2.2	0.4
Total FSFI		21.7±14.3	19.8±10.1	0.7

Total numbers represent patients with this data

Discussion

Obstetric-related RVF are usually caused by injury sustained during vaginal childbirth associated commonly with poor healing of the primary repair of a third or fourth degree perineal tear.[3,14] Cryptoglandular-associated RVF arise secondary to cryptoglandular sepsis. When reported, they typically represent only a small number in most series and are rarely documented separately so the success rate after treatment is not well established. In some series, it appears that cryptoglandular-associated fistulas have a poorer healing rate than RVF from other etiologies after treatment.[15–17]

There is no "best" treatment option for all patients with RVF, and patient selection and preparation is the key to achieving satisfactory outcome. Many techniques have been developed in the attempt to treat RVF with a wide range of success rates in the literature. Successful repair of RVF due to obstetric and cryptoglandular etiologies range from 50% to 100% in the literature.[7,15–19]

Ozuner et al. reported long-term recurrence rate of 23% and 32% for obstetric and cryptoglandular fistulas, respectively.[17] Mazier et al. reported less than 5% recurrence rate for both obstetric and cryptoglandular fistulas.[16] Sonoda et al reported 60% and 23% recurrence rate for obstetric and cryptoglandular fistulas, respectively.[20] Halverson et al. studied 15 women with obstetric-related RVF where all healed after a combined 23 operations. Two other patients

Table 5 Multivariable Logistic Regression Model for Recurrence

Variable	Parameter estimate	Standard error	Odds ratio (95% CI)	p Value
BMI	0.822	0.200	2.27 (1.54–3.37)	0.001
Number of Repairs	0.411	0.173	1.51 (1.07–2.12)	0.02
Smoker	0.078	0.593	1.08 (0.34–3.46)	0.9
Follow-up time	0.010	0.008	1.01 (1.00–1.03)	0.2

with cryptoglandular RVF healed after a combined four operations.[21] In the present study, after multiple repairs and mean 46 months follow-up, the overall recurrence rate was 32% (31.7% obstetric and 32.5% cryptoglandular). This was consistent with other studies.[17,20,21]

We did not observe any correlation between method of repair and subsequent success of repairs except in the episioproctotomy group where there was a significant increase in number of healed patients (p=0.04); however, this finding should be taken cautiously as most of these patients underwent more than one repair before the successful episioproctotomy. The repair methods used were chosen according to each patient's anatomic defects and underlying pathology along with the surgeon's preference. The value of a protecting stoma remains unclear. Our study, like prior studies, did not demonstrate a significant difference (p=0.9) when using a diverting stoma.[16,21–23] Forty patients (46%) in this study were transferred to us from outside hospitals and most of them came to us with a diverting stoma. Our current practice is to avoid diversion prior to repair unless there is uncontrolled sepsis. The decision is made at the time of repair regarding diversion. Patients with recurrent RVF and/or extensive scar tissue are usually diverted.

There was no difference in mean length of time from prior repair to current repair between healed and unhealed patients and this may be due to our unit's view, to wait at least 3 months between repairs.

On multivariate analysis the obese patients (mean BMI 34.2 kg/m^2) had a significant lower healing rate (p=0.001), and this finding does not appear to be previously reported in the literature with obstetric and cryptoglandular RVF. Also, the number of previous repairs was a statistically significant variable with poor healing associated with an increased number of repairs (p=0.02; Table 5). This was consistent with other studies.[17,21,24–26] Lowry et al. reported a success rate of 88% in patients undergoing a primary repair of a RVF. The success rate after one previous failed attempt was 85%, and if the patients had two prior repair attempts, the success rate dropped to 55%.[24] Decreased success with subsequent repairs may be attributed to poor blood supply in an area of scar tissue, unresolved inflammation, or may simply reflect a difficult fistula to repair.

Sexual function and QOL following RVF surgery are rarely documented separately in the literature. In the present study, dyspareunia and the sexual function were not significantly different between healed and unhealed patients. This may be due to the small number of patients who responded to the female sexual function questionnaire or may be due to the limitations of current method of sexual function evaluation which did not assess sexual function before, and 6 months and 1 year following surgery.

Our study is a large series from a single institution attempting to evaluate the long-term outcome of surgical repair and QOL of obstetric and cryptoglandular RVF. However, this study is limited by its retrospective design. Although this study has a longer follow-up compared to previous reports from this institution, the success rate of healing is comparable to our previous reports.[17,20–22,27]

It has been published that the best prospect for cure of the fistula is at the first operation. Repair of a RVF should only be undertaken by surgeons who have the appropriate experience in these operations.[28] Although the condition is very distressing, surgeons should not rush to operate until complete resolution of infection and induration occurs. Most authorities recommend a minimum waiting period of 3 months;[21,28,29] otherwise, surgical success is likely to be compromised.

Conclusion

Patients with higher BMI and more repairs had decreased healing rates for repair of cryptoglandular and obstetrical related RVF. Despite surgical healing, sexual function, and QOL were similar between women who were healed versus unhealed.

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2010 SSAT POSTER PRESENTATION

Hemostasis after Liver Resection Improves after Single Application of Albumin and Argon Beam Coagulation

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Abstract
Background Bleeding from the liver surface is common after hepatic resection. Animal studies have demonstrated superiority of argon beam coagulation (ABC) and 38% human serum albumin when applied together after partial liver resection when compared to ABC alone. There are no data addressing the combination of albumin and argon beam coagulation (ABCA) applied to the bleeding liver after resection in humans. The aim of this study was to evaluate the safety and efficacy of ABCA on hemostasis when applied to the surface of the liver remnant post-hepatic resection.
Methods Ten patients underwent liver resection and were treated with ABCA immediately after the liver was divided. The liver surface was coated with albumin and ABC applied simultaneously, the liver was covered with gauze for 3 min, and ABCA was repeated if necessary. Number of rebleeding episodes requiring re-application of ABCA, time of ABCA application, overall blood loss, and liver functions were monitored. Patients were followed for at least 6 months.
Results Nine of 10 patients required a single application of ABCA, and one patient required two treatments. Average time of ABC use was 5±3 min. Median blood loss was 230 ml. Liver functions returned to near normal within 4 days of resection.
Conclusions ABCA performed well with respect to hemostatic properties, much like previous observations in animal studies. Further clinical trials are justified using this technique.

Keywords Liver · Hemostasis · Albumin · Argon beam coagulation

Background/Introduction

The liver is the most common site of metastases for many tumors, especially those originating in the gastrointestinal tract. A more common problem worldwide is primary hepatocellular carcinoma, the third leading cause of cancer death overall which accounts for nearly 700,000 deaths worldwide.[1] In the USA, most liver resections are done for colorectal metastases followed by resections for primary hepatocellular carcinoma. Approximately 160,000 patients present with colorectal cancer each year in the USA, and 40,000 will develop liver metastases.[2] Overall, 30,000 patients will have liver only disease during some of their disease course and may be candidates for resection. Patients with other tumors metastatic to the liver will be offered surgery; these tumors include soft tissue sarcoma, melanoma, gynecologic tumors, neuroendocrine tumors, and others.[3] With disease limited to the liver, patients undergoing complete resection of primary or metastatic tumor may be cured. Typically, series report 5-year survival of 20% to 60% following such resections.[4–7] Median survival for patients with unresected primary liver tumor or colorectal metastases is closer to 6 to 12 months.

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Major risks associated with liver resection are related mainly to intraoperative bleeding, bile leak, infectious complications, and liver failure.[8–10] Typical blood loss in major hepatic resection ranges from 800–3,000 ml, although novel instrumentation and division of liver parenchyma with decreased central venous pressure has lead to decreased intraoperative bleeding.[11–16] Up to 80% of patients undergoing resection will require transfusion.[9] Operative time is a significant risk factor for perioperative complications associated with resection.[17] Liver injuries from blunt or penetrating trauma or iatrogenic liver injuries may produce similar complications.[6] Following trauma to the liver, bleeding is normally reduced by vasoconstriction, platelet activation, and adherence to the injured surface and blood clotting occurs. If the liver injury or resection is complex, these hemostatic mechanisms may not be sufficient. Increased serum levels of tissue plasminogen activator are associated with surgery and this can be problematic in situations associated with significant bleeding such as liver transplantation.[18] In these instances, diffuse oozing from the liver will not stop spontaneously and normal hemostatic mechanisms are inadequate.

Surgery of visceral organs such as liver, spleen, and kidney can be challenging, not only in controlling hemorrhage but also in preventing complications following surgery. Rapid, hemostatic and durable sealing of the injury site is the key to successful soft tissue surgery. Traditional surgical techniques such as gauze packing, mesh sutures, and staples can fail to seal the resected surface initially.[11] Patients most vulnerable are those with diffuse bleeding caused by hypothermia, coagulopathy, extreme blood loss, electrolyte disturbance, or acidosis.[19] Fibrin glue seals wound surfaces, but it sometimes performs poorly when bonded to a liver surface with active bleeding.[20] Data regarding fibrin sealants and liver surgery are mixed; some authors report superior results with fibrin glue[12], but one large randomized controlled trial of 300 patients found no difference with respect to blood loss or bile leak when fibrin glue was compared to controls.[21] Suture is inadequate for diffuse bleeding, seen sometimes after prolonged resection or in cirrhotic patients. Packing is an effective but temporary solution. Most superficial applications to the liver are not effective during active bleeding because flow of blood prevents contact of the agent to the liver surface.[22]

Thermal techniques have been used in surgery for many years by coagulating tissue and fusing small vessels. The extracellular collagen in the coagulated tissue acts as a biologic glue that bonds the contiguous tissues. Chemical cautery and electrocautery have been found to control bleeding, but neither are particularity efficacious in stopping moderate active bleeding from the liver. The argon beam coagulator (ABC) is frequently used in surgery for hemorrhage control of solid visceral organs[23–26] and is more effective for mild to moderate rates of bleeding. The bond strength from ABC application can be improved significantly by adding exogenous protein before heating. This concept has been studied extensively in our laboratory. We have heated liver and other organ surfaces coated with albumin using a 800 nm Diomed laser or ABC, resulting in tissue welding in which albumin is used as a solder to join tissues.[22,23,27,28] Laser energy applied to tissue surfaces coated with albumin (Fig. 1) in this manor results in a durable coating with considerable strength and resistance to disruption, with burst strength comparable to the liver itself.[27] This technique relies on heating of the albumin, unraveling of some of the extracellular matrix proteins, followed by cooling and adherence of albumin with adjacent tissue proteins.[29]

A series of pre-clinical animal studies have been performed in order to optimize bonding, by adjusting the energy source, the concentration of albumin and method of application. We have established that administration of topically applied 38% albumin to the resected liver surface along with argon beam coagulation significantly reduces bleeding from the liver.[22,23] Albumin applied in this fashion is well tolerated and appeared to add no specific toxicity, with acute and long-term animal data demonstrating equivalence to argon beam coagulation alone, with respect to complications, histology, and adhesion formation.[29] Both methods readily stop bleeding of the liver, leave residual coagulated albumin remnants, and encapsulate and these remnants up to a year postoperatively. A study was designed to evaluate the efficacy of argon beam coagulation either with 38% albumin applied to the resected liver (ABCA) or without albumin (ABC) as previously described.[22] Animals treated with ABCA had significantly fewer rebleeding episodes when compared to the control group (0.5 vs. 1.5 average rebleeds per surgery, respectively). Although blood loss in the two groups was not significantly

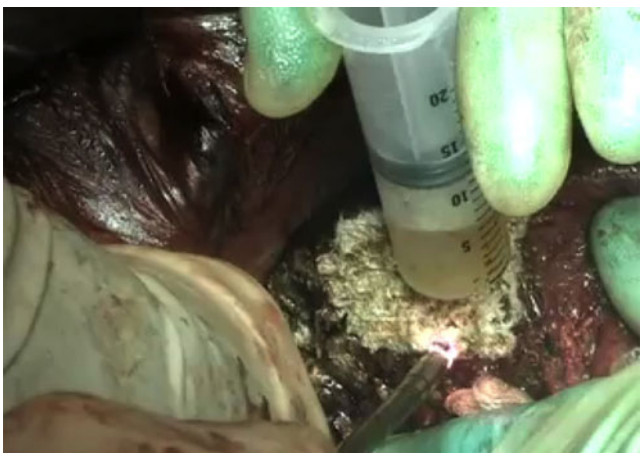

Fig. 1 38% HSA application on resected surface of liver post right hepatectomy.

different, a trend toward less blood loss in the ABCA group was apparent.[22,23]

Based on the success of the acute study, a chronic preclinical study was performed to compare healing responses between ABC and ABCA repairs at one and three months. Histology and adhesions observed in the two animal groups were not different at 12 months.[23]

We hypothesize that ABCA applied to human patients undergoing major hepatic resection will have benefits similar to those observed in our animal patients. To assess safety and feasibility of ABCA application in this setting, we report a series of patients treated prospectively with the similar methodology as outlined in our preliminary studies.

Materials and Methods

Study Population

Patients from two centers, Providence St. Vincent Medical Center and Providence Portland Medical Center, enrolled in the study between November 2006 and December 2008. Participating patients were undergoing major liver resections, either formal lobectomy, segmentectomy, or equivalent non-anatomic wedge resection. Previous chemotherapy (usually FOLFOX) or antibody therapy (Bevacizumab, Genentech, South San Fransisco) was allowed. Patients were considered not eligible for the study if they were less than 18 years of age, had a history of allergic reactions to albumin or were at risk for significant coagulopathy. All patients gave written informed consent to participate. The protocol and informed consent form were reviewed and approved by our institutional review board prior to recruitment of subjects for the study.

Study Design

The study design required evaluation and treatment of patients using albumin with argon beam coagulation to control liver surface bleeding after hepatic resection. Eligibility and screening procedures, including physician evaluation and blood samples, were performed at the pretreatment visit and the day of procedure. On the day of procedure, immediately following hepatic resection, 38% human serum albumin (HSA) applied through a syringe and 18-gauge blunt tip needle to the resected hepatic surface and cauterized using ABC. Lap sponges were then applied and pressure held for 3 min. Hemostasis was evaluated immediately following the 3-min hold. Patient blood test follow-up was done at 1 day post-op, 4 days post-op, discharge, 1 month, and 6 months.

Albumin

The albumin used in this study was concentrated to 38% on two separate occasions. Two separate lots of 25% HSA were purchased from Baxter CORP (Deerfield, IL), Buminate 25% USB Lot # 1123451 and Buminate 25% USB #11234442 expiration date 08242006 and 08062008, respectively. The 25% HSA was then concentrated to 38% on two occasions using passive diffusion in a good manufacturing practices (GMP) facility in accordance with FDA standards. Samples were sent to NAMSA for bactericidal and fungicidal sterility testing. All samples were found to be sterile.

Argon Beam Coagulator

An ABC is a non-contact device that conducts radiofrequency current to tissue along a jet of inert, nonflammable argon gas. The ABC used in this study was a ConMed System 7500 (ConMed, Utica, NY). For open applications the settings were as follows: power of 120 W, Argon gas flow rate of 9.0 L/min, and spark setting of 70. For laparoscopic applications, the settings were as follows: power of 80 W, argon gas flow rate of 4.5 L/min, and spark setting of 70.

Surgery

Eligible patients were offered entry into the study and receive the informed consent prior to surgery. Blood was drawn to measure preoperative serum AST, ALT, alkaline phosphatase, and albumin were drawn if not available or not performed within 30 days prior to surgery. The operation proceeded with an incision appropriate for planned intervention. Both open and laparoscopic resections were included. The technique of liver resection and method of parenchymal division, vascular isolation, and wedge vs. segment or sector resection was at the discretion of the attending surgeon.

For open surgical resections, crush/clamp technique, linear stapler, and harmonic scalpel (Ethicon, Cincinnati, OH) were utilized to divide liver tissue, and vessels larger than 5 mm within the liver were ligated. Intraoperative ultrasound and cholecystectomy were performed when appropriate. For laparoscopic resections, the liver was divided using the harmonic scalpel, linear stapler, and 38% albumin was applied through an 18-gauge spinal needle. In both open and laparoscopic procedures, the bleeding liver surface was packed with gauze sponges prior to argon beam coagulation with albumin. The bleeding hepatic parenchyma was coated with a thin layer of 38% human albumin. The albumin layer was then “soldered” to the liver surface using the argon beam coagulator in the

fulgurate setting at up to 125 W with an argon flow rate of between 4–9 L/min. The volume of albumin used and the total seconds of argon beam coagulator use were recorded. Once gross hemostasis was achieved, the resected surface was packed with gauze for three minutes. The resected surface was then inspected. If hemostasis was not complete, a reapplication of albumin with argon beam coagulation was performed. The liver surface was then packed with lap pads for three minutes. This process was repeated until hemostasis was complete. Once hemostasis was complete, the surgery proceeded as directed by the attending surgeon.

Results

Thirteen patients were registered for the study and underwent elective laparotomy or laparoscopy followed by liver resection unless contraindicated by initial findings at surgery (Fig. 2). Three patients did not complete the study due to lack of liver resection secondary to benign findings at surgery (one patient) or advanced disease despite initially more favorable clinical impression (two patients). Characteristics of the patient population are summarized in Table 1. Indications for surgery include colorectal carcinoma (five patients), gall bladder carcinoma (three patients), adenoma (one patient), and cholangiocarcinoma (one patient). Comorbidities were typical for this patient population and notable only for significant obesity and fatty liver in patient 1 and advanced aged with relatively small remnant liver in patient 3.

Results of ABCA are detailed in Table 2. Average time for ABCA application was just over 3 min, with one patient requiring over 10 min of post-resection hemostasis time. Amount of albumin applied was between 20 and 40 ml. ABCA treatment was immediately efficacious in nine out of 10 patients. The patient in which ABCA treatment did not achieve immediate hemostasis underwent repeat application of ABCA and pressure application for 3 min, and hemostasis was then achieved. Blood loss, operative times, and length of stay are listed. Morbidity observed included a postoperative abscess near the remaining liver in patient 4 and death from multisystem organ failure (patient 1) and liver failure (patient 3).

Discussion

Albumin concentrated to 38% and added to the resected liver surface with argon beam coagulation (ABCA) was found to be safe and efficacious with respect to providing hemostasis during liver surgery in a group of 10 patients. Significant blood loss was not observed during or after application of ABCA. We are not aware of other reports documenting this novel technique of hemostasis. The design of this study was essentially a phase 1 study, demonstrating the treatment was well tolerated and effective with respect to stopping bleeding after major liver resection.

Patient selection for this trial was essentially consecutive recruitment of eligible patients at the two study sites, by the

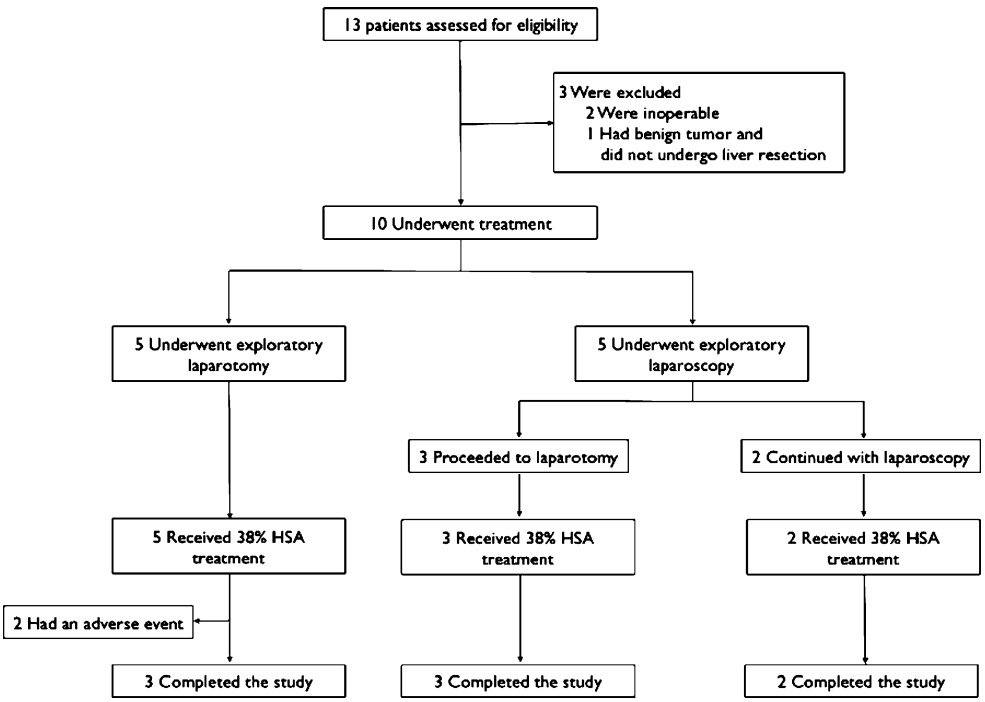

Fig. 2 Study flow chart.

Table 1 Demographics, Presentations, and Co-Morbidities for Study Patient Population

Patient	Sex	Age (years)	BMI (Kg/m^2)	Presentation	Co-Morbidity
1	M	66	36.5	Cholangiocarcinoma	Type 2 diabetes mellitus, osteoarthritis, obesity, hypertension
2	F	49	28.7	Colorectal carcinoma, hepatic metastases	
3	M	81	24.3	Colorectal carcinoma, hepatic metastases	Hypertension, gout, prostate cancer, weight loss
4	F	50	28.3	Gallbladder carcinoma	
5	M	70	28.7	Gallbladder carcinoma	Hypertension
6	F	37	18.4	Giant central hepatic adenoma	
7	M	60	26.6	Gallbladder carcinoma	
8	M	74	24.4	Colorectal carcinoma, hepatic metastases	Diverticular disease, coronary artery disease, renal insufficiency
9	M	58	22.4	Colorectal carcinoma, hepatic metastases	
10	M	74	30.8	Colorectal carcinoma, hepatic metastases	Hepatitis C, cirrhosis, bradycardia
MEAN		62	26.9		
STDEV		14	5.0		

two surgeons involved in the study. Relatively high risk patients were accepted, including patient 3 with abutment of tumor along a long segment of inferior vena cava adjacent to segment 8. Earlier treatment with FOLFOX chemotherapy had lead to complete response of hepatic metastases and resection was performed for rapidly growing late recurrence, not amenable to radiofrequency ablation secondary to size and location. Blood loss was significant and the patient developed liver failure postoperatively. In retrospect, remnant liver size and patient age were relative contraindications for resection. Patient #1 had cholangiocarcinoma and had portal vein involvement, requiring vein resection and re-anastomosis at the bifurcation. Multiple co-morbidities and major hepatic steatosis were present, and the patient died after surgery from multiple system organ failure, with portal venous and hepatic inflow present on several studies post operatively. In both cases, infectious complications related to the albumin were not present. The only other complication was associated with an otherwise event free liver resection. Patient #4 returned 30 days postoperatively with inflammatory signs, and a perihepatic abscess was seen and drained with CT guidance. Gram negative bacteria were found in culture; it is relatively unlikely that the abscess was related to the presence of coagulated albumin. The patient did well, and all other patients had treatment without known complications. The postoperative rate for all perihepatic abscess at Providence Portland Medical Center is 6.8%.

The present study demonstrates results as favorable or better than our animal data using ABCA, with respect to

Table 2 Surgical Summaries for Study Patients

	Time of ABCA (min:s)	Amount of albumin applied (mL)	Incidence of rebleed	Resected surface (cm^2)	Blood loss (mL)	Surgical time (hr:min)	Time in hospital (days)
1	4:40	40	0	195	6,300	14:30	10
2	3:12	20	0	36	450	3:43	5
3	13:00	30	1	145	2,100	7:40	31
4	3:40	20	0	42	450	4:36	4
5	3:54	40	0	40	1,700	4:45	4
6	3:42	30	0	54	1,300	9:45	4
7	5:38	30	0	96	800	4:55	4
8	7:32	40	0	108	1,300	7:10	8
9	2:15	30	0	46	100	2:30	2
10	3:45	30	0	60	900	5:13	8
MEAN	5:08	31	0	82	1,540	6:28	8
STDEV ±	3:07	7	0	53	1,780	3:30	8

blood loss. We reported that one half of animals needed repeat albumin/argon application after the initial treatment, whereas one of 10 patients needed reapplication of ABCA in this study. Other potential advantages of ABCA include more effective sealing of bile leaks, cost savings (compared to fibrin glue or radiofrequency probes) and shorter operative times. None of these issues could be assessed with a study of this size and design. ABCA applications times were short, ranging from 2 to 13 min, with volume of albumin no greater that 40 ml per patient. Observed mean length of stay of 8 days is typical for major hepatectomy. Results of the present study are comparable to a much larger trial examining FLOSEAL (Baxter) application after liver resection reported by Izzo and others.[30] In this series, 367 of 375 sites were hemostatic and the remaining sites had reduced bleeding after fibrin glue application. Average time to hemostasis was 2.9 min.[30] Another report of fibrin glue after liver resection mentions bile leak present in 10% of the patients.[19] We did not observe bile leaks in this series.

In conclusion, ABCA application was effective at promoting hemostasis after major liver resection. Further studies are warranted to document equivalence or superiority to other hemostatic methods, including fibrin glue preparations in the setting of a larger, randomized Phases II or III study.

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2010 SSAT QUICK SHOT PRESENTATION

Pre-operative Nomogram to Predict Risk of Peri-operative Mortality following Liver Resections for Malignancy

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Abstract
Introduction The majority of liver resections for malignancy are performed in older patient with major co-morbidities. There is currently no pre-operative, patient-specific method to determine the likely peri-operative mortality for each individual patient. The aim of this study was to develop a pre-operative nomogram based on the presence of co-morbidities to predict risk of peri-operative mortality following liver resections for malignancy.
Methods The Nationwide Inpatient Sample database was queried to identify adult patients that underwent liver resection for malignancy. The pre-operative co-morbidities, identified as predictors were used and a nomogram was created with multivariate regression using Taylor expansion method in SAS software, SURVEYLOGISTIC procedure. Training set (years 2000–2004) was utilized to develop the model and validation set (year 2005) was utilized to validate this model.
Results A total of 3,947 and 972 patients were included in training and validation sets, respectively. The overall actual-observed peri-operative mortality rates for training and validation sets were 4.1% and 3.2%, respectively. The decile-based calibration plots for the training set revealed good agreement between the observed probabilities and nomogram-predicted probabilities. Similarly, the quartile-based calibration plot for the validation set revealed good agreement between the observed and predicted probabilities. The accuracy of the nomogram was further reinforced by a good concordance index of 0.80 with a 95% confidence interval of 0.72 and 0.87.
Conclusions This pre-operative nomogram may be utilized to predict the risk of peri-operative mortality following liver resection for malignancy.

Keywords Nomogram · Liver resections · Malignancy · Peri-operative mortality

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Introduction

Liver resection is a well-accepted modality in the treatment algorithm of patients with primary and secondary malignancies involving the liver. Several studies have demonstrated that the number of liver resections being performed for malignancy have significantly increased in the past decade.[1,2] The availability of portal vein embolization,[3] two-stage hepatectomies,[4] abalation techniques,[5,6] modern chemotherapy,[7] expanding criteria for resection,[8,9] and improved surgical techniques are some of the factors noted to have contributed to this increase in liver resections.

Despite the increasing number of procedures being performed, liver resections are major operations that are associated with significant mortality and morbidity.[2,10,11] The majority of these operations are also performed in middle aged to elderly individuals who have multiple pre-existing co-morbidities. The pre-operative counseling of

these potentially operable and high-risk patients is critical to obtaining an adequately informed consent. Majority of the surgeons rely on the published literature to educate the individual patient on the likely rates of peri-operative mortality associated with the proposed procedures. Although we have seen an improvement in outcomes, the published data demonstrates a difference in peri-operative mortality rates between literature based single or multi-institutional studies (3.6%, overall 0–14%)[2,12–14] and population-based studies (5.6%).[12] In addition, data from either of these settings may not be accurately applicable to patients on an individual basis.

Recent studies have attempted to devise different risk scoring systems for predicting in-hospital mortality following operative intervention for various malignancies.[15–18] The presumed benefit of these scoring systems is the improved applicability to individual patients in predicting their rate of peri-operative mortality. One of the more specific methods available to predict an outcome for an individual patient includes nomograms, which are graphical tools that use mathematical formulae for predictive accuracy. We have previously developed a pre-operative nomogram which was shown to accurately predict the peri-operative mortality following pancreatic resection for malignancy for individual patients.[19] The aim of the current study was therefore to develop and validate a pre-operative nomogram consisting of easily available variables to predict peri-operative mortality following liver resection for malignancy.

Materials and Methods

The Nationwide Inpatient Sample (NIS) database was used to determine inpatient mortality following lobectomy or wedge resection for liver neoplasms (primary and metastatic but excluding benign neoplasms). The training set (years 2000–2004) was used to create a predictive model, and the validation set (year 2005) was used for subsequent validation of the model. The analysis was limited to adults (age, ≥18 years) undergoing liver resection for malignant neoplasms of the liver.

Data Source

Data was obtained from the NIS (http://www.hcup-us.ahrq.gov/nisoverview.jsp) 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 community hospitals. In 2005, the NIS database 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). Data for this study was compiled from the 2000 to 2005 versions of the NIS. All patients discharged with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) primary procedure code for hepatic wedge resection (code 50.22) or hepatic lobe resection (code 50.3) were included in the study. Diagnoses codes 155.0 and 155.1 were used for primary liver malignancies whereas code 197.7 was used for secondary malignancies of the liver. Data on patient age and sex, admission type, hospital size and type, and resection type were extracted from the database. The patients that underwent lobectomy plus wedge resection were included in the lobectomy group although the sample size was noted to be small. Co-morbidities were identified using the taxonomy published by Elixhauser et al.[20] Elixhauser's list is a very comprehensive list, specifically designed for administrative databases and includes co-morbidities which can potentially impact outcomes including length of stay, hospital cost, and in-hospital mortality. Table 1 summarizes a partial list of definition of some of the pre-operative co-morbidities used to construct the nomogram. A comprehensive list has been previously published by Elixhauser et al.[20]

Statistical Methods

SAS software (SAS Institute Inc., Cary, NC, USA) and SUDAAN software were used for all statistical analysis to account for the complex sampling design of NIS. Weighted sample estimates, standard errors, and 95% confidence intervals (CI) were calculated using the Taylor expansion method. All statistical tests were two-sided and p values less than 0.05 are considered to be statistically significant. These statistical methods have been described previously in detail by Are et al.[19]

Results

A total of 4,919 subjects were included in the current study, with 3,947 in the training set and 972 in the validation set. The overall peri-operative mortality rate for the entire cohort was 3.9%, whereas mortality rates for the training and validation sets were 4.1% and 3.2%, respectively. Tables 2 and 3 summarize the demographic characteristics, diagnosis, type of procedure, and co-morbidities for the patients in the training and validation sets. Briefly, the distributions of these patient characteristics were almost similar amongst the training and validation sets.

Table 4 summarizes the effect of tested variables on the peri-operative mortality in a univariate fashion. Patients with over 70 years of age, non-whites, males, length of stay greater than 10 days, emergent/urgent admission, patients undergoing lobectomy, those with a primary liver malignancy, those having co-morbidities in the form of congestive heart failure, cardiac arrhythmias, other neurological disorders, chronic

Table 1 Definition of some of the pre-operative co-morbidities used to construct the nomogram as per the taxonomy published by Elixhauser et al.[20]

Other neurological disorders	
331.9	Cerebral degeneration, unspecified
332	Parkinson's disease
333.4	Huntington's chorea
333.5	Other choreas
334.0–335.9	Spinocerebellar disase, anterior horn cell disease
340	Multiple sclerosis
341.1–341.9	Other demyelinating diseases of CNS (not neuromyelitis optica)
345.00–345.11	Epilepsy
345.40–345.51	Partial epilepsy
345.80–345.91	Other epilepsy
348.1	Anoxic brain damage
348.3	Encephalopathy, unspecified
780.3	Convulsions
784.3	Aphasia
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	
70.32	Viral hepatitis B without mention of hepatic coma, chronic without mention of hepatitis delta
70.33	Viral hepatitis B without mention of hepatic coma, chronic with hepatitis delta
70.54	Chronic hepatitis C without mention of hepatic coma
456	Esophageal varices with bleeding
456.1	Esophageal varices without mention of bleeding
456.2	Esophageal varices in diseases classified elsewhere, with bleeding
456.21	Esophageal varices in diseases classified elsewhere, without mention of bleeding
571	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 sequele of chronic liver disease
V42.7	Liver transplant

obstructive pulmonary disease, renal failure, liver disease, AIDS, coagulopathy, fluid and electrolyte disorders, loss of weight prior to procedure, and three or more co-morbidities were more likely to die after liver resection in the training set. Similar, analysis was carried out for the validation set and the results are summarized in Table 4.

Multivariate logistic regression analysis was performed as summarized in Table 5. The variables selected for the

Table 2 Demographic characteristics, diagnosis, and procedure types amongst patients in the training set (years 2000–2004) and validation set (year 2005)

		Training set (years 2000–2004)			Validation set (year 2005)		
		Frequency	Weighted frequency	Percent	Frequency	Weighted frequency	Percent
Age (years)	70 or less	2,994	1,4731	75.8	762	3,857	78.4
	Over 70	953	4,692	24.2	210	1,062	21.6
Race	White	2,387	11,769	60.6	496	2,532	51.5
	Non-white	699	3,444	17.7	155	779	15.8
	Unknown	861	4,210	21.7	321	1,607	32.7
Sex	Male	2,212	10,884	56.1	552	2,789	56.9
	Female	1,733	8,529	43.9	416	2,109	43.1
Length of stay	10 days or less	3,246	15,992	82.3	809	4,100	83.4
	More than 10 days	701	3,431	17.7	163	818	16.6
Admission type	Elective	3,110	15,198	78.2	703	3,579	72.8
	Emergent/Urgent	347	1,713	8.8	71	348	7.1
	Unknown	490	2,512	12.9	198	991	20.1
Hospital size	Small	231	1,112	5.7	68	388	7.9
	Medium	493	2,367	12.2	138	686	13.9
	Large	3,223	15,944	82.1	766	3,844	78.2
Hospital location	Rural	71	381	2	26	135	2.7
	Urban	3,876	19,042	98	946	4,783	97.3
Teaching hospital	Non-teaching	632	3,035	15.6	146	727	14.8
	Teaching	3,315	16,387	84.4	826	4,191	85.2
Median income, by zip code	$1–24,999	451	2,166	11.5	169	853	17.9
	$25,000–34,999	825	4,026	21.3	219	1,095	22.9
	$35,000–44,999	908	4,513	23.9	265	1,347	28.2
	$45,000 and above	1,653	8,197	43.4	290	1,479	31
Liver procedures	Lobectomy and (wedge+lobectomy)	1,799	8,836	45.5	460	2,329	47.4
	Wegde	2,148	10,587	54.5	512	2,589	52.6
Liver primary	No	2,727	13,410	69	677	3,443	70
	Yes	1,220	6,013	31	295	1,476	30

multivariate model were chosen from a combination of clinical experience and statistical significance, i.e., if the variables were significant at the 0.05 level from the univariate chi-square tests presented in Table 4 they were included in the model. If the variables were not significant at the 0.05 level but were deemed important based on the clinical experience, they were included in the model. Since the length of stay is not known prior to the operation it was not included in the multivariate analysis. Similarly, weight loss and AIDS (Yes vs. no) were not included in the multivariate model due to the small sample sizes. Table 5 summarizes the odds ratios with 95% confidence intervals, beta coefficient, standard error, Wald p value, and the total points for each variable estimated from the multivariate logistic model. These variables were used to construct the nomogram as shown in Fig. 1. For each patient, all the variables would be plotted in the nomogram to calculate the total number of points. The total points would then be added to obtain an estimate of the likely peri-operative mortality following liver resection. For example a patient with the pre-operative co-morbidities as shown in Fig. 2 will be assigned a total of 215 points that translates to a nomogram-predicted peri-operative mortality of approximately 8%.

Design and Validation of the Nomogram

The total numbers of points were calculated for each person in the training set. The mean total points for the training set were 128.7 (SE=2.01; range, 0–469) corresponding to a mortality rate of approximately 1.6%. The overall observed mortality rate for training set was 4.1%. The nomogram was validated using 2005 dataset, referred to as validation

Table 3 Co-morbidities amongst patients in the training set (years 2000–2004) and validation set (year 2005)

		Training set (years 2000–2004)			Validation set (year 2005)		
		Frequency	Weighted frequency	Percent	Frequency	Weighted frequency	Percent
CHF	No	3,846	18,927	97.4	949	4,802	97.6
	Yes	101	495	2.6	23	116	2.4
Cardiac arrhythmia	No	3,624	17,851	91.9	878	4,447	90.4
	Yes	323	1,572	8.1	94	472	9.6
Valvular disease	No	3,861	18,999	97.8	941	4,761	96.8
	Yes	86	424	2.2	31	157	3.2
Pulmonary circulation disorder	No	3,933	19,355	99.7	968	4,899	99.6
	Yes	14	68	0.3	4	19	0.4
Peripheral vascular disorder	No	3,905	19,218	98.9	960	4,858	98.8
	Yes	42	205	1.1	12	60	1.2
Hypertension	No	2,573	12,655	65.2	591	2,992	60.8
	Yes	1,374	6,768	34.8	381	1,926	39.2
Paralysis	No	3,941	19,394	99.9	972	4,918	100
	Yes	6	29	0.1	0		
Other neurological disorders	No	3,916	19,263	99.2	969	4,903	99.7
	Yes	31	160	0.8	3	15	0.3
COPD	No	3,636	17,902	92.2	877	4,443	90.3
	Yes	311	1,521	7.8	95	475	9.7
Diabetes	No	3,362	16,537	85.1	830	4,205	85.5
	Yes	585	2,886	14.9	142	713	14.5
Hypothyroidism	No	3,720	18,294	94.2	916	4,634	94.2
	Yes	227	1,129	5.8	56	285	5.8
Renal failure	No	3,919	19,280	99.3	964	4,878	99.2
	Yes	28	142	0.7	8	41	0.8
Liver disease	No	3,346	16,452	84.7	842	4,259	86.6
	Yes	601	2,971	15.3	130	659	13.4
Peptic ulcer	No	3,909	19,233	99	964	4,878	99.2
	Yes	38	190	1	8	41	0.8
AIDS	No	3,941	19,393	99.8	971	4,913	99.9
	Yes	6	30	0.2	1	5	0.1
Obesity	No	3,867	19,031	98	944	4,781	97.2
	Yes	80	392	2	28	137	2.8
Lymphoma	No	3,923	19,302	99.4	963	4,872	99.1
	Yes	24	121	0.6	9	47	0.9
Rheumatoid arthritis	No	3,907	19,227	99	962	4,869	99
	Yes	40	195	1	10	50	1
Coagulopathy	No	3,727	18,347	94.5	906	4,581	93.1
	Yes	220	1,076	5.5	66	338	6.9
Weight loss	No	3,864	19,014	97.9	947	4,792	97.4
	Yes	83	409	2.1	25	126	2.6
Fluid and electrolyte disorders	No	3,426	16,876	86.9	800	4,049	82.3
	Yes	521	2,546	13.1	172	870	17.7
Blood loss anemias	No	3,925	19,313	99.4	959	4,854	98.7
	Yes	22	110	0.6	13	65	1.3
Deficiency anemias	No	3,716	18,275	94.1	889	4,502	91.5
	Yes	231	1,148	5.9	83	417	8.5
Alcohol abuse	No	3,868	19,039	98	952	4,820	98

Table 3 (continued)

		Training set (years 2000–2004)			Validation set (year 2005)		
		Frequency	Weighted frequency	Percent	Frequency	Weighted frequency	Percent
	Yes	79	384	2	20	98	2
Drug abuse	No	3,936	19,368	99.7	967	4,893	99.5
	Yes	11	55	0.3	5	26	0.5
Psychoses	No	3,913	19,251	99.1	958	4,849	98.6
	Yes	34	172	0.9	14	69	1.4
Depression	No	3,840	18,896	97.3	946	4,786	97.3
	Yes	107	526	2.7	26	132	2.7
Number of co-morbidities	3 or more	2,350	11,565	59.5	639	3,231	65.7
	Less than 3	1,597	7,857	40.5	333	1,687	34.3

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

set. The mean total points for the validation set were 128.5 (SE=3.6; range, 3–370) corresponding to a mortality rate of approximately 1.8%. The overall observed mortality rate in the validation set was 3.2%. The concordance index was found to be 0.80 with a 95% confidence interval of 0.72 to 0.87. The nomogram was further validated by creating calibration plots (Fig. 3). Decile-based calibration plot for the training set and quartile-based calibration plot for the validation set revealed good agreement between the observed and predicted probabilities although there appears to be mild overestimation of predicted probabilities in the last two quartiles of the validation set.

Discussion

We have recently demonstrated the utility of a pre-operative nomogram in predicting the peri-operative mortality amongst patients undergoing pancreatic resections for malignancy.[19] In the current study, we have devised a nomogram to predict patient-specific peri-operative mortality following liver resection for malignancy. The nomogram was constructed using variables that are readily available in the pre-operative setting which makes it possible to use the nomogram as an additional tool in the pre-operative counseling of patients prior to liver resection.

There is a wide variability in the published mortality rates following liver resection.[2,10,12–14] Institutional series report a peri-operative mortality rate of 3.6% with many of the studies reporting a mortality rate of 0%.[14,21–23] On the contrary, population-based mortality rates are much higher, up to 5.6%.[12] The wide variability in the reported peri-operative mortality rates may make patient counseling difficult prior to liver resection. Different staging systems such as Cancer of the Liver Italian Program (CLIP), Japan Integrated Staging (JIS), Barcelona Clinic Liver Cancer Staging system (BCLC) and American Joint Committee on Cancer/International Union Against Cancer(AJCC/UICC) are reliable predictors of overall survival but were not specifically designed to predict procedural mortality.[17,24–27] These staging systems are mainly utilized for predicting outcomes in patients with primary liver malignancies in the background of underlying liver disease and are used to determine the appropriate treatment options. Similarly, the accuracy of MELD score to predict peri-operative/procedural mortality remains contradictory[28–30] and the variables used to calculate the MELD score may not be applicable to the broader population without underlying liver disease.

Several alternative systems such as risk scores and nomograms are being developed to improve the accuracy of predicting peri-operative mortality following operative intervention for malignant diagnoses.[15–19] Simons et al. developed a risk score system for predicting peri-operative mortality following liver resection for neoplasms.[16] The NIS database was utilized to design a risk score system based on the chosen explanatory variables. The Charlson index was used to categorize co-morbidities and due to sample sizes the patients were collapsed into four groups. By using a multivariate logistic regression model an integer based scoring system was designed, that predicted mortality rates ranging from 0.9% to 35.9%. The scoring system was noted to discriminate well with c-statistics of 0.76 and 0.70 for the development and validation set of patients. Although risk score systems are useful, it is thought that nomograms are superior to risk scores or risk grouping systems in predicting probabilities tailored to an individual patient.[31,32] Although this scoring system developed by Simons et al.[16] is easy to use, the methodology reflects some of the inherent advantages of nomograms. Due to

Table 4 Univariate analysis: effect of variables on the peri-operative mortality following liver resections for malignancy in the training set (years 2000–2004) and validation set (year 2005)

		Training set (years 2000–2004)				Validation set (year 2005)			
		Number died	Weighted frequency	Mortality percentage	*p* Value	Number died	Weighted frequency	Mortality percentage	*P* value
Age (years)	70 or less	96	470	3.2	<0.0001	23	115	3	0.35
	Over 70	68	332	7.1		9	45	4.2	
Race	White	87	423	3.6	0.013	20	100	4	0.37
	Non-white	41	205	6		5	25	3.3	
	Unknown	36	175	4.1		7	34	2.1	
Sex	Male	114	561	5.2	0.0001	22	107	3.8	0.27
	Female	50	241	2.8		10	52	2.5	
Length of stay	10 days or less	63	311	1.9	<0.0001	14	70	1.7	<0.0001
	More than 10 days	101	491	14.4		18	90	10.9	
Admission type	Elective	119	583	3.8	0.0016	23	115	3.2	0.97
	Emergent/Urgent	27	128	7.5		3	13	3.7	
	Unknown	18	91	3.6		6	31	3.1	
Hospital size	Small/Medium	28	136	3.9	0.73	6	31	2.9	0.76
	Large	136	667	4.2		26	128	3.3	
Hospital location	Rural	4	19	5	0.7	2	9	6.7	0.072
	Urban	160	783	4.1		30	150	3.1	
Teaching hospital	Non-teaching	36	168	5.5	0.034	7	34	4.6	0.34
	Teaching	128	634	3.9		25	126	3	
Median income, by zip code	$1–24,999	26	124	5.7	0.36	6	29	3.4	0.11
	$25,000–34,999	34	164	4.1		12	59	5.4	
	$35,000–44,999	36	177	3.9		4	20	1.5	
	$45,000 and above	63	316	3.9		10	51	3.5	
Liver procedures	Lobectomy and (wedge+lobectomy)	100	491	5.6	<0.0001	24	121	5.2	0.0005
	Wedge	64	311	2.9		8	38	1.5	
Liver primary	No	68	336	2.5	<0.0001	14	68	2	0.0011
	Yes	96	466	7.8		18	91	6.2	
CHF	No	149	731	3.9	<0.0001	31	154	3.2	0.69
	Yes	15	71	14.4		1	5	4.7	
Cardiac arrhythmia	No	127	623	3.5	<0.0001	29	144	3.2	0.99
	Yes	37	179	11.4		3	15	3.2	
Valvular disease	No	158	774	4.1	0.19	30	149	3.1	0.26
	Yes	6	28	6.7		2	10	6.7	
Pulmonary circ disorder	No	163	797	4.1	0.49	32	159	3.3	NE
	Yes	1	5	8		0			
Peripheral vascular disorder	No	162	792	4.1	0.78	32	159	3.3	NE
	Yes	2	10	5		0			
Hypertension	No	135	661	5.2	<0.0001	27	134	4.5	0.005
	Yes	29	141	2.1		5	25	1.3	
Paralysis	No	164	802	4.1	NE	32	159	3.2	NE
	Yes	0				0			
Other neurological disorders	No	154	752	3.9	<0.0001	31	154	3.1	0.0048
	Yes	10	51	31.7		1	5	32.9	
COPD	No	143	699	3.9	0.014	30	150	3.4	0.47
	Yes	21	103	6.8		2	10	2	
Diabetes	No	139	681	4.1	0.94	29	144	3.4	0.4

Table 4 (continued)

		Training set (years 2000–2004)				Validation set (year 2005)			
		Number died	Weighted frequency	Mortality percentage	*p* Value	Number died	Weighted frequency	Mortality percentage	*P* value
	Yes	25	121	4.2		3	15	2.1	
Hypothyroidism	No	160	782	4.3	0.085	32	159	3.4	NE
	Yes	4	21	1.8		0			
Renal failure	No	155	755	3.9	<0.0001	30	149	3.1	0.0001
	Yes	9	47	34.4		2	10	24.1	
Liver disease	No	104	509	3.1	<0.0001	22	108	2.5	0.002
	Yes	60	293	9.9		10	51	7.7	
Peptic ulcer	No	163	797	4.1	0.74	32	159	3.3	NE
	Yes	1	6	3		0			
AIDS	No	162	792	4.1	0.0003	32	159	3.2	NE
	Yes	2	10	34.7		0			
Obesity	No	164	802	4.2	NE	31	154	3.2	0.9
	Yes	0				1	5	3.7	
Lymphoma	No	163	798	4.1	0.99	32	159	3.3	NE
	Yes	1	5	4.2		0			
Rheumatoid arthritis	No	162	793	4.1	0.85	32	159	3.3	NE
	Yes	2	9	4.7		0			
Coagulopathy	No	104	512	2.8	<0.0001	21	104	2.3	<0.0001
	Yes	60	291	27		11	55	16.3	
Weight loss	No	150	738	3.9	<0.0001	30	148	3.1	0.16
	Yes	14	65	15.8		2	11	8.7	
Fluid and electrolyte disorders	No	92	452	2.7	<0.0001	23	116	2.9	0.22
	Yes	72	351	13.8		9	43	4.9	
Blood loss anemias	No	164	802	4.2	NE	32	159	3.3	NE
	Yes	0				0			
Deficiency anemias	No	157	769	4.2	0.34	29	144	3.2	0.87
	Yes	7	34	2.9		3	15	3.6	
Alcohol abuse	No	161	787	4.1	0.95	31	154	3.2	0.67
	Yes	3	15	4		1	5	4.9	
Drug abuse	No	163	798	4.1	0.43	32	159	3.3	NE
	Yes	1	5	8.9		0			
Psychoses	No	163	797	4.1	0.74	32	159	3.3	NE
	Yes	1	5	3		0			
Depression	No	163	797	4.2	0.099	31	154	3.2	0.85
	Yes	1	5	1		1	5	3.9	
Number of co-morbidities	3 or more	128	626	5.4	<0.0001	24	120	3.7	0.27
	Less than 3	36	177	2.2		8	39	2.3	

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

differences in sample sizes, patients with different Charlson scores were grouped together.[16–18] Any type of grouping of patients can lead to a compromise in the predictive accuracy for individual patients. Nomograms on the other hand do not utilize data based on grouping and tend to be more accurate for each individual patient. This is further reflected by the fact that in grouped patients, it is likely that the type of co-morbidities for each patient within the group may be different although the total number of co-morbidities may be the same.

Our nomogram is very detailed and more specific, as we assessed the influence of almost 39 variables on the peri-

Table 5 Multivariate analysis: effect of variables on the peri-operative mortality following liver resections for malignancy in the training set (years 2000–2004)

Effect		OR	Lower 95% CI	Upper 95% CI	B estimate	SE	*p* Value	Total points
Intercept					−6.625	0.481	<0.0001	
Coagulopathy	Yes vs. No	7.08	4.48	11.19	1.958	0.233	<0.0001	100
Other neurological disorders	Yes vs. No	6.4	2.42	16.92	1.857	0.496	0.0002	95
Renal failure	Yes vs. No	5.44	1.83	16.2	1.694	0.557	0.0024	87
Hypertension	No vs. Yes	3.28	2.12	5.06	1.187	0.222	<0.0001	61
Age (Years)	>70 vs. 18–54	2.89	1.78	4.69	1.06	0.248	<0.0001	54
	55–70 vs. 18–54	1.65	1.05	2.57	0.498	0.228		25
Fluid and electrolyte disorders	Yes vs. No	2.76	1.94	3.94	1.017	0.181	<0.0001	52
CHF	Yes vs. No	2.59	1.32	5.1	0.952	0.345	0.0059	49
Cardiac arrhythmia	Yes vs. No	2.51	1.59	3.95	0.92	0.232	<0.0001	47
Liver disease	Yes vs. No	2.22	1.42	3.46	0.796	0.227	0.0005	41
Admission type	Emergency/Urgent vs. unknown	1.87	0.98	3.58	0.626	0.331	0.12	32
	Elective vs. unknown	1.18	0.69	2	0.163	0.271		8
Liver procedures	Lob, W/L vs. Wed	1.69	1.19	2.4	0.523	0.179	0.0035	27
Liver primary	Yes vs. No	1.64	1.07	2.5	0.492	0.216	0.023	25
Race	Non-white vs. White	1.5	0.97	2.33	0.408	0.222	0.18	21
	Unknown vs. White	1.06	0.65	1.72	0.056	0.249		3
Sex	Male vs. Female	1.44	1	2.09	0.368	0.189	0.051	19
COPD	Yes vs. No	1.4	0.82	2.39	0.34	0.272	0.21	17

CHF congestive heart failure, *Lob, W/L vs. Wed* lobectomy and (wedge+lobectomy) vs.Wedge, *COPD* chronic obstructive pulmonary disease

operative mortality following hepatic resection for malignancy. In addition, after excluding demographic and hospital data, we utilized 27 well-established and readily available pre-operative co-morbidities to determine their influence on peri-operative mortality. Based on this we noted that almost 59.5% of the patients were noted to have three or more co-morbidities. This is in contrast to the study by Simons et al. where only 6.1% of the patients had three or more co-morbidities. This low rate could lead to underestimation of the presence of pre-operative co-morbidities and thereby affect the predictive accuracy. Furthermore, the inclusion of factors such as coagulopathy a known determinant of outcomes following liver resection as a separate variable in addition to liver disease in the initial analysis attests to the detailed accuracy of the nomogram. The robustness of this approach is also evidenced by the statistical significance and inclusion of several other co-morbidities known to affect the outcome following liver resection in the construction of the nomogram. In addition to coagulopathy, these include liver disease, liver primary, and renal failure. Coagulopathy is marker of severity of underlying liver disease as shown by Child Pugh and MELD scoring systems and may also reflect the functional capacity of the liver. Presence of renal failure which may stem from hepatorenal syndrome or may be a pre-existing condition may significantly affect mortality. Recently, hyponatremia which can be characterized as a fluid and electrolyte disorder has been shown to affect mortality in liver transplant candidates awaiting transplant and has been found to be an independent predictor of complications in patients with cirrhosis.[33,34] The exact reasons for the impact of these co-morbidities in patients undergoing malignant liver resections need to be further investigated and were beyond the objectives of the current study.

There were several limitations to the current study. The ability to use the co-morbidities as continuous rather than categorical variables would add to the accuracy of the nomogram. Similarly the lack of inclusion of several other variables known to affect the outcomes following liver resection for malignancy needs to be noted. These include ASA status, pre-operative albumin, platelet counts, blood loss, degree of steatosis, pre-operative chemotherapy (type and duration), extent of disease, and the size of future liver remnant. Although this data is important, the limitations of the NIS database need to be borne in mind. This underscores the fact that the nomogram is meant to be used as an additional tool and is not meant to replace the surgeons assessment based on adequate clinical parameters.

Inspite of its limitations, the current study may have several clinical implications. Our nomogram is simple, has

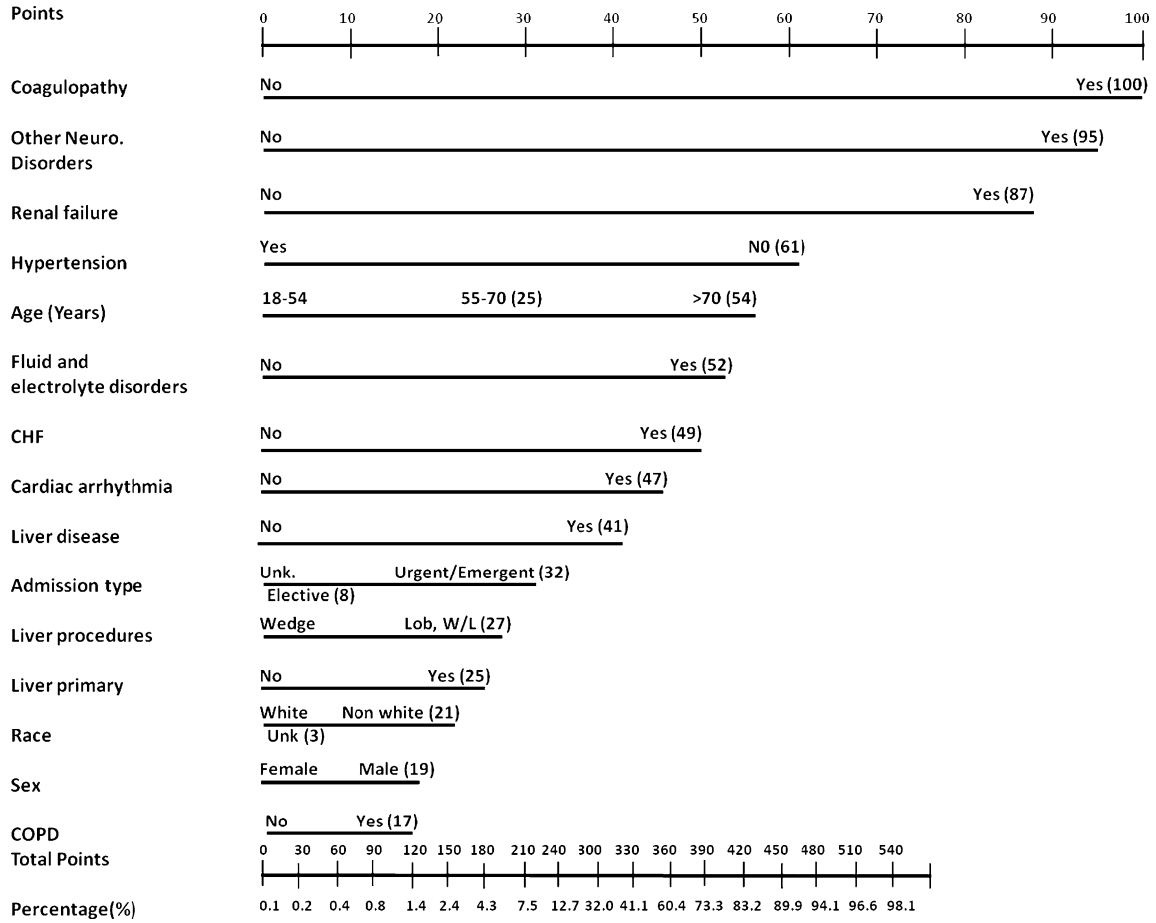

Fig. 1 Nomogram to predict perioperative mortality in patients undergoing resections for primary or secondary liver malignancies

a good accuracy (Concordance index 0.80) as shown by calibration plots, is applicable to both primary and secondary liver malignancies and is available in the pre-operative setting. The current nomogram is a patient-specific tool currently available to predict individual patient-specific peri-mortality rate following liver resections for malignancy. It may play a role in optimization of peri-operative care of these patients as it highlights many co-morbidities which can affect mortality in these patients. Additionally, our nomogram can also be used for testing clinical trial eligibililty as patients with very high peri-operative mortality may be candidates for the use of novel therapeutic agents and use of such agents may not be justified in low mortality groups. Since our nomogram is derived from a population-based database it can be utilized across different institutions for patient counseling. Kattan et al.[32] have previously stated that graphical tools such as nomograms are better and easier to explain especially in emotional situations such as informed consent and patient counseling. In combination with good clinical judgment, this nomogram can become an effective tool in individual patient counseling. The simple format of the nomogram may help explain the impact of risk factors to the patients easily. At the institutional level, the universal application of this nomogram by all surgeons undertaking liver resections in an institution will add uniformity to pre-operative counseling and risk stratification. This uniformity may also help in undertaking research into the risk factors as it provides a consistent platform to assess potential peri-operative mortality rates.

In conclusion, our study has led to the design of a simple pre-operative nomogram to predict peri-operative patient-specific mortality in patients undergoing liver resection for primary and secondary liver malignancies. The nomogram was developed using variables that are easily available in the pre-operative setting using a large population-based dataset. The ease of use of this nomogram will make it an adjunctive clinical tool in the pre-operative setting and combined with good clinical judgment, make it useful for patient counseling, obtaining informed consent, optimizing perioperative care, and possibly for assessment of clinical trial eligibility. Further studies are required to obtain external validation of this nomogram.

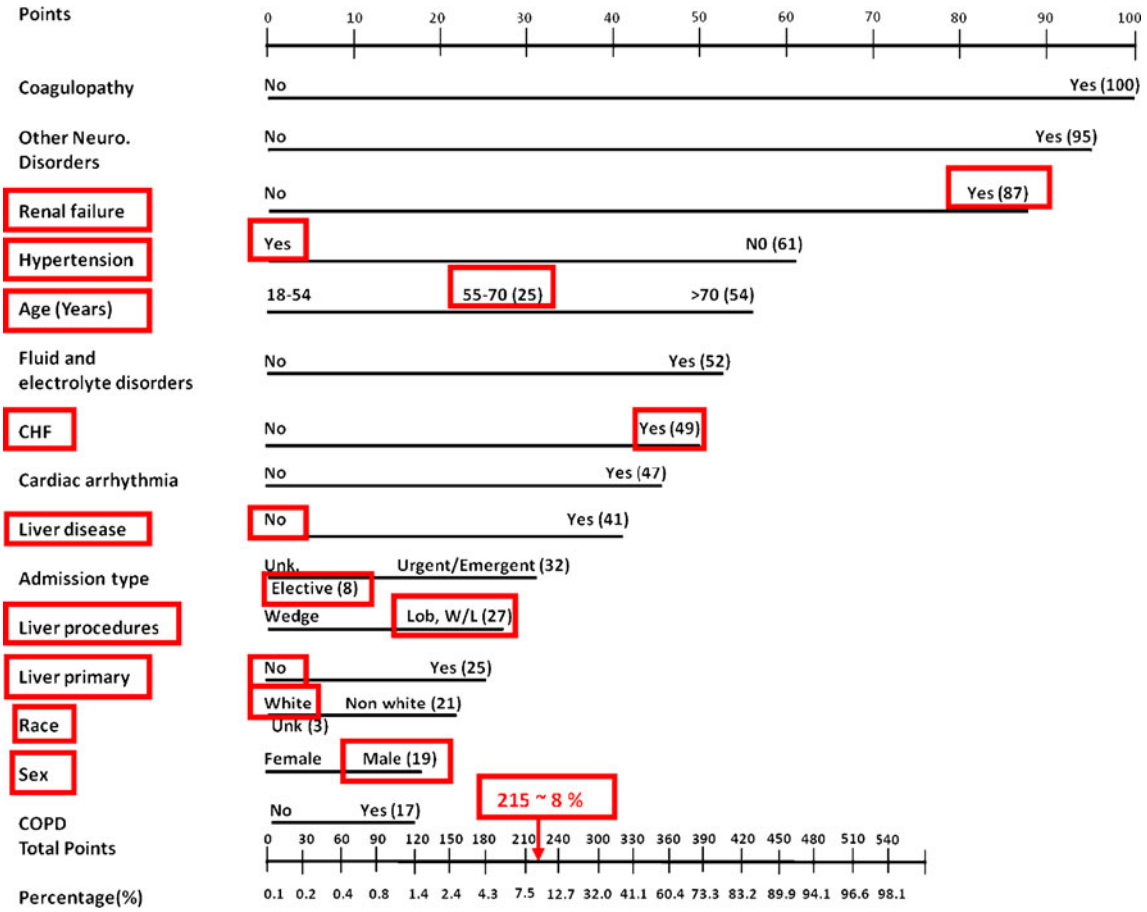

Fig. 2 An example demonstrating the use of nomogram. A 65-year-old white male with multiple pre-operative co-morbidities who presents for a lobectomy for secondary liver metastases. As per the nomogram, his total assigned points are 215, which translate into a nomogram-predicted peri-operative mortality rate of approximately 8%. *Other Neuro. Disorders* other neurological disorders, *Unk.* unknown, *Lob.W/L* lobectomy with or without wedge resection

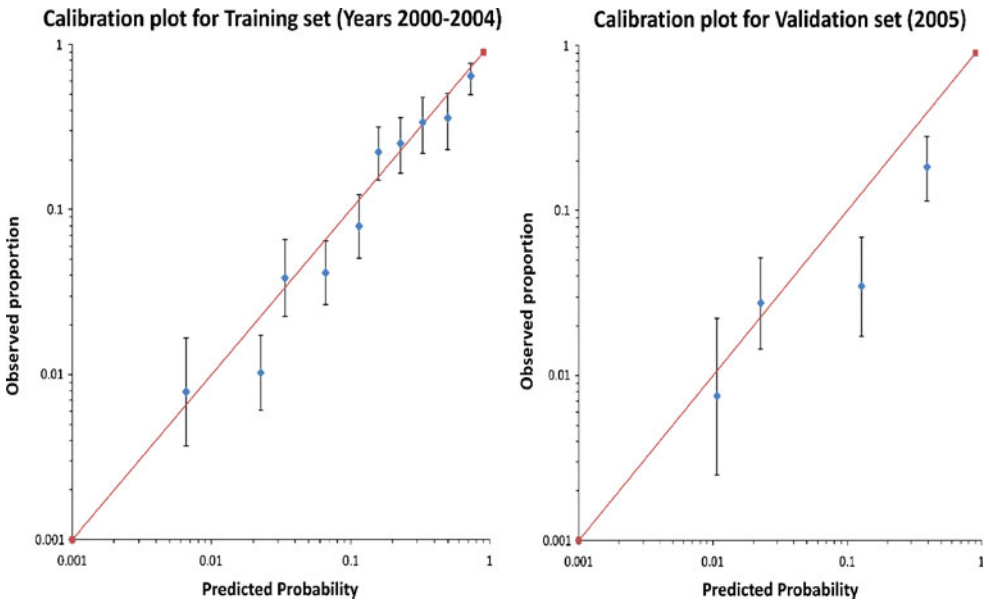

Fig. 3 Calibration plots for the training set (2000–2004 data) and validation set (2005). The observed mortality rates were calculated for the predicted probability deciles along with 95% confidence intervals and plotted against the predicted probabilities for training set. The *45° line on the plot* shows where the observed probabilities should fall for perfect agreement with the nomogram-predicted probabilities. Calibration plots for the validation set demonstrates quartiles instead of deciles due to smaller sample set

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2010 SSAT QUICK SHOT PRESENTATION

Emergency Portacaval Shunt Versus Rescue Portacaval Shunt in a Randomized Controlled Trial of Emergency Treatment of Acutely Bleeding Esophageal Varices in Cirrhosis—Part 3

Marshall J. Orloff · Jon I. Isenberg · Henry O. Wheeler · Kevin S. Haynes · Horacio Jinich-Brook · Roderick Rapier · Florin Vaida · Robert J. Hye

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Abstract
Background Emergency treatment of bleeding esophageal varices in cirrhosis is of singular importance because of the high mortality rate. Emergency portacaval shunt is rarely used today because of the belief, unsubstantiated by long-term randomized trials, that it causes frequent portal-systemic encephalopathy and liver failure. Consequently, portacaval shunt has been relegated solely to salvage therapy when endoscopic and pharmacologic therapies have failed. Question: Is the regimen of endoscopic sclerotherapy with rescue portacaval shunt for failure to control bleeding varices superior to emergency portacaval shunt? A unique opportunity to answer this question was provided by a randomized controlled trial of endoscopic sclerotherapy versus emergency portacaval shunt conducted from 1988 to 2005.
Methods Unselected consecutive cirrhotic patients with acute bleeding esophageal varices were randomized to endoscopic sclerotherapy (n=106) or emergency portacaval shunt (n=105). Diagnostic workup was completed and treatment was initiated within 8 h. Failure of endoscopic sclerotherapy was defined by strict criteria and treated by rescue portacaval shunt (n=50) whenever possible. Ninety-six percent of patients had more than 10 years of follow-up or until death.
Results Comparison of emergency portacaval shunt and endoscopic sclerotherapy followed by rescue portacaval shunt showed the following differences in measurements of outcomes: (1) survival after 5 years (72% versus 22%), 10 years (46% versus 16%), and 15 years (46% versus 0%); (2) median post-shunt survival (6.18 versus 1.99 years); (3) mean requirements of packed red blood cell units (17.85 versus 27.80); (4) incidence of recurrent portal-systemic encephalopathy (15% versus 43%); (5) 5-year change in Child's class showing improvement (59% versus 19%) or worsening (8% versus 44%); (6) mean quality of life points in which lower is better (13.89 versus 27.89); and (7) mean cost of care per year ($39,200 versus $216,700). These differences were highly significant in favor of emergency portacaval shunt (all p<0.001).

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Conclusions Emergency portacaval shunt was strikingly superior to endoscopic sclerotherapy as well as to the combination of endoscopic sclerotherapy and rescue portacaval shunt in regard to all outcome measures, specifically bleeding control, survival, incidence of portal-systemic encephalopathy, improvement in liver function, quality of life, and cost of care. These results strongly support the use of emergency portacaval shunt as the first line of emergency treatment of bleeding esophageal varices in cirrhosis.

Keywords Cirrhosis · Varices · Shunt · Sclerotherapy · Bleeding

Abbreviations

BEV	Bleeding esophageal varices
EST	Endoscopic sclerotherapy
EPCS	Emergency portacaval shunt
PCS	Portacaval shunt
UGI	Upper gastrointestinal
ICU	Intensive care unit
PRBC	Packed red blood cells
PSE	Portal-systemic encephalopathy
EVL	Endoscopic variceal ligation
QOL	Quality of life

Introduction

Emergency treatment of bleeding esophageal varices (BEV) in patients with cirrhosis of the liver is of singular importance because of the high mortality rate surrounding the episode of acute bleeding.[1–9] The most widely used emergency treatment of BEV is endoscopic sclerotherapy (EST) or endoscopic variceal ligation (EVL), with or without the addition of pharmacologic measures.[10–12] When it is believed that portal decompression is needed, transjugular intrahepatic portosystemic shunt (TIPS) has become the most widely used procedure of choice despite the facts that, as we have pointed out previously, TIPS has a high rate of stenosis and occlusion, a resultant high incidence of portal-systemic encephalopathy (PSE), and limited durability. TIPS occlusion rate has been reduced by the recent introduction of the polytetrafluorethylene-coated stent, but the rates of occlusion and PSE are still much higher than the incidences of these serious complications following portacaval shunt in all of our studies.

Emergency portacaval shunt (EPCS) is rarely used today because of the belief, unsubstantiated by randomized controlled trials involving unselected patients, that EPCS causes frequent portal-systemic encephalopathy and liver failure.[4,13–21] Consequently, portacaval shunt (PCS) has been relegated solely to the salvage of failed endoscopic and pharmacologic treatment. An important question is: is the regimen of EST or ligation with rescue PCS for failure to control BEV superior to EPCS? A unique opportunity to compare the regimen of EST with rescue PCS with EPCS was provided by our randomized controlled trial (RCT) of EST versus EPCS known as the San Diego Bleeding Esophageal Varices Study.

From April 8, 1988 to December 31, 2005, we conducted a RCT in 211 unselected, consecutive patients with cirrhosis and acute BEV in whom emergency and long-term EST was compared with direct EPCS, otherwise known as total shunt. The trial was a community-wide endeavor that involved patients referred from four adjacent counties to the University of California, San Diego (UCSD) Medical Center. In two recent publications, we described the study in detail and reported the outcomes first with regard to control of bleeding and survival[22] and second with regard to the development of PSE.[23] This report focuses on a comparison of outcomes following the regimen of EST with rescue PCS to outcomes following EPCS.

Patients and Methods

The reader is directed to our two recent publications[22,23] that provide detailed descriptions of the following methods and protocols used in this RCT:

1. Design of study[24,25]
2. Patient eligibility
3. Definitions of:
   (a) Bleeding esophageal varices
   (b) Unselected patients (all comers)
   (c) Emergency EST
   (d) Long-term EST
   (e) Emergency portacaval shunt
   (f) Failure of emergency primary therapy
   (g) Failure of long-term therapy
   (h) Rescue therapy
   (i) Informed consent
4. Randomization
5. Diagnostic workup[26]
6. Quantitative Child's classification[27,28]
7. Initial emergency therapy during workup
8. Endoscopic sclerotherapy
9. Emergency portacaval shunt[29]
10. Lifelong follow-up
11. Quantitation of PSE

In addition, the RCT involved the following protocols that have not been described previously.

Rescue Portacaval Shunt

Rescue PCS was performed in 50 patients as soon as possible after failure of EST was declared. Direct side-to-side PCS was done in 46 patients (92%), and direct end-to-side PCS was done in four patients (8%). Operative technique and intraoperative pressure measurements were identical to those used in EPCS.

QOL Score

Quality of life (QOL) was measured by assessing the following factors: (1) liver function as determined by quantitative Child's risk class; (2) development of recurrent PSE; (3) number of PSE episodes; (4) units of packed red blood cell (PRBC) transfusion for upper gastrointestinal bleeding; (5) number of hospital readmissions; (6) days of hospitalization during readmission; (7) return to work, including housekeeping; (8) abstinence from alcoholism; and (9) portacaval shunt patency. These nine factors were weighted numerically so as to produce a QOL score in which the lower the score, the better the QOL.

Direct Cost of Care

All hospital and outpatient facility charges and all professional fee bills from UCSD and from referring hospitals and physicians were obtained continuously for every patient entered into the study for 10 years.

Figure 1 is a Consort flow diagram that shows the overall design and conduct of the RCT.[22,23]

Statistical Analysis

The comparison between Emergency and Rescue PCS groups used Fisher's exact test for binary outcomes (e.g., control of bleeding, incidence of recurrent PSE) and Wilcoxon rank-sum test (WRT) for continuous outcomes (e.g., units of PRBC transfusion, number of recurrent PSE episodes, number of hospital readmissions). The length of survival was compared using Gehan–Wilcoxon rank test. The change in Child's class was compared for each time interval using the exact WRT, adjusted for ties. The average change in Child's class during the first 5 years was computed by averaging the duration of time in years spent by the patients at risk (alive) in each category (improved, unchanged, or worse). The comparison of the cause of recurrent PSE episodes used Pearson's chi-squared test. The overall quality of life score was computed for each group and each year by adding up the scores of the nine components. This score was compared between the two groups assuming a Poisson (log-linear) model, with different means for the different categories, and a constant group effect. At the beginning of the study, it was decided in advance not to perform an interim analysis of the data.

Results

EPCS Versus EST—Outcome Data

Our recent publications should be consulted for detailed data on the clinical characteristics of the 211 patients, findings on upper endoscopy and liver biopsy, results of laboratory blood tests, data on rapidity of therapy, data on control of bleeding, operative and endoscopic data, data on PSE, and data on survival.[22,23] There were no significant differences in the clinical characteristics of the two groups on entry in the RCT. Cirrhosis was demonstrated by liver biopsy in all patients. Definitive treatment was initiated in <24 h after onset of bleeding in all patients. EPCS controlled bleeding permanently in all patients, while EST achieved permanent control of bleeding in only 20%. Survival rates were significantly higher after EPCS than after EST at all time intervals and in all Child's classes ($p<0.001$). Patients with the most severe liver disease in Child's risk class C realized substantial long-term survival after EPCS.

The incidence of recurrent PSE following EST was 35%, which was more than twice the 15% incidence following EPCS ($p<0.001$). EST patients had a total of 179 episodes of PSE and 146 PSE-related hospital admissions compared with EPCS patients who had 94 episodes of PSE and 87 hospital admissions ($p=0.003$). Recurrent UGI bleeding, which was rare in the EPCS group, was a major causative factor of PSE in the EST patients.

EST with Rescue PCS Versus EPCS

Patient Characteristics

Table 1 summarizes the clinical characteristics at the time of entry in the San Diego BEV study of the 105 patients who were randomized to EPCS and the 50 patients who failed EST and underwent rescue PCS. There were no significant differences between the two groups in any important characteristics of cirrhosis and BEV. Thirty-one patients failed EST but did not undergo rescue PCS for various reasons, most prominent of which were death from recurrent BEV at home or at a distant hospital and death from massive recurrence of BEV before a rescue PCS could be done. As others have found, failure of patients to take advantage of rescue treatment reflects the realities of treating BEV in the cirrhotic population. Although these 31 patients were excluded from the analysis, their deaths have a negative impact on the concept of rescue PCS for failed EST.

Table 2 summarizes data on rapidity of therapy and indicates clearly that all patients underwent rapid diagnosis and treatment upon entry in the RCT. Median time from onset of bleeding to the start of therapy was <24 h in both groups of patients. The time from initial contact at UCSD

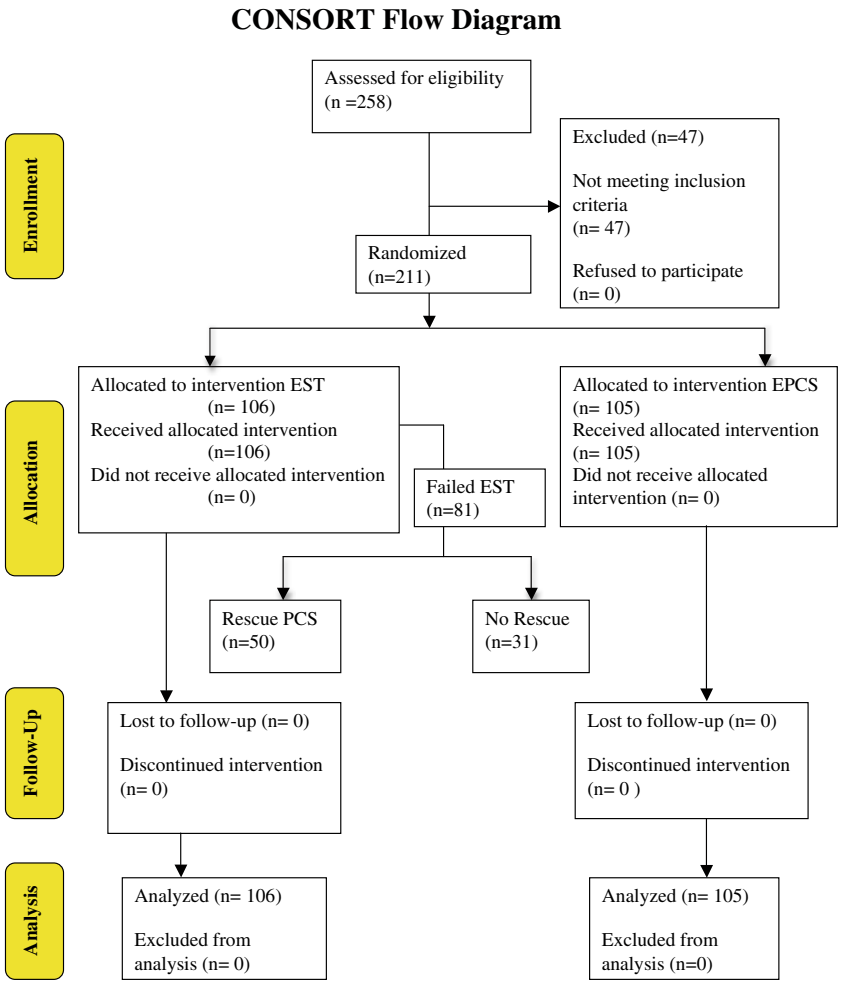

Fig. 1 Consort flow diagram showing the overall design and conduct of the prospective randomized controlled trial.[22,24,25]

Medical Center to start of therapy was <8 h in every patients in the EST group and in 102 of the 105 patients in the EPCS group. Active bleeding was observed within 4 h of entry in the study in 83% of the 155 patients.

Control of Bleeding

Table 3 provides data on control of BEV by EPCS and by EST with rescue PCS. EPCS promptly and permanently controlled bleeding in every patient. In contrast, EST failed to control bleeding in any of the 50 patients, and that is why they underwent rescue PCS. Failure of EST in 106 patients in the EST group was based on one or more of the criteria established in advance by the study protocol, which included: (1) in 15 patients, variceal bleeding continued or recurred during the first 7 days after initial EST and required ≥6 U blood transfusion; (2) in 47 patients, recurrent variceal bleeding required ≥8 U of blood transfusion during any 12-month period after the index hospitalization; (3) in 27 patients, variceal bleeding recurred after an experienced co-investigator faculty gastroenterologist had previously declared that the esophageal varices were obliterated or gone. In eight of these same patients, recurrent bleeding required ≥8 U of blood transfusion, so they met two criteria of failure.

Table 3 also summarizes the requirement for PRBC transfusions. Overall, patients treated by EST with rescue PCS required almost twice the number of PRBC transfusions as patients treated by primary EPCS ($p<0.001$).

Survival

Table 4 shows data on survival in the two groups of patients, and Fig. 2 shows 15-year Kaplan–Meier estimated survival plots. All patients in the EST-rescue PCS group and 98 of the 105 patients in the EPCS group were eligible for ten or more years of follow-up. The remaining seven EPCS patients had follow-up for 9.4–9.9 years. No patients were lost to follow-up. After the first year, there were highly significant differences in the survival rates of the two study groups at all

Table 1 Clinical Characteristics at Study Entry in Patients with Cirrhosis and Bleeding Esophageal Varices Undergoing Primary EPCS or EST with Rescue PCS

	Primary EPCS (n=105)	Rescue PCS (n=50)	p value
History			
Age (years)			
Mean/median	49.9/47	47.7/44.5	0.27
Range	28–82	30–75	
Male gender, n (%)	81 (78)	39 (78)	1.0
Race, n (%)			0.43
Caucasian	58 (55)	23 (46)	
Hispanic	39 (37)	24 (48)	
Other	8 (8)	3 (6)	
Cause of cirrhosis, n (%)			0.93
Alcoholism alone	54 (51)	27 (54)	
Hepatitis B or C alone	8 (8)	4 (8)	
Alcoholism and hepatitis	33 (31)	16 (32)	
Other	10 (10)	3 (6)	
Chronic alcoholism, n (%)	87 (83)	43 (86)	0.82
Years of alcoholism median/range	25/7–54	24/5–59	0.69
Recent alcohol ingestion ≤7 days, n (%)	74 (70)	33 (66)	0.58
Past history, n (%)			
Jaundice	58 (55)	27 (54)	1.00
Ascites	48 (46)	31 (62)	0.062
Portal-systemic encephalopathy	30 (29)	7 (14)	0.069
Physical examination, n (%)			
Jaundice	38 (36)	19 (38)	0.86
Ascites	54 (51)	30 (60)	0.39
Portal-systemic encephalopathy	19 (18)	8 (16)	0.82
Severe muscle wasting (2+ or 3+ on 0–3+ scale)	67 (64)	25 (50)	0.12
PSE index			
Median (interquartile range)	0 (0–0.15)	0 (0–0.9)	0.066
Child's risk class, n (%)			0.58
A (5–8 points)	26 (25)	14 (28)	
B (9–11 points)	49 (47)	26 (52)	
C (12–15 points)	30 (29)	10 (20)	
Child's risk class points			
Mean/median	10.0/10	9.8/9	0.37
Liver biopsy—cirrhosis			
n (%)	105 (100)	50 (100)	1.0
Findings on endoscopy, n (%)			
Esophageal varices	105 (100)	50 (100)	1.0
Size 2 + to 4 + (on scale of 0–4+)	105 (100)	49 (98)	0.85
Active bleeding	29 (28)	24 (48)	0.018[a]
Clot on varices	51 (49)	25 (50)	1.0
Red color signs on varices	66 (63)	29 (58)	0.60
Gastric varices on endoscopy	17 (16)	10 (20)	0.65
Portal hypertensive gastropathy	22 (21)	12 (24)	0.68
Gastritis/erosions	14 (13)	7 (14)	1.0
Reason for not undergoing rescue PCS, n (%)			
BEV and death elsewhere, not at UCSD		13 (42)	
Massive recurrent BEV and death		11 (35)	

Table 1 (continued)

	Primary EPCS (n=105)	Rescue PCS (n=50)	p value
Refused rescue PCS		2 (6)	
Died in hepatic coma with liver failure		2 (6)	
Liver transplantation		2 (6)	
Perforated esophagus with sepsis		1(3)	

EPCS emergency portacaval shunt, *PCS* portacaval shunt, *PSE* portal-systemic encephalopathy, *BEV* bleeding esophageal varices

[a] Statistically significant difference

long-term time intervals. The 5-, 10-, and 15-year survival rates in the EST-rescue PCS group were 22%, 16%, and 0%, respectively, and in the EPCS group were 72%, 46%, and 46%, respectively ($p<0.001$). Median survival was 6.15 years in patients randomized to EPCS compared to 3.1 years in EST-rescue PCS patients ($p<0.001$). Hepatic failure was the primary cause of death in 44% of patients who underwent EST with rescue PCS compared to 22% of patients who received primary EPCS. In contrast to the entire group of 106 EST patients in which 26% died from variceal bleeding, none of the 105 EPCS patients died of bleeding.

As expected, the survival rate was related to the severity of liver disease at the time of entry in the study, as expressed by quantitative Child's risk classes. In the EST group with rescue PCS, 5-year survival rates in Child's classes A, B, and C were 36%, 15%, and 20%, respectively, and 10-year survival rates in Child's classes A, B, and C were 29%, 12%, and 10%, respectively. In contrast, in the EPCS group, the corresponding survival rates in Child's classes A, B, and C were 89%, 76%, and 53% at 5 years and 62%, 47%, and 30% at 10 years. The differences in favor of EPCS were highly significant ($p=0.005$ to $p<0.001$).

Median survival of patients who failed EST and underwent a rescue PCS was 3.01 years compared to median survival of 2.36 years in the 38% of patients who failed EST but did not undergo a rescue PCS. Importantly, median postoperative survival following rescue PCS was only 1.99 years compared to 6.18 years following primary EPCS ($p<0.001$).

Portal Systemic Encephalopathy

Table 5 shows data on PSE in the two groups of patients. Calculations of the incidence of PSE are based on patients who were discharged from the index hospitalization and survived more than 30 days after study entry since deaths on or before 30 days were considered indeterminate and unrelated to PSE. As we have reported previously, the incidence of PSE was 35% in the primary EST group and 15% in the primary EPCS group ($p=0.001$).[23] The difference in incidence of PSE was even greater when the primary EPCS group with its 15% PSE incidence was compared to the EST-rescue PCS group in which the PSE incidence was 43% ($p<0.001$). Furthermore, as shown in Table 5, the number of episodes of PSE per patient and per

Table 2 Rapidity of Therapy of Patients with Cirrhosis and Bleeding Esophageal Varices Randomized to EPCS or EST followed by Rescue PCS

Hours	Primary EPCS (n=105)		EST then Rescue PCS (n=50)		p value
	Median/mean	Range	Median/Mean	Range	
Onset bleeding to study entry	16/19.5	0–95	10/17.5	0–144	0.038[a]
Onset bleeding to primary therapy	19/24.0	2.6–100.3	13.4/21.6	3–146.5	0.010[a]
Study entry to primary therapy	3.4/4.4	1.4–24.3	2.5/3.1	1.0–7.8	<0.001[a]
>8 h, n (%)	3 (2.9)		0 (0)		
Transfer patients, n (%)	80 (76)		33 (66)		0.61
Onset bleeding to entry in referring hospital	3.8/9.9	0–83.6	4.5/11.2	0–127.4	0.76
Entry in referring hospital to study entry	8.4/11.6	0–53	7/11.3	1.5–43	0.33
Last observation of bleeding to study entry	0/3.1	0–30	0/3.4	0–32	0.95
≤4 h, n (%)	88 (84)		41 (82)		
>4 h, n (%)	17 (16)		9 (18)		0.82

EST endoscopic sclerotherapy, *EPCS* emergency portacaval shunt, *PCS* portacaval shunt

[a] Statistically significant difference

Table 3 Control of Bleeding in Patients with Cirrhosis and Bleeding Esophageal Varices Randomized to EPCS or EST followed by Rescue PCS

	Primary EPCS (n=105)	Primary EST then Rescue PCS (n=50)	p value
Success of primary therapy, n (%)			
Indeterminate—non-bleeding death ≤14 days	11 (10)	0 (0)	0.017[a]
Indeterminate—non-bleeding death ≤30 days	15 (14)	2 (4)	0.060
Successful control by primary therapy			
Excluding indeterminates for at least 14 days	94 (100)	0 (0)	<0.001[a]
Excluding indeterminates for at least 30 days	90 (100)	0 (0)	<0.001[a]
>30 days	89 (100)	0 (0)	<0.001[a]
Reason in EST group for declaration of primary therapy failure, n (%)			
Required ≥6 U PRBC in first 7 days	–	15 (19)	
Required ≥8 U PRBC in any 12 months	–	47 (58)	
Recurrent variceal bleeding after variceal obliteration was declared	–	27 (34)	
More than one criterion for failure	–	8 (10)	
Successful control of bleeding by rescue PCS			
n (%)	–	50 (100)	
PRBC transfusion—units PRBC, mean/median (range)			
Index hospitalization			
Before primary treatment	5.78/5 (2–17)	4.48/4 (2–10)	0.005[a]
During primary treatment	6.31/3 (0–68)	0.62/0 (0–6)	<0.001[a]
Catch-up after primary treatment	1.17/0 (0–21)	0.26/0 (0–4)	0.14
Post-therapy bleeding			
Variceal	0/0 (0–0)	6.92/2 (0–35)	<0.001[a]
Non-variceal	1.75/0 (0–29)	0.38/0 (0–5)	0.30
Total PRBC units	14.99/10 (2–81)	12.66/7 (2–44)	0.16
Readmission for bleeding			
Variceal bleeding	0.36/0 (0–26)	10.58/9 (0–60)	<0.001[a]
Non-variceal bleeding	3.45/0 (0–33)	5.19/0 (0–36)	0.93
Total PRBC units	3.81/0 (0–33)	15.77/10 (0–60)	<0.001[a]
Grand total PRBC units			
Variceal bleeding	13.56/10 (2–73)	22.44/19 (7–64)	<0.001[a]
Variceal and non-variceal bleeding	17.83/14 (2–81)	27.80/23 (7–64)	<0.001[a]

EPCS emergency portacaval shunt, *EST* endoscopic sclerotherapy, *PCS* portacaval shunt, *U* units, *PRBC* packed red blood cells

[a] Statistically significant difference

year and the number of hospital readmissions per patient and per year were all significantly more frequent in the EST-rescue PCS group than in the EPCS group (p<0.001). Additionally, the EST-rescue PCS patients with PSE had a median survival from the time of study entry of 3.44 years, which was longer than the 2.45 years of survival of the patients free of PSE, but the difference was not significant. In contrast, the patients in the primary EPCS group had a significantly longer survival than those in the EST-rescue PCS group (p<0.001), and their median survival was 5.18 years for those with PSE and 10.43 years in those free of PSE (p<0.001).

Dietary indiscretion with regard to protein restriction was the most frequent cause of recurrent PSE in both groups of patients. Portal hypertension-related UGI bleeding, usually from BEV, was the main cause of PSE in 23% of the episodes of PSE in the EST-rescue PCS group and was a contributing cause in an additional 16%. PSE episodes occurred more frequently prior to performance of rescue PCS than after rescue PCS. UGI bleeding was infrequently responsible for PSE in patients randomized to EPCS, occurring in only 8% of the patients even though they survived more than twice as long as the EST-rescue PCS patients (p<0.001).

Table 4 Survival of Patients with Cirrhosis and Bleeding Esophageal Varices Randomized to EPCS or EST Followed by Rescue PCS

Survival data	Primary EPCS (n=105)	Primary EST then Rescue PCS (n=50)	p value
Overall survival—Pr (95% CI)			
30 days	0.86 (0.79–0.93)	0.96 (0.91–1.00)	0.073
1 year	0.80 (0.73–0.88)	0.80 (0.70–0.92)	1.0
5 years	0.72 (0.64–0.82)	0.22 (0.13–0.37)	<0.001[a]
10 years	0.46 (0.37–0.56)	0.16 (0.08–0.30)	<0.001[a]
15 years	0.36 (0.27–0.47)	NA (NA, NA)	
Median survival, years (95% CI)	6.15 (5.58–10.43)	3.00 (1.51–4.33)	<0.001[a]
Hazard ratio of death (95% CI)	1	2.24 (1.50–3.35)	
Survival by Child's risk class—Pr (95% CI)			
5 years			
Class A, n (26 EPCS, 14 rescue)	0.89 (0.77–1.00)	0.36 (0.18–0.72)	0.001[a]
Class B, n (49 EPCS, 26 rescue)	0.76 (0.64–0.89)	0.15 (0.06–0.38)	<0.001[a]
Class C, n (30 EPCS, 10 rescue)	0.53 (0.38–0.75)	0.20 (0.06–0.69)	0.058
10 years			
Class A	0.62 (0.45–0.83)	0.29 (0.13–0.65)	0.010[a]
Class B	0.47 (0.35–0.63)	0.12 (0.04–0.33)	0.005[a]
Class C	0.30 (0.17–0.52)	0.10 (0.02–0.64)	0.29
Median survival—years (95% CI)			
Class A	10.43 (5.58 to >10.68)	4.33 (1.46, >10.82)	0.031[a]
Class B	6.24 (5.44 to >11.02)	2.71 (1.48–4.51)	<0.001[a]
Class C	5.17 (0.04 to 10.16)	1.37 (0.12 to >11.72)	0.35
Postoperative survival years—Pr (95% CI)	6.18 (5.61, 10.38)	1.99 (1.34–3.73)	<0.001[a]

EPCS emergency portacaval shunt, *EST* endoscopic sclerotherapy, *PCS* portacaval shunt, *Pr* probability, *CI* confidence interval

[a] Statistically significant difference

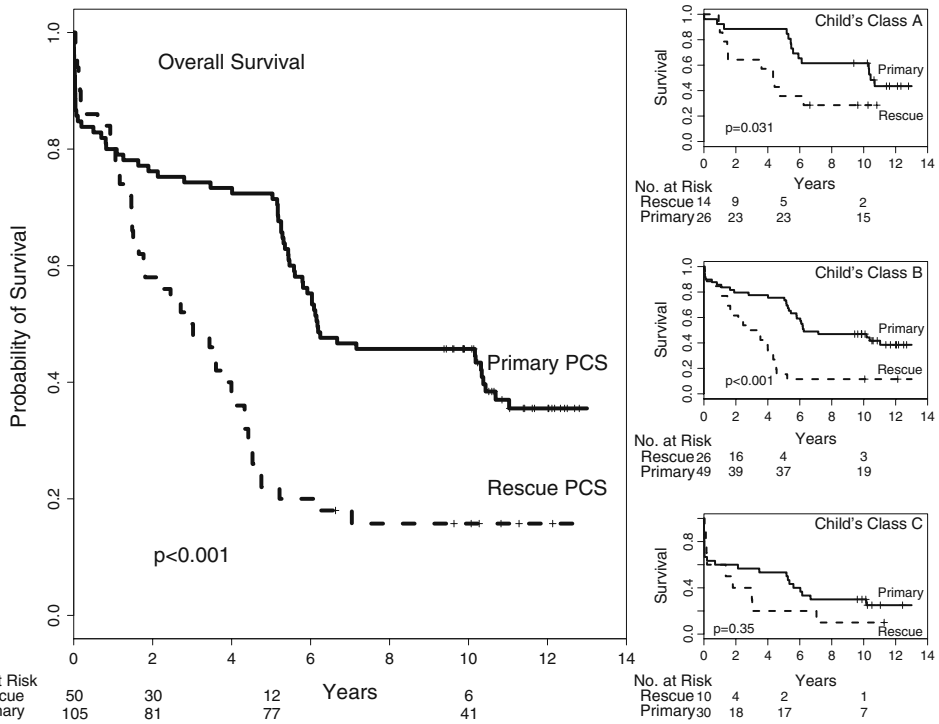

Fig. 2 Kaplan–Meier estimates of overall survival after emergency portacaval shunt (*EPCS*, n=105) and after failed endoscopic sclerotherapy (*EST*) with rescue portacaval shunt (*PCS*, n=50).

Table 5 Recurrent Portal-Systemic Encephalopathy in Patients with Cirrhosis and Bleeding Esophageal Varices Randomized to EPCS or EST Followed by Rescue PCS

PSE data	Primary PCS (n=88)	Primary EST then rescue PCS (n=47)	p value
Incidence of recurrent PSE, n (%)	13 (15)	20 (43)	<0.001[a]
Length of survival			<0.001[a]
Total days	269,927	69,060	
Total years	739.0	189.1	
Total days/patient	3,067.4	1,469.4	
Total years/patient	8.40	4.02	
Recurrent PSE episodes			<0.001[a]
Total episodes, n	94	118	
Episodes/patient	1.07	2.51	
Episodes/year of follow-up	0.13	0.62	
Interval between episodes (in years)	7.86	1.60	
Hospital readmissions for recurrent PSE			0.001[a]
Total readmissions, n	87	91	
Readmissions/patient	0.99	1.94	
Readmissions/year of follow-up	0.12	0.48	
Interval between episodes (years)	8.49	2.08	
Cause of recurrent PSE episodes, n (%)			<0.001[a]
Dietary protein indiscretion	60 (61)	61 (50)	
UGI bleeding	8 (8)	28 (23)	
Infection	12 (12)	4 (3)	
Alcoholism	4 (4)	22 (18)	
Uncontrolled diabetes	11 (11)	2 (2)	
Hepatic failure	0 (0)	3 (2)	
Other	3 (3)	2 (2)	
Relationship of PSE to survival			
Median (95% CI, in years)			
Patients with recurrent PSE			
Overall survival	5.18 (1.26, Inf)	3.44 (1.81–7.04)	
Survival after first PSE	4.15 (1.17, Inf)	2.01 (1.08–4.54)	
Patients free of recurrent PSE			
Overall survival	10.43 (6.24, Inf)	2.45 (1.46–4.42)	
p value (recurrent versus no PSE)	<0.001[a]	0.62	
High PSE index, n (%)			
Patients with PSE index ≥0.33	12 (14)	10 (22)	0.23
Patients with PSE index ≥0.33 who had recurrent PSE clinically	4 (33)	10 (100)	0.002[a]

PSE portal-systemic encephalopathy, *EPCS* emergency portacaval shunt, *PCS* portacaval shunt, *UGI* upper gastrointestinal, *CI* confidence interval

[a] Statistically significant difference

Change in Liver Function

Improvement or worsening of liver function was determined by serial quantitative measurements of Child's risk class monthly during the first year after study entry and every 3 months thereafter. An increase or decrease in two or more Child's class points reflected, respectively, improvement or worsening of liver function. Table 6 presents a summary of yearly changes in Child's risk class using Child's class on study entry as a baseline and combining Child's classes A, B, and C. Results in patients randomized to EPCS are compared to results in the EST-rescue PCS patients. In every year, there was a statistically significant difference between the EPCS group and the EST-rescue PCS group, with the patients randomized to EPCS having more improvement and less worsening of liver function than the patients in the EST-rescue PCS group

Table 6 Changes in Child's Class Compared to Child's Class on Study Entry in Patients with Cirrhosis and Bleeding Esophageal Varices Randomized to EPCS or EST Followed by Rescue PCS

Years after study entry	Changes in Child's classes—A, B, and C combined	Primary EPCS	Primary EST, then rescue PCS	*p* value
1	*n*	89	45	0.008[a]
	Improved, *n* (%)	53 (60)	17 (38)	
	Unchanged, *n* (%)	26 (29)	16 (36)	
	Worse, *n* (%)	10 (11)	12 (27)	
2	*n*	82	39	<0.001[a]
	Improved, *n* (%)	50 (61)	12 (31)	
	Unchanged, *n* (%)	24 (29)	14 (36)	
	Worse, *n* (%)	8 (10)	13 (33)	
3	*n*	77	28	0.054
	Improved, *n* (%)	44 (65)	11 (57)	
	Unchanged, *n* (%)	25 (27)	10 (32)	
	Worse, *n* (%)	8 (8)	7 (10)	
4	*n*	75	24	<0.001[a]
	Improved, *n* (%)	45 (60)	6 (25)	
	Unchanged, *n* (%)	24 (32)	7 (29)	
	Worse, *n* (%)	6 (8)	11 (46)	
5	*n*	76	16	<0.001[a]
	Improved, *n* (%)	45 (59)	3 (19)	
	Unchanged, *n* (%)	25 (33)	6 (38)	
	Worse, *n* (%)	6 (8)	7 (44)	
1–5-year average	*n*	89	45	<0.001[a]
	Improved (%)	59	32	
	Unchanged (%)	31	35	
	Worse (%)	10	33	

EPCS emergency portacaval shunt, *PCS* portacaval shunt

[a] Statistically significant difference. Changes indicate an increase or decrease of two or more Child's class points

(p=0.008 to <0.001). Overall, the 1- to 5-year average change in Child's classes comparing EPCS versus EST-rescue PCS, respectively, showed improvement in 59% versus 32% and worsening in 10% versus 33% (p<0.001). The differences in liver function between the EPCS and EST-rescue PCS groups were particularly striking in Child's class C where improvement in liver function was most important. Five years after entry in the RCT, liver function had improved in 94% of the EPCS group compared to 65% in the EST-rescue PCS group, and liver function had worsened in 4% of the EPCS group compared to 30% of the EST-rescue PCS group. The difference in favor of EPCS was significant (p<0.001).

Quality of Life Score

Table 7 summarizes data on QOL for 5 years in the 105 patients randomized to EPCS and the 50 patients who failed EST and underwent rescue PCS. QOL score was based on nine criteria shown at the bottom of Table 8. In the comparison, a lower score indicates a better QOL. Overall, during each year and for the entire 5-year period of study, QOL was significantly better, i.e., the QOL score was lower in the EPCS group than in the EST-rescue PCS group (p<0.001).

Direct Costs of Care

Table 8 summarizes the total charges over a 10-year period for hospitalization and outpatient care in thousands of US dollars in patients randomized to EPCS and those randomized to EST-rescue PCS. The mean grand total charges over the entire length of the study were $150,400 in the EPCS patients and $263,600 in the EST-rescue PCS patients, a highly significant difference (p<0.001). More importantly, the mean grand total charges per year amounted to $39,200 in the EPCS patients and $216,700 in the EST-rescue PCS patients, 5.5 times greater (p<0.001).

Discussion

Comment is warranted regarding the use of EST rather than EVL in this RCT. In 1988 when the San Diego BEV Study was initiated, EST was a mainstay of therapy of BEV and

Table 7 Quality of Life Score Based on Nine Criteria in Survivors Who Were Discharged from the Index Hospitalization After Undergoing EPCS or EST Followed by Rescue PCS (Lower Score is Better QOL)

Years after study entry	QOL score	Primary EPCS	Primary EST, then rescue EPCS	*p* value
1	Number of patients	75–105	40–49	<0.001[a]
	Total points	1810	2002	
	Mean points	20.73	45.62	
2	Number of patients	71–97	29–43	<0.001[a]
	Total points	1279	1004	
	Mean points	15.51	27.72	
3	Number of patients	69–88	26–32	<0.001[a]
	Total points	1034	473	
	Mean points	13.18	16.96	
4	Number of patients	67–83	19–29	<0.001[a]
	Total points	774	403	
	Mean points	10.08	17.35	
5	Number of patients	66–80	11–22	<0.001[a]
	Total points	666	212	
	Mean points	8.81	13.63	
0–5	Number of patients	348–453	125–175	<0.001[a]
	Total points	5,563	4,094	
	Mean points	13.89	27.89	

EPCS emergency portacaval shunt, *EST* endoscopic sclerotherapy, *PCS* portacaval shunt, *QOL* quality of life

QOL Criteria: (1) Change in Child's class; (2) recurrent PSE; (3) no. of PSE episodes; (4) PRBC units; (5) no. of readmissions; (6) readmission days; (7) alcoholism; (8) return to work; (9) PCS patency

[a] Statistically significant difference

the sole form of endoscopic therapy in use. When EVL was introduced generally, as well as at our institution, we were well into our RCT and our investigators and senior advisors made the unanimous decision not to change from EST to EVL. That decision has received strong support from studies published in 2003, 2005, and 2006 that have questioned replacement of EST by EVL. In a survey reported in 2003 of 93 gastroenterologists who treated 725 patients with BEV, EST was used more frequently than EVL for control of BEV and as frequently as EVL for initial control of acute bleeding.[11] Trials published in 2005 and 1999 reported a significantly higher failure rate with band ligation of actively bleeding varices and an overall higher recurrence rate of varices treated by EVL.[12,30] Moreover, EST has been reported to be more cost-effective if active variceal hemorrhage is present at the index endoscopy procedure, as was the case in our RCT.[30] It is noteworthy that none of nine randomized clinical trials summarized in 2005 observed a statistically significant difference in survival rate between EVL and EST.[12] In a meta-analysis of emergency EST in 40 trials involving 4031 patients reported by Triantos et al.[10] in 2006, there was no statistically significant difference in survival rate between EVL and EST. The authors concluded that "the conclusive evidence for substituting banding ligation or the combination of vasoconstrictors with sclerotherapy as better therapeutic approaches has not been provided in randomized trials. Sclerotherapy can remain a gold standard in variceal bleeding…."

It is widely agreed that portal-systemic shunts are very effective in controlling BEV. The results of our RCT confirm such effectiveness since both EPCS and rescue PCS promptly and permanently controlled BEV in every patient. Nevertheless, according to numerous statements in the literature, surgical shunts control bleeding at the expense of an unacceptably high rate of PSE as well as progressive liver failure, and that is the main reason why portal-systemic shunts have been relegated to a secondary salvage role for use solely as a last resort when endoscopic and pharmacologic measures have failed.[4,13–21] The results of our RCT, which involved unselected, consecutive cirrhotic patients with all degrees of liver dysfunction, including patients in Child's class C, contradict the widely held beliefs about the appropriate role of portal-systemic shunts. According to our findings which have been reported in detail recently,[23] the incidence of PSE following EPCS was significantly lower (15%) than the incidence following primary EST (35%) or after EST with rescue PCS (43%). The protocol of our RCT describes the requirements for achieving a low incidence of PSE.[23] These are: (1) diagnosis and EPCS within 24 h of onset of BEV; (2) operation by surgeons experienced in portal hypertension

Table 8 Total Facility and Professional Fee Charges for Patients with Cirrhosis and Bleeding Esophageal Varices Randomized to EPCS or EST Followed by Rescue PCS

Total charges and charges per day or per year in $1,000	Primary EPCS			Primary EST, then Rescue PCS			*p* value
	n	Mean and (SD)	Range	*n*	Mean and (SD)	Range	
Index admission	105			50			
1. Total hospital charges		69.1 (56.1)	23.1–352.6		67.6 (65.6)	7.5–433.9	0.34
Hospital charges per day		5.60 (5.85)	1.98–52.06		4.19 (2.62)	0.83–16.98	0.024[a]
2. Total physician charges		11.1 (5.4)	3.3–34.8		9.1 (8.6)	1.6–50.4	<0.001[a]
Physician charges per day		1.05 (1.21)	0.16–7.28		0.61 (0.48)	0.18–3.15	<0.001[a]
3. Total overall charges		80.2 (60.0)	33.7–380.5		76.7 (70.9)	9.4–458.5	0.20
Overall charges per day		6.65 (6.83)	2.41–58.11		4.80 (2.81)	1.04–17.70	0.009[a]
Readmission post-index	88			47			
1. Total hospital charges		56.6 (71.3)	0–262.0		150.2 (183.9)	0–911.4	<0.001[a]
Hospital charges per year		20.4 (48.2)	0–262.3		124.6 (273.4)	0–1642.0	<0.001[a]
2. Total physician charges		8.6 (10.5)	0–49.2		19.7 (18.8)	0–89.0	<0.001[a]
Physician charges per year		2.6 (5.6)	0–35.8		17.0 (35.5)	0–180.6	<0.001[a]
3. Total overall charges		65.2 (80.6)	0–284.2		169.8 (195.0)	0–926.1	<0.001[a]
Overall charges per year		23.0 (53.6)	0–298.1		141.5 (306.8)	0–1823.0	<0.001[a]
Outpatient post-index	88			47			
1. Total hospital charges		8.4 (4.9)	0–27.7		16.4 (40.3)	0–267.3	0.49
Hospital charges per year		1.3 (1.2)	0–7.5		4.4 (7.5)	0–34.3	<0.001[a]
2. Physician charges		6.3 (3.6)	0–12.8		6.4 (6.1)	0–19.7	0.35
Physician charges per year		0.8 (0.5)	0–2.7		2.1 (2.6)	0–14.7	<0.001[a]
3. Total overall charges		14.7 (7.6)	0–33.2		22.8 (44.0)	0–286.9	0.36
Overall charges per year		2.1 (1.5)	0–9.5		6.6 (9.6)	0–48.4	<0.001[a]
Total post-index charges	88	79.9 (79.8)	0–302.0	47	192.6 (198.5)	11.2–958.4	<0.001[a]
Total post-index charges per year		25.1 (54.0)	0–302.1	47	148.1 (308.4)	1.5–1824.0	<0.001[a]
Grand total charges	88	150.4 (100.8)	41.4–682.5	47	263.6 (192.9)	27.5–982.8	<0.001[a]
Grand total charges per year		39.2 (70.5)	2.6–374.5	47	216.7 (397.1)	8.0–1954.0	<0.001[a]

After index admission, patients who died during index admission were excluded

EPCS emergency portacaval shunt, *EST* endoscopic sclerotherapy, *PCS* portacaval shunt

[a] Statistically significant difference

surgery; (3) postoperative care in an ICU by trained and experienced nurses and physicians; and (4) regular, long-term follow-up that includes concerted efforts to promote abstinence from alcohol and repeated emphasis on reasonable restriction of dietary protein intake. It is our conviction that these requirements can be fulfilled by most trained surgeons and by most general hospitals in the USA.

Regarding the matter of post-shunt liver failure, the concept that direct portacaval shunts cause liver failure because of diversion of essential portal blood flow began over a century ago with the animal experiments of Eck and Hahn and associates in Pavlov's laboratory[31,32] and has been suggested repeatedly but not substantiated since then.[33–35] The concept has led to the invention of a number of operations that are purported to maintain portal blood flow to the liver while overcoming portal hypertension. These include distal splenorenal shunt, small-diameter prosthetic, H-graft portacaval shunt, and small-diameter direct side-to-side portacaval shunt. However, the concept is contradicted by two important hemodynamic facts. The first is that whether or not a PCS is constructed, BEV arise as a consequence of progressive diversion of a substantial portion of venous blood flow away from the liver and into portal-systemic collaterals so that, with regard to creation of a PCS, the cirrhotic liver with BEV is markedly different from the normal liver. The second important hemodynamic fact is that a fundamental physiologic response to diversion of portal venous flow is a compensatory increase in hepatic arterial blood flow to the liver.[36–38] It is not possible by any currently available practical method to predict the adequacy of hepatic arterial compensation prior to performance of a

PCS. Substantial data from preoperative and intraoperative measurements of both pressure and blood flow in the portal vein in large numbers of patients have failed to show a correlation between any hemodynamic measurements performed prior to PCS and survival, hepatic function, or development of PSE after PCS.[36–40] Our studies of portal vein hemodynamics before PCS showed no statistically significant correlation between pre-shunt maximum perfusion pressure and post-shunt survival, liver function, hepatic failure, or development of PSE.[38] It is noteworthy that Burchell and colleagues in their extensive intraoperative hemodynamic studies observed the largest post-shunt increments in compensatory hepatic arterial flow following side-to-side PCS, the procedure performed in 99 of the 105 EPCS patients in our RCT. In the final analysis, the long-term improvement in liver function following EPCS observed in the current trial provides the most meaningful and objective information regarding the effect of portal venous flow diversion on the cirrhotic liver. Each year for 5 years after EPCS, liver function improved in 59–65% of patients, and liver function declined in only 8–11%.

The San Diego BEV Study provided a unique opportunity in a RCT to compare EPCS, a treatment that is infrequently used today, with a conventional treatment regimen consisting of rescue PCS following failure of EST to control BEV. Not only did EPCS prove to be superior to EST, but also, by every measure of effectiveness, EPCS proved to be significantly better than the combination of EST with rescue PCS. How can this striking difference be explained? A likely explanation is that patients who require rescue PCS are much more severely ill than patients who undergo a diagnostic workup and a definitive operation within 24 h of the onset of bleeding. They are poorer candidates for operation or, for that matter, for any other form of rescue therapy. There is little doubt that persistent variceal bleeding, repeated readmissions to the hospital, and repeated bouts of PSE in the EST patients take their toll. In point of fact, by the time rescue PCS was required, many of the patients had experienced a decline in liver function reflected by a negative change in Child's risk class. Furthermore, one third of the patients who failed EST died before having the opportunity to undergo rescue PCS, a common occurrence in programs that treat cirrhotic patients with BEV.

Kahn et al.,[5] in their extensive review of emergency treatment of BEV, identified serious shortcomings in many of the reported studies. The San Diego BEV Study was designed to overcome these shortcomings and was unique in the following respects: (1) the 211 patients with acute BEV were unselected and consecutive; (2) physicians from four California counties with a population of 8.5 million agreed to participate in the study; (3) the diagnostic workup was completed rapidly in a mean 3.1–4.4 h, entirely at the bedside in the ICU; (4) unlike any reported study to date, definitive treatment with EST or EPCS was started within 8 h of study entry in 208 of 211 patients; (5) the surgeons and gastroenterologists were experienced senior faculty physicians; (6) follow-up was 100%, was regular, and extended for 9.4 to more than 10 years or until death; (7) concerted, organized, and often successful efforts were made to control dietary protein intake and alcoholism; (8) PSE was determined and prevented according to a clearly defined protocol by a "blinded" senior gastroenterologist; and (9) consistent with our past experience following EPCS, only 2 of 105 patients developed shunt occlusion, which prevented recurrent BEV and PSE.

Conclusion

In this RCT of emergency treatment of acute BEV in 211 unselected, consecutive patients with cirrhosis of all grades of severity, EPCS was strikingly superior to EST as well as to the combination of EST and rescue PCS in regard to all outcome measures, specifically control of bleeding, survival, incidence of PSE, improvement in liver function, quality of life, and cost of care. These results contradict the widespread belief that PCS, otherwise known as total shunt, is associated with a high incidence of PSE and causes liver failure. Moreover, these results call into question the widespread practice of relegating PCS solely to salvage failure of endoscopic therapy of BEV and strongly support the use of EPCS as the first line of emergency treatment of BEV in cirrhosis.

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Author Contributions Orloff, Isenberg, Wheeler contributed to the study conception and design. Acquisition of data was done by Orloff, Isenberg, Haynes, Jinich-Brook, Rapier, Hye. Analysis and interpretation of data was done by Orloff, Isenberg, Vaida. Orloff, Haynes, Vaida, Hye took care of the drafting of the manuscript. Orloff, Haynes, Jinich-Brook, Vaida, Hye did the critical revision.

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2010 SSAT POSTER PRESENTATION

Surgical Resection and Multidisciplinary Care for Primary and Metastatic Pancreatic Islet Cell Carcinomas

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Abstract
Introduction The role of multidisciplinary management of islet cell cancers (ICC) has not been fully investigated in a population-based setting.
Methods The Los Angeles County Cancer Surveillance Program was assessed for patients with ICC between the years 1982 to 2006. Patients were stratified by treatment received and clinicopathologic characteristics and survival were compared.
Results We identified 236 patients with ICC; 86 patients underwent curative-intent surgery with median survival for local, regional, and distant disease of 17.3, 12.2, and 4.0 years, respectively. In comparison, 102 patients underwent medical management alone; survival was significantly shorter when compared to the surgical cohort for local, regional, and distant disease ($p<0.05$). To determine whether adjuvant chemotherapy was associated with improved survival, we compared patients who underwent surgery alone compared to patients who underwent surgery followed by adjuvant chemotherapy. Although patients with metastatic disease had 3-year longer survival with adjuvant chemotherapy, these improvements in survival were not statistically significant.
Conclusion Surgical resection was associated with improved survival compared to medical management for any extent of disease in patients with ICC. Furthermore, adjuvant chemotherapy was not associated with survival but does warrant further examination in patients with metastatic disease.

Keywords Islet cell carcinoma · Pancreatic resection · Chemotherapy · Multimodality therapy

Introduction

Pancreatic islet cell carcinomas (ICC) are rare, malignant tumors also known as neuroendocrine tumors that arise from cells in the pancreatic islets of Langerhans. They account for approximately 1% to 2% of all pancreatic neoplasms and exhibit mostly indolent behavior when compared to the more common pancreatic duct cancers.[1,2] The combination of low incidence and sporadically uncharacteristic clinical behavior has precluded the controlled evaluation and development of multimodal treatment regimens.[3–5] However, the optimal management of gastrointestinal malignancies has increasingly necessitated multidisciplinary approaches with input from both medical and surgical specialties. Our objective was to examine the multidisciplinary management of patients with ICC within a large population-based cancer registry to determine the role of surgical and medical therapies in the management of ICC.

Surgical resection has been the gold standard curative therapy for patients with ICC and long-term survival after curative resection is routine in patients with localized disease.[6–10] Unfortunately, most patients with ICC present

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with regional or distant disease, and unresectable disease at initial presentation or recurrent disease after curative resection is also common.[7–13] Multimodal treatment regimens would appear warranted in this setting, but they have not been well-described. Using the State of California Cancer Surveillance Program (CSP), we sought to evaluate the multidisciplinary management of patients with pancreatic ICC in the Los Angeles County population.

Table 1 Characteristics of Patients with Islet Cell Carcinomas

Factors	Entire cohort (*N*=236)	Surgical cohort (*N*=86)
Age (mean ± SD)	58.7±14.7	55.9±13.1
≤50	73 (31%)	31 (36%)
51–64	70 (30%)	31 (36%)
≥65	93 (39%)	23 (28%)
Sex		
Male	141 (60%)	45 (52%)
Female	95 (40%)	41 (48%)
Race		
White	140 (59%)	46 (54%)
Black	19 (8%)	5 (6%)
Hispanic	42 (18%)	13 (15%)
Asian	24 (10%)	15 (17%)
Other/unknown	11 (5%)	7 (8%)
Tumor location		
Head	66 (28%)	27 (31%)
Body	19 (8%)	9 (11%)
Tail	54 (23%)	33 (38%)
Other/NOS	97 (41%)	17 (20%)
Grade		
Well	24 (10%)	14 (16%)
Moderate	14 (6%)	8 (9%)
Poor	11 (5%)	3 (5%)
Undifferentiated	2 (1%)	0 (0%)
Unknown	185 (78%)	57 (70%)
LN status		
Negative	N/A	39 (45%)
Positive		31 (36%)
Unknown		16 (19%)
Stage		
Local	42 (18%)	25 (29%)
Regional	82 (35%)	40 (47%)
Distant	95 (40%)	20 (23%)
Unknown	17 (7%)	1 (1%)
Chemotherapy		
No	77 (33%)	47 (55%)
Yes	51 (21%)	13 (15%)
Unknown	108 (46%)	26 (30%)
Radiation therapy		
No	175 (74%)	80 (93%)
Yes	9 (4%)	5 (6%)
Unknown	52 (22%)	1 (1%)
Surgery		
No	102 (43%)	N/A
Yes	86 (35%)	
Unknown	48 (20%)	

SD standard deviation, *NOS* not otherwise specified, *LN* lymph node, *N/A* not applicable

Materials and Methods

Patient Selection

We utilized the Los Angeles County CSP to identify all patients with ICC during the period of 1982–2006. Although a contributor to the Surveillance, Epidemiology and End Results (SEER) registry, the CSP contains more treatment data than SEER, notably chemotherapy. We have previously described this database for other population-based analyses.[14] Institutional Review Board approval was obtained from City of Hope and the State of California to conduct this study.

ICC tumor location, histology, staging, and differentiation were coded and reported according to the International Classification of Diseases for Oncology (ICD-0) for cases diagnosed from 1982 to 2006. Topography codes for the pancreas included head (C25.0), body (C25.1), and tail of pancreas (C25.2). Other and overlapping lesions (C25.3–C25.9) were included and categorized together. The ICD-0 histology codes included ICC not otherwise specified (NOS; 8,150), insulinoma (8,151), glucagonoma (8,152), gastrinoma (8,153), mixed islet cell and exocrine adenocarcinoma (8,154), VIPoma (8,155), somatostatinoma (8,156), and enteroglucagonoma (8,157).

Pancreatic resection included the site-specific surgery codes for local tumor excision, partial pancreatectomy, total pancreatectomy, extended pancreatoduodenectomy, and pancreatectomy NOS. Histology was graded as well, moderate, poor, and undifferentiated. Stage classification of disease in CSP was "local" for disease confined to the pancreas, "regional" for disease extending beyond the pancreas into contiguous tissues or regional lymphatics, and "distant" for metastatic disease. Lymph node (LN) involvement was categorized as positive or negative. Patients receiving chemotherapy were treated with single agent, multiple agents, or NOS regimens. Radiation therapy was classified as positive or negative. Patients receiving radiation were treated with beam, implants, isotopes, NOS, or a combination of treatments. Radiation or chemotherapy regimens were considered adjuvant if administered after pancreatic resection.

Table 2 Comparison of Treatment Cohorts

Factors	Medical management (N=102)	Curative surgery (N=86)	p value
Age (mean ± SEM)	61.0±1.5	55.3±1.5	0.001
≤50	31 (30%)	31 (36%)	
51–64	23 (23%)	31 (36%)	
≥65	48 (47%)	23 (28%)	
Sex			0.11
Male	65 (64%)	45 (52%)	
Female	37 (36%)	41 (48%)	
Race			0.07
White	59 (60%)	46 (58%)	
Black	11 (11%)	5 (6%)	
Hispanic	21 (21%)	13 (17%)	
Asian	7 (8%)	15 (19%)	
Tumor site			0.04
Head	30 (60%)	27 (39%)	
Body	7 (14%)	9 (13%)	
Tail	13 (26%)	33 (48%)	
Stage			<0.001
Local	12 (13%)	25 (29%)	
Regional	19 (21%)	40 (47%)	
Distant	60 (66%)	20 (24%)	
Chemotherapy			0.001
No	61 (62%)	70 (84%)	
Yes	38 (38%)	13 (16%)	
Radiation therapy			0.99
No	95 (94%)	80 (93%)	
Yes	6 (6%)	5 (7%)	

SEM standard error of mean

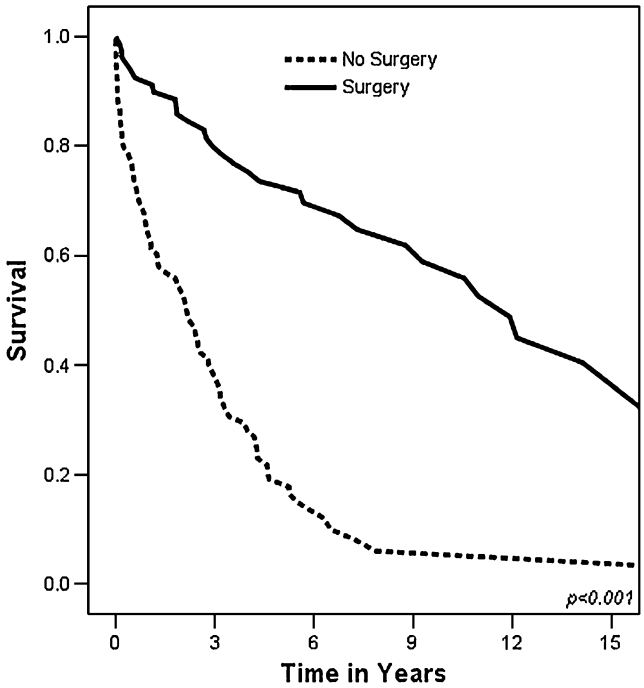

Fig. 1 Kaplan–Meier survival curves for patients with islet cell carcinoma treated with pancreatic resection (surgery) versus medical management (no surgery).

Statistical Analysis

Patients with ICC were stratified into treatment groups of curative-intent surgical resection and medical management for comparative analysis. The surgical cohort included patients who underwent surgical resection alone and surgical resection with adjuvant chemotherapy and/or radiation therapy. The medical management cohort included patients who received any combination of chemotherapy, radiation therapy, or supportive care, but no surgical intervention. Patients with unconfirmed treatment were excluded from analysis.

Patient characteristics were compared by one-way analysis of variance and Student's t test for continuous variables and the χ^2 test for categorical variables. Characteristics assessed included age, gender, race, tumor location, grade, LN status, stage, chemotherapy, radiation therapy, and surgery. Patients were censored at the last follow update (April 13, 2008) or the date the patient was last known to be alive. Survival curves were calculated by the Kaplan–Meier method and compared using the log-rank test. Univariate analysis was performed to identify predictors of survival. Multivariate Cox proportional hazard method was used to examine the association of treatment with survival, while controlling for other clinicopathologic factors. Results were reported as hazard ratios (HR) with 95% confidence intervals (CI). All reported p values were two-sided with a value of <0.05 considered to be statistically significant.

Results

Patient Characteristics

Two hundred thirty-six patients were diagnosed with and treated for ICC in Los Angeles County during the study period of 1982–2006. Characteristics of the entire cohort are presented in Table 1. Mean age at diagnosis was 59 years and 60% (n=141) of patients were male. The majority of patients (75%) presented with either regional (35%) or distant (40%) disease. Regarding treatment, 35% (n=86) of patients underwent curative-intent surgical resection and 21% (n=51) received chemotherapy. A small minority (16%; n=13) of patients had both surgery and chemotherapy.

Comparison of the Treatment Cohorts

The clinicopathologic characteristics of patients who underwent pancreatic resection were compared to patients who received medical management (Table 2). Surgical patients were younger (56 vs. 61 years, p=0.018) and more likely to have ICC located in the pancreatic tail (48% vs. 26%, p=0.043) compared to medical patients. There was no

Table 3 Overall Survival Stratified by Therapy Administered and Extent of Disease

	Entire cohort		Local disease		Regional disease		Distant disease	
	MS	5years (%)	MS	5years (%)	MS	5years (%)	MS	5years (%)
Pancreatic resection	11.9	73	17.3	86	12.2	76	4.0	49
Pancreatic resection and adjuvant chemotherapy	5.7	67	N/A	N/A	5.6	60	6.0	71
Pancreatic resection alone	14.1	74	17.3	86	12.2	78	2.7	32
Medical management	2.4	23	5.8	55	1.8	28	1.9	13
Medical management without chemotherapy	2.5	26	5.8	55	4.2	40	1.1	8
Medical management including chemotherapy	2.2	20	7.3	0	0.9	13	2.2	21

MS median survival (in years), *5 years* 5-year survival, *N/A* not applicable (chemotherapy not given), *MM* medical management

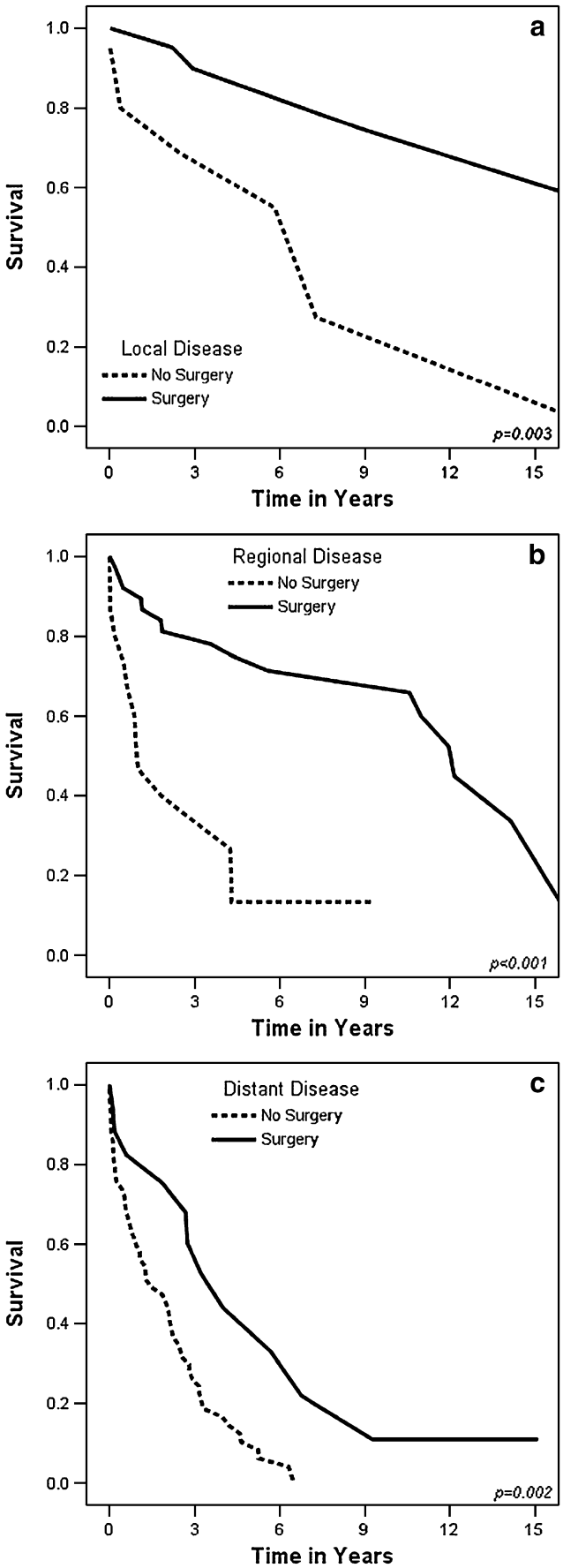

Fig. 2 Kaplan–Meier survival curves for patients with islet cell carcinoma with (**a**) local disease, (**b**) regional disease, and (**c**) metastatic disease. The surgical cohort includes patients who underwent curative-intent pancreatic resection; the no surgery cohort includes patients who received medical management alone.

difference in gender or race/ethnicity between the two cohorts. However, surgical patients were more likely to present with local or regional disease (31% vs. 13%, $p<0.001$, and 48% vs. 21%, $p<0.001$, respectively), whereas distant disease was more frequent in the medical management cohort (66% vs. 24%, respectively, $p<0.001$).

Survival of the Treatment Cohorts Stratified by Stage

Median survival (MS) of the entire patient cohort was 3.2 years with 5- and 10-year survival rates of 39% and 25%, respectively. When the treatment cohorts were compared, overall survival was significantly higher in the surgical cohort than the medical management cohort (MS 11.9 vs. 2.4 years, respectively; log-rank test, $p<0.001$; Fig. 1). Pancreatic resection was associated with improved survival compared to medical management even when stratified by extent of disease (local disease, MS 17.3 vs. 5.8 years, $p=0.002$; regional disease, MS 12.1 vs. 1.8 years, $p=0.002$; and distant disease, MS 4.0 vs. 1.9 years, $p=0.01$, respectively; Table 3; Fig. 2a–c).

Impact of Multimodal Therapy

The impact of chemotherapy and radiation therapy on survival was assessed for our entire cohort. Given the small numbers that received radiation therapy ($n=9$), we were unable to appropriately evaluate its impact on patient survival. Furthermore, none of the surgical cohort with local disease received adjuvant chemotherapy (Table 3). When adjuvant chemotherapy was administered to patients with regional and distant disease, we observed no improvements in survival compared to surgical resection alone (MS 5.6 vs.12.2 years, $p=0.33$, and MS 6.0 vs. 2.7 years, $p=0.79$, respectively).

In the medical management cohort, patients were further stratified by the receipt of chemotherapy (yes, $n=38$; no, $n=30$). Interestingly, the administration of chemotherapy provided no survival benefit compared to medical management without chemotherapy for any extent of disease (regional disease, MS 0.9 vs. 4.2 years, respectively, $p=0.12$, and distant disease, MS 2.2 vs. 1.1 years, respectively, $p=0.10$).

Univariate and multivariate Cox regression analysis was performed for the entire patient cohort to identify predictors of survival (Table 4). On univariate analysis, female gender, younger age, well-differentiated tumors, early stage, no chemotherapy, and surgical resection were all associated

Table 4 Univariate and Multivariate Analysis of the Entire Cohort

Factors	Median survival (years)	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age			<0.001		0.001
≤50	6.0	1.0	–	1.0	–
51–64	3.2	1.30 (0.86–1.96)	0.21	0.95 (0.54–1.66)	0.86
≥65	2.0	2.27 (1.56–3.32)	<0.001	2.14 (1.33–3.46)	0.002
Sex			0.03		0.54
Male	2.9	1.0	–	–	–
Female	4.4	0.70 (0.51–0.96)	0.03	0.87 (0.56–1.36)	0.54
Race			0.59		0.11
White	2.9	1.0	–	1.0	–
Black	3.3	0.85 (0.47–1.55)	0.61	0.57 (0.25–1.28)	0.17
Hispanic	3.2	0.95 (0.64–1.42)	0.81	1.54 (0.94–2.51)	0.08
Asian	10.6	0.68 (0.39–1.19)	0.18	1.43 (0.73–2.83)	0.30
Tumor location			0.39		0.62
Head	3.4	1.0	–	1.0	–
Body	2.9	0.91 (0.49–1.69)	0.77	0.93 (0.44–1.95)	0.84
Tail	4.4	0.73 (0.46–1.15)	0.17	0.77 (0.42–1.38)	0.38
Grade			<0.001	N/A	N/A
Well	6.4	1.0	–		
Moderate	4.6	1.34 (0.58–3.13)	0.50		
Poor/undifferentiated	0.1	11.37 (4.14–31.25)	<0.001		
Stage			<0.001		<0.001
Local	11.2	1.0	–	1.0	–
Regional	4.3	1.85 (1.09–3.13)	0.02	1.60 (0.82–3.10)	0.17
Distant	2.10	3.58 (2.15–5.95)	<0.001	3.46 (1.80–6.68)	<0.001
Chemotherapy			<0.001		0.85
No	10.6	1.0	–	1.0	–
Yes	3.0	2.58 (1.64–4.05)	<0.001	1.04 (0.65–1.68)	0.85
Radiation therapy			0.35		0.37
No	4.2	1.0	–	1.0	–
Yes	3.4	1.41 (0.69–2.89)	0.35	1.42 (0.66–3.03)	0.37
Surgery			<0.001		<0.001
No	2.4	1.0	–	1.0	–
Yes	11.9	0.29 (0.20–0.44)	<0.001	0.38 (0.22–0.63)	<0.001

HR hazard ratio, *CI* confidence interval

with improved survival. In contrast, race/ethnicity, tumor location, and radiation therapy had no impact on survival. On multivariate analysis, surgical resection was an independent predictor of improved survival (HR 0.35, CI 0.19–0.66, $p=0.001$).

Discussion

The role of surgical resection in patients with local or regional pancreatic ICC has been well-established and prognostic factors including patient and pathologic characteristics have been validated.[4,6–10,12,15–19] In our series, age, stage, and surgical resection were independent predictors of survival, and the survival advantage with surgical resection was observed even for patients with distant disease. Selected studies have shown either a survival benefit or questioned the safety and efficacy of surgery for metastatic pancreatic ICC.[7,8,13,17,20–23] Our results demonstrate an unequivocal improvement in survival of over 2 years with surgical resection compared to medical management alone.

Given its rarity, multimodal therapy for pancreatic ICC has never been assessed in a prospective, randomized trial. Furthermore, the role of systemic chemotherapy in patients with pancreatic ICC has been difficult to establish. For example, previous trials have included patients with neuroendocrine tumors from nonpancreatic locations, and they reported ICC to be responsive to chemotherapy without impacting overall survival.[3,5,18,24,25] Here, we did not observe a survival advantage with systemic chemotherapy as primary or adjuvant therapy in patients with regional or distant disease. However, there was prolonged survival in patients receiving chemotherapy compared to medical management or surgical resection alone. Unfortunately, the number of patients receiving chemotherapy in those groups was far too small for meaningful conclusions. This limitation was similar regarding the utility of radiation therapy, which was rarely administered in our series.

We are unaware of investigations to determine the role of systemic chemotherapy in a large population-based analysis or to compare surgical resection to systemic therapy for pancreatic ICC. Small trials have examined the role of streptozocin-based regimens in patients with unresectable ICC. Response rates of 40–60% were reported with 2-year median survival, consistent with our observed results.[25,26] In contrast, the role of adjuvant chemotherapy for locally advanced or distant disease has not been well described. In a study primarily examining the role of surgery for ICC, Bilimoria et al. reported that adjuvant chemotherapy did not confer a survival benefit.[18] Maire et al. also evaluated adjuvant chemotherapy for patients with resected neuroendocrine hepatic metastases.[27] However, <60% of patients had primary pancreatic ICC, and no survival advantage was observed with the addition of chemotherapy.[27]

In our cohort, we could not determine whether patients underwent metastasectomy of their distant disease along with resection of the primary pancreatic lesion; and our data do not demonstrate a statistically significant survival advantage with adjuvant chemotherapy. However, the greater than 3-year survival advantage in patients with surgical resection and chemotherapy compared to surgical resection alone appears to warrant further investigation. Furthermore, the prolonged survival in patients with resectable local and regional disease is a clear indication to identify treatment strategies to downstage patients with unresectable disease.

The interpretation of our results mandates thoughtful consideration given the inherent limitations to registry investigations. While the use of heterogeneous patient populations may limit single-institution treatment biases, there is a potential for patient selection bias in our registry analysis. For example, the surgical resection and medical management cohorts are clinically distinct patient populations and may preclude unbiased head-to-head comparisons. Aside from our comparative analyses, our data nonetheless demonstrate extended survival in surgically resected patients and a potential benefit for a multidisciplinary approach for patients with metastatic disease. This registry investigation also could not determine the role of somatostatin and interferon-based regimens in the patient cohorts. This limitation may also carry little weight because these agents do not provide a durable survival benefit.[28–30]

Establishing a role for adjuvant systemic chemotherapy for pancreatic ICC would require a multicenter prospective randomized trial. Accrual for such a trial, given the rarity of ICC and the biases against aggressive approaches to a presumed indolent disease, may be difficult. Recent trials with molecular targets have been initiated, and we recommend active participation in ongoing or future clinical trials evaluating multidisciplinary approaches to patients with distant ICC to further improve outcomes.[5,26]

Conclusion

We have evaluated the role of multimodal therapy in the management of patients with pancreatic ICC. Curative-intent surgical resection remains the only treatment modality associated with improved survival. The evaluation of a multidisciplinary approach to management of metastatic pancreatic ICC appears warranted to improve outcomes.

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2010 SSAT POSTER PRESENTATION

Laparoscopic Distal Pancreatectomy Offers Shorter Hospital Stays with Fewer Complications

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Abstract
Background Laparoscopic distal pancreatectomy (LDP) is increasingly performed for lesions of the body and tail of the pancreas. The aim of this study was to investigate short-term outcomes after LDP compared to open distal pancreatectomy (ODP) at a single, high-volume institution.
Methods We reviewed records of patients who underwent distal pancreatectomy (DP) and compared perioperative data between LDP and ODP. Continuous variables were compared using Student's *t* or Wilcoxon rank-sum tests. Categorical variables were compared using chi-square or Fisher's exact test.
Results A total of 360 patients underwent DP. Beginning in 2001, 95 were attempted, and 71 were completed laparoscopically with a 25.3% conversion rate. Compared to ODP, LDP had similar rates of splenic preservation, pancreatic fistula, and mortality. LDP had lower blood loss (150 vs. 900 mL, $p<0.01$), smaller tumor size (2.5 vs. 3.6 cm, $p<0.01$), and shorter length of resected pancreas (7.7 vs. 10.0 cm, $p<0.01$). LDP had fewer complications (28.2% vs. 43.8%, $p=0.02$) as well as shorter hospital stays (5 vs. 6 days, $p<0.01$).
Conclusions LDP can be performed safely and effectively in patients with benign or low-grade malignant neoplasms of the distal pancreas. When feasible in selected patients, LDP offers fewer complications and shorter hospital stays.

Keywords Distal pancreatectomy · Laparoscopic distal pancreatectomy · Open distal pancreatectomy

Introduction

The laparoscopic approach continues to gain acceptance as an option for the surgical management of diseases of the distal pancreas. After initial reports in the mid-1990s,[1–4] several small series began to emerge in the literature documenting the safety and feasibility of laparoscopic distal pancreatectomy (LDP).[5–9] Although prospective, randomized trials are lacking, a growing number of single- and multi-institution case series affirm the benefits of LDP vs. open distal pancreatectomy (ODP).[10–13] We herein report a large, single-institution series of distal pancreatectomy (DP) and compare differences in clinical outcomes between the laparoscopic and open approaches.

Materials and Methods

We performed a retrospective review of a prospectively maintained database of patients with pancreatic disease. The database is maintained by The Pancreas Center of Columbia University Medical Center (CUMC) and includes the patients of four surgeons (J.A., J.C., J.L., and B.S.). After approval from the Institutional Review Board and in

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compliance with the Health Insurance Portability and Accountability Act regulations, we queried our database to identify all patients who underwent DP at CUMC from 1991 through 2009.

For the purposes of comparing LDP to ODP, we used inclusion and exclusion criteria to define each group as follows. We included only those patients who underwent LDP or ODP during the same time period, beginning with the first attempted LDP in 2001. For the LDP group, we excluded patients who underwent laparoscopic-assisted DP, which was defined as the preoperative plan to perform only part of the operation laparoscopically prior to laparotomy. For the ODP group, we excluded patients who underwent DP as part of a completion pancreatectomy as well as those who underwent concomitant portomesenteric venous resection and reconstruction. We also excluded patients who underwent DP secondary to debridement for necrotizing pancreatitis, oncologic resection for non-pancreatic primary neoplasms invading the pancreas, and pancreatic injury during another operation. We included the laparoscopic-converted-to-open procedures in the ODP group for all statistical analyses except for the subsets in which the LDP, ODP, and converted groups were examined independently.

Descriptive data were collected by review of patients' medical records. Preoperative variables included age, gender, race, and significant comorbidity, defined as the presence of coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), or chronic kidney disease (CKD). Intraoperative variables were obtained from nurse, anesthesiologist, and surgeon reports. Operating room (OR) time was defined as the time between patient entry into and exit from the OR. Anesthesia time was defined as the time between start of anesthesia care in the OR and patient exit from the OR. Incision time was defined as the time between incision start and incision close. Pathologic diagnosis, greatest lesion diameter, length of resected pancreas, margin status, and regional lymph node status were determined from final pathology reports. Perioperative complications were gathered from daily progress notes and discharge summaries and graded using the system proposed by DeOliveira et al.[14] Overall morbidity was defined as any complication, and major morbidity was defined as complications grade III and greater. Pancreatic fistula was assessed and graded according to the International Study Group on Pancreatic Fistula recommendations.[15] Length of stay (LOS) was calculated from date of operation to date of hospital discharge. Readmission rate was defined as readmission within 30 days of hospital discharge. Perioperative mortality was defined as death within 30 days of the operation or within the same hospital admission as the operation.

All operations were performed by four pancreatic surgeons (J.A., J.C., J.L., and B.S.) using our institution's standardized technique. For the laparoscopic cases, a four-port technique was used with 5-, 10-, and 12-mm trocars in varying combinations at the surgeon's discretion. One of the trocar incisions was extended to remove the specimen intact. For the open cases, a single incision was used, either upper vertical midline or left subcostal, depending on patient body habitus and individual surgeon's preference. Conduct of the operation, including lesion identification with ultrasound, splenic mobilization (if applicable), and pancreatic exposure and mobilization, were similar for both the laparoscopic and open approaches. For spleen-preserving DPs, an attempt to spare the splenic artery and vein was made in all patients. A variety of techniques was used to control the pancreas stump based on individual surgeon's preference. Examples of these techniques included sutures, staples, sutures and staples combined, or staples with bioabsorbable staple-line reinforcement. Operative drains were placed at the surgeon's discretion.

Continuous variables were compared using Student's *t* test or Wilcoxon rank-sum test. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test as appropriate. Continuous variables were reported as mean±standard deviation (SD) or median and interquartile range (IQR). Categorical variables were reported as number and percentage. A p value of less than 0.05 was considered statistically significant. Statistical analyses were conducted using the R statistical software program (version 2.8).

Results

From March 11, 1991 through December 31, 2009, a total of 387 DPs were attempted, with 360 (93%) completed and 27 (7%) aborted. Fifty-nine (16.4%) of the completed DPs were performed prior to use of the laparoscopic approach in 2001 and were excluded from further analysis. Eight open completion pancreatectomies, six open DPs with concomitant portomesenteric venous resections, and four laparoscopic-assisted DP cases were excluded. Ten DPs performed during debridement for necrotizing pancreatitis, seven performed during oncologic resection for non-pancreatic primary neoplasms, and three performed secondary to pancreatic injury during other operations also were excluded. Of the remaining 263 DPs, 168 (63.9%) were open, 71 (27%) were laparoscopic, and 24 (9.1%) were laparoscopic-converted-to-open, with a laparoscopic-to-open conversion rate of 25.3%.

Patient Characteristics

There were no statistically significant differences in demographics and preoperative comorbidities between the LDP and ODP groups. The mean age was 58.2±14.1 years in the LDP group and 60.2±15.2 years in the ODP group (p=0.36). There

were 49 (69%) women and 22 (31%) men in the LDP group and 119 (62%) women and 73 (38%) men in the ODP group, with the majority being Caucasian in both groups. The incidences of CAD, COPD, DM, and CKD were similar between the two groups (Table 1).

Intraoperative Characteristics

Intraoperative ultrasound was used to identify lesions in 37 (52.1%) LDP cases and 83 (43.2%) ODP cases (p=0.20). Various methods were employed to control the distal pancreatic remnant in both groups. Stapler and bio-sealant were used most commonly in the LDP group (77.5%), whereas suture (44.8%) and stapler with bio-sealant (39.1%) were most common in the ODP group. The rates of splenic preservation were similar in both groups (15.5% vs. 15.6%, p=0.93). Patients had lower median blood loss in the LDP group (150 mL; IQR, 100–250 mL) compared to the ODP group (900 mL; IQR, 400–1,400 mL; p<0.01). Operative drains were placed with comparable frequency in both groups (56.3% vs. 67.2%, p=0.10). Median OR time (250 min; IQR, 225–285 vs. 270 min; IQR, 235–345 min; p<0.01) and median anesthesia time (229 min; IQR, 205–259 vs. 237 min; IQR, 205–314 min; p<0.01) were shorter in the LDP group compared to the ODP group. There was no statistically significant difference in median incision times between the groups (191 min; IQR, 163–214 vs. 195 min; range, 166–263 min; p=0.35; Table 2).

Table 1 Demographics and Preoperative Comorbidities for Patients Undergoing Distal Pancreatectomy

Variable	LDP (n=71)	ODP (n=192)	p value
Demographics			
Age, year, mean (SD)	58.2 (14.1)	60.2 (15.2)	0.36
Gender, M/F	22/49	73/119	0.29
Race (%)[a]			
Caucasian	57 (80.3)	139 (72.4)	0.19
Black	5 (7.1)	6 (3.1)	
Asian	1 (1.4)	5 (2.6)	
Hispanic	4 (5.6)	23 (12.0)	
Other	4 (5.6)	19 (9.9)	
Comorbidities (%)[b]			
CAD	6 (8.5)	18 (9.4)	1.00
COPD	4 (5.6)	12 (6.3)	1.00
DM	13 (18.3)	35 (18.2)	1.00
CKD	1 (1.4)	1 (0.5)	0.47

SD standard deviation, *CAD* coronary artery disease, *COPD* chronic obstructive pulmonary disease, *DM* diabetes mellitus, *CKD* chronic kidney disease

[a] Statistical analysis was performed on Caucasian vs. all other races

[b] Some patients had more than one comorbidity

Postoperative Outcomes

Patients in the LDP group had fewer overall complications (28.2% vs. 43.8%, p=0.02) and fewer major complications (8.5% vs. 18.8%, p=0.04) than those in the ODP group. There were no statistically significant differences in overall pancreatic fistula rate (11.3% vs. 14.1%, p=0.55) and clinically significant pancreatic rate (7% vs. 12.5%, p=0.27) between the LDP and ODP groups. There were no statistically significant differences in rates of reoperation (5.6% vs. 3.6%, p=0.50) and readmission (4.2% vs. 8.9%, p=0.30) between the groups. Patients in the LDP group had shorter median LOS compared to those in the ODP group (5 days; IQR, 4–6 vs. 6 days; IQR, 5–8 days; p<0.01). Nineteen (26.8%) patients vs. 118 (61.5%) patients had median LOS longer than 5 days (p<0.01). The mortality rate was nil in the LDP group vs. 1% in the ODP group (p=1.00; Table 3). In a subset analysis of spleen-preserving DP vs. en bloc DP with splenectomy, there were no statistically significant differences in morbidity, pancreatic fistula, LOS, and mortality (Table 4).

Final Pathology

Sixty-two (87.3%) patients had benign pathology in the LDP group vs. 118 (61.5%) in the ODP group (p<0.01). Nine (12.7%) patients had malignant pathology in the LDP group vs. 74 (38.5%) in the ODP group (p<0.01). The laparoscopic approach was less likely to be used for pancreatic ductal adenocarcinoma (4.2% vs. 30.2%, p<0.01). Patients in the LDP group had shorter average length of pancreas resected (7.7±3.2 vs. 10.0±3.6 cm, p<0.01) for smaller median tumor size (2.5 cm; IQR, 1.5–4.0 vs. 3.6 cm; IQR, 2.0–6.0 cm; p<0.01) than patients in the ODP group. The median number of lymph nodes resected was similar between both groups (6; IQR, 2.5–12.0 vs. 8; IQR, 3.0–13.0; p=0.29). The number of patients with positive lymph nodes was 6 (8.5%) in the LDP group vs. 36 (18.8%) in the ODP group (p=0.04). Two (2.8%) patients had positive margins in the LDP group vs. 25 (13%) patients in the ODP group (p=0.01). Of the two patients with positive margins in the LDP group, one had a low-grade nonfunctional pancreatic neuroendocrine neoplasm, and one had pancreatic ductal adenocarcinoma on final pathology (Table 5).

Laparoscopic-to-Open Conversion

Reasons for conversion included nine (37.5%) bleeding, seven (29.1%) adherent tumor, four (16.6%) difficult anatomy, one (4.2%) abdominal adhesions, one (4.2%) difficult localization of tumor, one (4.2%) enterotomy, and one (4.2%) large tumor. Of the converted cases, seven

Table 2 Intraoperative Characteristics for Patients Undergoing Distal Pancreatectomy

Variable	LDP (n=71)	ODP (n=192)	p value
Operating room time, min			
Median (IQR)	250 (225–285)	270 (235–345)	<0.01
Anesthesia time, min			
Median (IQR)	229 (205–259)	237 (205–314)	<0.01
Incision time, min			
Median (IQR)	191 (163–214)	195 (166–263)	0.35
Intraoperative blood loss, mL			
Median (IQR)	150 (100–250)	900 (400–1,400)	<0.01
Splenic preservation (%)	11 (15.5)	30 (15.6)	0.93
Prior splenectomy	0 (0)	4 (2.1)	
Intraoperative ultrasound (%)	37 (52.1)	83 (43.2)	0.20
Intraoperative drain (%)	40 (56.3)	129 (67.2)	0.10
Distal pancreas control			
Suture	1	86	
Staple	15	7	
Suture and staple	0	12	
Suture and bio-sealant	0	2	
Staple and bio-sealant	55	75	
Suture, staple, and bio-sealant	0	6	
Pancreaticojejunostomy	0	3	
Cystogastrostomy	0	1	

IQR interquartile range

(29.2%) had malignant pathology (six pancreatic ductal adenocarcinoma and one intraductal papillary mucinous carcinoma), and 17 (70.8%) had benign pathology on final histological examination. When the converted cases were compared separately to the LDP group, the converted cases had significantly larger intraoperative blood loss and longer median OR, anesthesia, and incision times (Table 6). When compared separately to the patients who had open DP, the converted cases had significantly longer median OR, anesthesia, and incision times, but were statistically similar with regard to pathology and postoperative outcomes (Table 7).

Discussion

The laparoscopic approach is being used with increasing frequency for the surgical management of pancreatic disease, particularly benign or low-grade disease of the distal body and tail. Laparoscopic distal pancreatic resection was first reported by Cuschieri in 1994[1] and later described by Gagner in 1996.[4] Since then, a growing body of case reports and single- and multi-institution series suggest that LDP can be performed with morbidity and mortality rates comparable to those of ODP and with the added benefit of shorter hospital stays.[5–12,16]

Table 3 Postoperative Outcomes for Patients Undergoing Distal Pancreatectomy

Variable	LDP (n=71)	ODP (n=192)	p value
Overall morbidity (%)	20 (28.2)	84 (43.8)	0.02
Major morbidity (%)	6 (8.5)	36 (18.8)	0.04
Pancreatic fistula (%)	8 (11.3)	27 (14.1)	0.55
Grade A	3	3	
Grade B	2	6	
Grade C	3	18	
Reoperation (%)	4 (5.6)	7 (3.6)	0.50
Readmission (%)	3 (4.2)	17 (8.9)	0.30
Mortality (%)	0 (0)	2 (1.0)	1.00
Length of stay, days			
Median (IQR)	5 (4–6)	6 (5–8)	<0.01
Length of stay greater than 5 days (%)	19 (26.8)	118 (61.5)	<0.01

IQR interquartile range

Table 4 Postoperative Outcomes for Patients Undergoing Distal Pancreatectomy: Splenic Preservation vs. Splenectomy

Variable	Splenic preservation (n=41)	Splenectomy (n=218)	p value
Overall morbidity (%)	18 (43.9)	85 (39.0)	0.56
Major morbidity (%)	6 (14.6)	36 (16.5)	0.76
Pancreatic fistula (%)	6 (14.6)	29 (13.3)	0.82
Reoperation (%)	2 (4.9)	9 (4.1)	0.69
Readmission (%)	2 (4.9)	18 (8.3)	0.75
Mortality (%)	1 (2.4)	1 (0.5)	0.29
Length of stay, days			
Median (IQR)	5 (4–7)	6 (5–8)	0.13

IQR interquartile range

Eom et al.[17] used a case–control design with 2:1 matching to compare 62 patients who underwent ODP with 31 patients who underwent LDP. The authors demonstrated similar morbidity and shorter hospital stays in the LDP group compared to the ODP group (11.5 vs. 13.5 days, p= 0.049). Likewise, Nakamura et al.[18] compared the outcomes of 21 patients who underwent LDP with 16 patients who underwent ODP and found no difference in morbidity

Table 5 Pathology Characteristics for Patients Undergoing Distal Pancreatectomy

Variable	LDP (n=71)	ODP (n=192)	p value
Benign (%)	62 (87.3)	118 (61.5)	<0.01
Mucinous cystic neoplasm	17	26	
Serous cystadenoma	8	17	
Intraductal papillary mucinous neoplasm	7	24	
Pancreatitis	1	9	
Solid pseudopapillary neoplasm	0	7	
Pseudocyst	1	9	
Simple cyst	3	1	
Pancreatic neuroendocrine tumor	20	22	
Other	5	3	
Castleman disease	0	1	
Vascular malformation	0	1	
Islet cell hyperplasia	0	1	
Pancreatic intraepithelial neoplasia	1	0	
Acinar cell nodule	1	0	
Calcified vessels	1	0	
Heterotopic ossification	1	0	
Schwannoma	1	0	
Malignant (%)	9 (12.7)	74 (38.5)	<0.01
Pancreatic ductal adenocarcinoma	3	58	<0.01
Intraductal papillary mucinous carcinoma	0	2	
Pancreatic neuroendocrine carcinoma	5	9	
Other	1	5	
Renal cell carcinoma	0	5	
Leiomyosarcoma	1	0	
Lesion size, cm			
Median (IQR)	2.5 (1.5–4.0)	3.6 (2.0–6.0)	<0.01
Length of resected pancreas, cm			
Mean (SD)	7.7 (3.2)	10.0 (3.6)	<0.01
Positive margin (%)	2 (2.8)	25 (13.0)	0.01
Number of lymph nodes evaluated			
Median (IQR)	6.0 (2.5–12.0)	8.0 (3.0–13.0)	0.29
Patients with positive lymph nodes (%)	6 (8.5)	36 (18.8)	0.04

IQR interquartile range, *SD* standard deviation

Table 6 Laparoscopic Distal Pancreatectomy vs. Laparoscopic-Converted-to-Open Distal Pancreatectomy

Variable	LDP (n=71)	Converted (n=24)	p value
Intraoperative characteristics			
Operating room time, min			
Median (IQR)	250 (225–285)	343 (315–400)	<0.01
Anesthesia time, min			
Median (IQR)	229 (205–259)	325 (295–365)	<0.01
Incision time, min			
Median (IQR)	191 (163–214)	275 (237–329)	<0.01
Intraoperative blood loss, mL			
Median (IQR)	150 (100–250)	1,000 (650–1,500)	<0.01
Splenic preservation (%)	11 (15.5)	4 (16.7)	1.00
Prior splenectomy	0 (0)	1 (4.2)	
Pathology			
Benign (%)	62 (87.3)	18 (75.0)	
Malignant (%)	9 (12.7)	6 (25.0)	
Pancreatic ductal adenocarcinoma	3	6	<0.01
Other	6	0	
Lesion size, cm			
Median (IQR)	2.5 (1.5–4.0)	4.0 (2.4–5.9)	0.01
Length of resected pancreas, cm			
Mean (SD)	7.7 (3.2)	11.2 (4.0)	<0.01
Postoperative outcomes			
Overall morbidity (%)	20 (28.2)	13 (54.2)	0.03
Major morbidity (%)	6 (8.5)	4 (16.7)	0.27
Pancreatic fistula (%)	8 (11.3)	2 (8.3)	1.00
Reoperation (%)	4 (5.6)	2 (8.3)	0.64
Readmission (%)	3 (4.2)	1 (4.2)	1.00
Mortality (%)	0 (0)	1 (4.2)	0.25
Length of stay, days			
Median (IQR)	5 (4–6)	6 (4.5–8.5)	0.01

IQR interquartile range, *SD* standard deviation

and shorter hospital stays in the LDP group (10.0 vs. 25.8 days, $p<0.0001$).

The largest single-institution series we encountered was by Kim et al.[19] who compared 93 LDP cases to 35 ODP cases, all performed by a single surgeon. Morbidity, mortality, and pancreatic fistula rates were similar in both groups, but the LDP group had shorter time to start of oral intake (2.8 vs. 4.5 days; $p<0.001$) and shorter hospital stays (10 vs. 16 days; $p<0.01$). The largest multi-institution series we encountered was by Kooby et al.[20] who compared 159 LDP patients to 508 ODP patients using data from eight different institutions. The authors reported no differences in operative times or pancreatic fistula rates between the LDP and ODP groups, but reported less blood loss (357 vs. 588 mL, $p<0.01$), fewer complications (40% vs. 57%, $p<0.01$), and shorter hospital stays (5.9 vs. 9.0 days, $p<0.01$). Other large series in the literature demonstrate similar LDP outcomes, but without comparison to the open approach.[10,21,22]

Our study is a large, single-institution retrospective series that evaluates the laparoscopic and open approaches to DP performed during the same time period. We excluded several cases from the ODP group based on procedure-specific characteristics and oncologic principles for a more accurate comparison to LDP. A patient who has an open distal pancreatic resection as part of a debridement for necrotizing pancreatitis, for example, should not be compared to a patient who has a LDP for an isolated lesion. Likewise, a patient who has an open distal pancreatic resection for an invasive adrenal cortical carcinoma should not be included. We included the laparoscopic-converted-to-open patients in the ODP group because they more closely resemble the open cases with regard to every variable except operative time. After inclusion and exclusion, the LDP and ODP groups were statistically similar with regard to demographics and preoperative comorbidities, further validating the comparison.

Our laparoscopic-to-open conversion rate of 25.3% is higher than those in the literature. Kooby et al.[20] reported a

Table 7 Open Distal Pancreatectomy vs. Laparoscopic-Converted-to-Open Distal Pancreatectomy

Variable	Open (n=168)	Converted (n=24)	p value
Intraoperative characteristics			
Operating room time, min			
Median (IQR)	265 (233–321)	343 (315–400)	0.02
Anesthesia time, min			
Median (IQR)	228 (199–285)	325 (295–365)	<0.01
Incision time, min			
Median (IQR)	192 (157–236)	275 (237–329)	<0.01
Intraoperative blood loss, mL			
Median (IQR)	800 (400–1,400)	1,000 (650–1,500)	0.09
Splenic preservation (%)	26 (15.5)	4 (16.7)	0.77
Prior splenectomy (%)	3 (1.8)	1 (4.2)	
Pathology			
Benign (%)	100 (59.5)	18 (75.0)	
Malignant (%)	68 (40.5)	6 (25.0)	
Pancreatic ductal adenocarcinoma	52	6	0.30
Other	16	0	
Lesion size, cm			
Median (IQR)	3.5 (2.0–6.0)	4.0 (2.4–5.9)	0.74
Length of resected pancreas, cm			
Mean (SD)	9.8 (3.6)	11.2 (4.0)	0.12
Postoperative outcomes			
Overall morbidity (%)	71 (42.3)	13 (54.2)	0.27
Major morbidity (%)	32 (19.0)	4 (16.7)	1.00
Pancreatic fistula (%)	25 (14.9)	2 (8.3)	0.54
Reoperation (%)	5 (3.0)	2 (8.3)	0.21
Readmission (%)	16 (9.5)	1 (4.2)	0.70
Mortality (%)	1 (0.6)	1 (4.2)	0.23
Length of stay, days			
Median (IQR)	6 (5–8)	6 (4.5–8.5)	0.66

IQR interquartile range, *SD* standard deviation

13% conversion rate, and a recent meta-analysis by Borja-Cacho et al.[13] cited a 9.2% conversion rate. At our institution, we are relatively aggressive with use of the laparoscopic approach to distal pancreatic disease because of measurable patient benefit. Although the conversion prolongs operative times, it does not affect LOS or morbidity, mortality, and pancreatic fistula rates when compared to traditional ODP. We continue to refine our preoperative selection criteria to maximize success with the laparoscopic approach, and our rate of conversion has steadily declined in recent years (Fig. 1).

Our rates of splenic preservation with both LDP (15.5%) and ODP (15.6%) are lower than those in the literature. Recent series in the literature report rates of splenic preservation that range from 31% to as high as 85% in select cases of benign and low-grade neoplasms using the laparoscopic approach.[23] Conventional DP includes splenectomy and is the procedure of choice to achieve adequate oncologic margins in patients with pancreatic ductal adenocarcinoma of the body or tail.[24] However, the hypothesis that alterations in the hematologic and immune systems after splenectomy give rise to increased postoperative complications has prompted a shift toward spleen-preserving DP in patients with benign or low-grade malignant disease.[25,26]

The role of splenic preservation remains controversial. Shoup et al.[27] from Memorial Sloan-Kettering Cancer Center noted that perioperative infectious complications (28% vs. 9%, p=0.01) and other severe complications (11% vs. 2%, p=0.05) were significantly higher with splenectomy compared to splenic preservation. They concluded that spleen-preserving DP can be performed safely with decreased perioperative morbidity. Other authors, however, report little or no benefit to splenic preservation, noting that it is more difficult, takes more time, and increases blood loss.[28,29] Benoist et al.[30] reported that DP with splenic preservation was associated with increased morbidity when compared to DP with splenectomy. Similarly, in a review of 49 laparoscopic pancreatic resections, Fernández-Cruz et

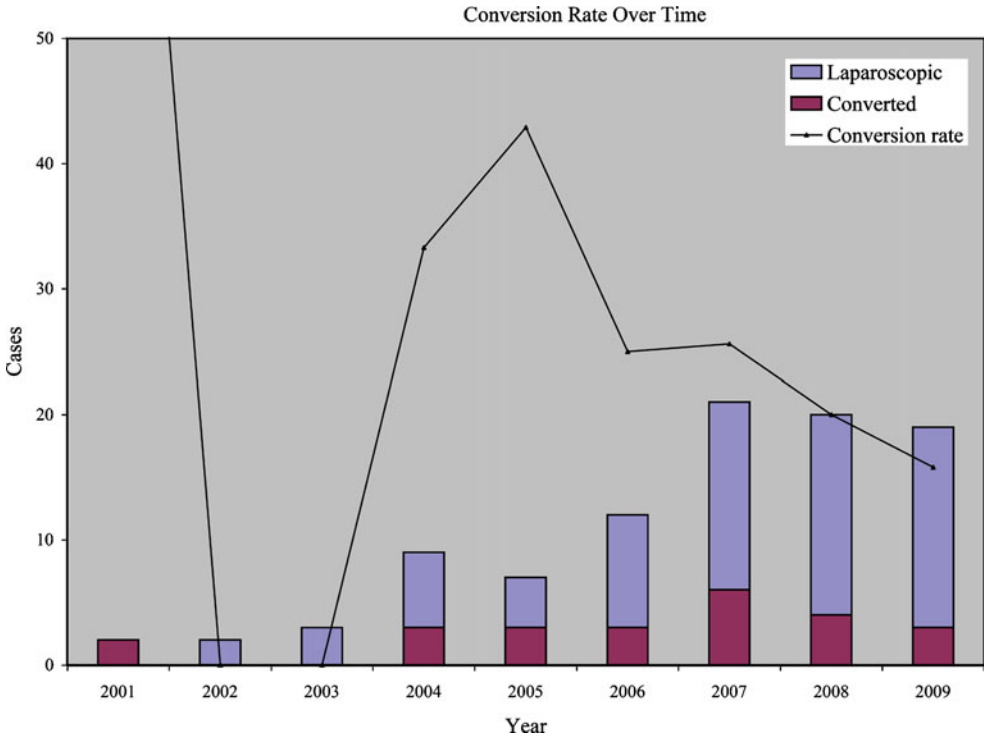

Fig. 1 A graph of conversion rate over time shows a recent decline in laparoscopic-to-open distal pancreatectomy conversions.

al.[31] noted significantly higher morbidity after laparoscopic DP with splenic preservation compared to laparoscopic DP with splenectomy. Our data suggest no difference in clinical outcomes between spleen-preserving DP and DP with splenectomy with regard to morbidity, pancreatic fistula, and LOS. Our bias is to perform DP with selective spleen preservation when oncologically appropriate.

The LDP patients had fewer overall complications than the ODP patients, but there was no difference in major complication, reoperation, readmission, and mortality rates. As in the literature, our data showed no difference in pancreatic fistula rates between the LDP and ODP groups (11.3% vs. 14.1%, p=0.68). In a case–control comparison of 15 laparoscopic and 15 open patients, for example, Velanovich[11] reported a pancreatic fistula rate of 13% in both groups. Kooby et al.[20] reported pancreatic fistula rates of 26% in 142 patients undergoing LDP and 32% in 200 patients undergoing ODP. Corcione et al.[12] reported an overall pancreatic fistula rate of 10.4% in their series of 19 patients undergoing LDP.

The laparoscopic approach has been shown to yield more rapid recovery and shorter hospitalizations in the treatment of several surgical diseases including colon cancer, cholecystitis, and appendicitis.[9,12] Our data echo the recent literature and suggest the same is true for select pancreatic disease.[16,18,32] When compared to ODP, the LDP group had statistically significant shorter hospital stays with markedly fewer patients staying longer than 5 days.

Our study's main limitation is its retrospective nature. Cases more amenable to the laparoscopic approach were specifically selected, and without randomization, our data reflect an inherent selection bias. Likewise, known cases of adenocarcinoma and suspected complex cases were routinely performed via laparotomy. Studies have shown that adenocarcinoma of the tail of the pancreas has a lower resectability rate than that of the head of the pancreas, likely secondary to patient presentation at a more advanced stage of disease.[11] Local fibrosis and inflammation incited by the tumor make mobilization difficult, and the laparoscopic approach may not allow sufficient regional dissection to perform an oncologically sound operation.[33,34] Distal pancreatic lesions thus need to be carefully evaluated preoperatively and selected for the laparoscopic approach. Postoperative pathologic examination has revealed successful laparoscopic removal of distal pancreatic adenocarcinoma in several reports, and recent studies suggest LDP for select cases of adenocarcinoma is acceptable provided that surgical margins are not compromised.[35]

Conclusion

Our experience affirms that LDP is a safe and effective option for select cases of distal pancreatic disease. When compared to ODP, successful LDP offers fewer complications and shorter hospital stays. Laparoscopic cases that are converted to open procedures have longer operative times, but clinical outcomes are comparable to conventional DP, supporting an aggressive but judicious use of the laparoscopic approach to DP. Additional research will better determine the role of splenic preservation during DP and clarify the best technique for

minimizing pancreatic fistulae from the pancreatic remnant. Finally, further analysis is needed to determine the feasibility, safety, and efficacy of laparoscopic resection of adenocarcinoma of the distal pancreas.

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2010 SSAT POSTER PRESENTATION

Preservation of Replaced or Accessory Right Hepatic Artery During Pancreaticoduodenectomy for Adenocarcinoma: Impact on Margin Status and Survival

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Abstract
Aim The aim of the study was to determine the impact of replaced or accessory right hepatic artery (RARHA) during pancreaticoduodenectomy (PD) for pancreatic adenocarcinoma (PA).
Methods Four hundred seventy-one consecutive patients underwent PD for PA at the two institutions; 47 patients (10%) had RARHA: 16 patients (*neoRARHA* group) received neoadjuvant chemoradiation, and 31 patients did not receive preoperative treatment (*RARHA* group). Thirty-one matched patients without RARHA comprised our *control* group.
Results RARHA was preserved in 44 patients; three patients with involved RARHA had reconstruction (n=2) or ligation (n=1). Patients with R1 resection (n=8) had tumor size ≥3 cm. Patients in the neoRARHA group had identical positive margin rate when compared with patients in RARHA group (p=0.6). No difference was noted in median or 3-year overall survival times between RARHA group and control group. Two patients in RARHA group with involved RARHA died of disease progression after 6 and 12 months of follow-up. One patient in neoRARHA group with involved RARHA was still alive without recurrence after 28 months' follow-up.
Conclusions Pathologic findings did not show increased positive margins despite preservation of RARHA. In contrast, patients with frank RARHA involvement seemed to have poor survival. Thus, patients with suspicion of involved RARHA should be considered for neoadjuvant chemoradiation.

Keywords Pancreaticoduodenectomy · Pancreatic adenocarcinoma · Margin · Hepatic artery · Neoadjuvant

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Pancreaticoduodenectomy (PD) is a complex procedure associated with high morbidity. Arterial anatomic variation during PD might lead to vascular injury with additional intra- or postoperative morbidity. Michels' classic autopsy series of 200 dissections defined the basic anatomic variations in hepatic arterial supply.[1] A replaced or accessory right hepatic artery (RARHA) (Michels type 3, 4, 6, 7, and 8; see Table 1) is present in 10% to 18% of the population,[2,3] arises from the superior mesenteric artery (SMA), and emerges in the posterior hepaticoduodenal ligament to provide arterial blood supply to the right lobe of the liver. Thus, unsuspected RARHA could be injured or ligated during PD with potential negative consequences.[4] Indeed, most of the blood supply to the common bile duct remnant is derived from the replaced or accessory vessel following ligation of the gastroduodenal artery during PD. Thus, interruption of RARHA flow has been associated with short-term morbidity, including biliary fistula or liver abscess, and in the long-term, stenosis of the biliary enteric

Table 1 Classification of Hepatic Artery Variants According to Michels[1]

Type	Description
1	Normal
2	Replace LHA from LGA
3	Replaced RHA from SMA
4	Replaced RHA+LHA
5	Accessory LHA
6	Accessory RHA
7	Accessory RHA+LHA
8	Replaced RHA+accessory LHA or replaced LHA+accessory RHA
9	CHA from SMA
10	CHA from aorta

LHA left hepatic artery, *LGA* left gastric artery, *RHA* right hepatic artery, *SMA* superior mesenteric artery, *CHA* common hepatic artery

anastomosis.[5,6] Pre- or intraoperative identification of RARHA might help reduce injury; however, RARHA could be encased by pancreatic adenocarcinoma (PA) necessitating intentional resection to achieve R0 tumor resection. Safe ligation of small caliber accessory right hepatic artery (Michels type 6, 7, or 8) has been described as has reconstruction of replaced right hepatic artery (Michels type 3, 4).[3,7,8] The aim of this study was to determine postoperative course, quality of oncologic resection, and overall survival in patients with RARHA undergoing PD for PA.

Methods

From January 1, 2000 to December 31, 2007, 471 patients with head PA underwent PD at Indiana University Hospital (Indianapolis, IN, USA) and Institut Paoli Calmettes (Marseille, France). All patient data were entered retrospectively into clinical databases approved by the Indiana University and Institut Paoli Calmettes Institutional Review Boards. PA was staged by physical examination, chest radiography, endoscopic ultrasound, and thin-section contrast-enhanced helical dual phase scanning (CT scan). All CT scan were performed with arterial and portal phases in order to identify the celiac trunk and SMA and corresponding branches. No patients were operated based on outside CT scan. Patients with adenocarcinoma of tail or neck of the pancreas, intraductal papillary mucinous adenocarcinoma, tumors of neuroendocrine origin or with carcinoma of the duodenum, distal common bile duct, or ampulla of Vater were excluded from this study. Patients who presented with metastatic disease or regionally advanced disease precluding resection were excluded. Arterial variations were established by CT scan findings and descriptions found in operative reports. One patient with a "loop" common hepatic artery coming from celiac axis and crossing the pancreatic head in the position of RARHA was included in the study group (Fig. 1). Three patients had RARHA Michels type 6, and 43 patients had RARHA Michels type 3 arterial anatomy. Sixteen patients (two Michels type 6 and 14 Michels type 3) with resectable head PA were enrolled in a neoadjuvant chemoradiation (CRT) trial and underwent PD after restaging (*neoRARHA* group). Thus, we identified 47 patients (10%) with RARHA (Fig. 1). Thirty-one patients without neoadjuvant treatment (RARHA group) were matched according to tumor size, tumor differentiation, no preoperative treatment, age, and gender, with 31 patients from 429 patients without hepatic arterial variants who underwent PD for PA during the same period. These 31 patients comprised our *control* group (Table 2).

Surgery PD was performed via subcostal or midline incision. After thorough abdominal exploration and a generous Kocher maneuver, the gallbladder was removed and the common bile duct was transected. The anterior aspect of the portal vein was then dissected free of the overlying pancreatic neck. Subsequently, the duodenum (pylorus-preserving procedure) or the stomach (classic procedure) was transected, followed by transection of the pancreatic neck, uncinate process, and jejunum distal to the ligament of the Treitz. Reconstruction was undertaken with an isoperistaltic limb of jejunum in retrocolic fashion and anastamosed with an end-to-side pancreaticojejunostomy, followed by an end-to-side choledochojejunostomy and either antecolic or retrocolic end-to-side duodenojejunostomy or gastrojejunostomy. The pancreaticojejunostomy was performed using either duct-to-mucosa or an invaginated anastomosis. No pancreaticogastrostomies were performed in this series. The pancreatic and biliary anastomoses were drained routinely with Penrose or closed-suction drains. Prophylactic octreotide was not routinely used.

End points studied We retrospectively analyzed the preoperative radiologic findings regarding arterial variation

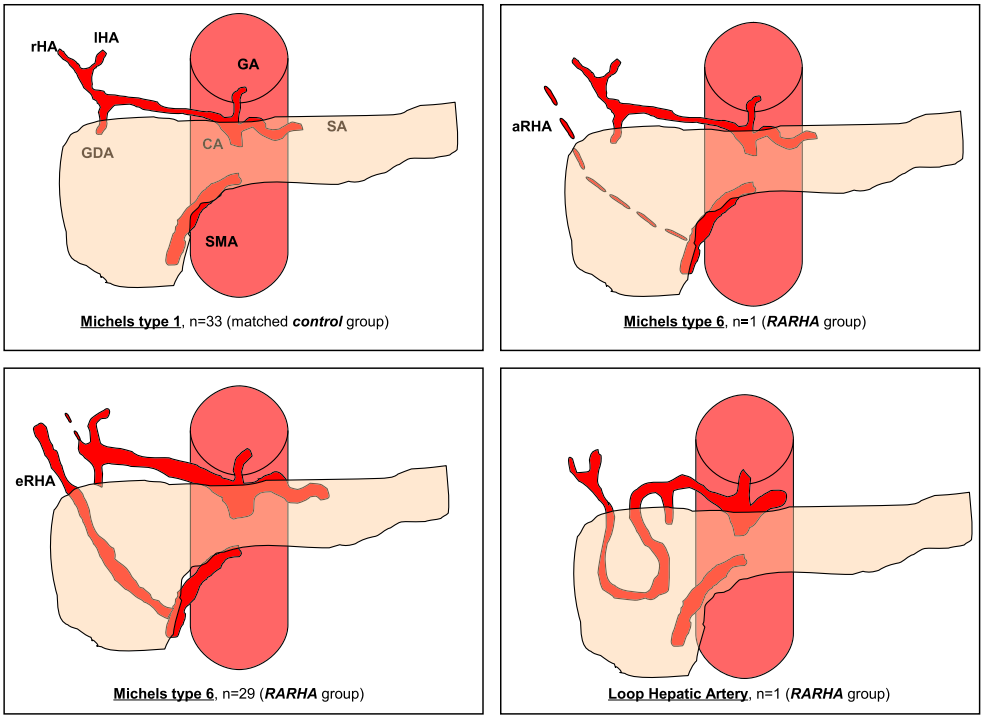


Fig. 1 Variation of hepatic arteries according to Michels.[1] *CA* celiac axis, *SMA* superior mesenteric artery, *GA* gastric artery, *SA* splenic artery, *GDA* gastro-duodenal artery, *rHA* right hepatic artery, *lHA* left hepatic artery, *aRHA* accessory right hepatic artery, *eRHA* exclusive or replaced right hepatic artery.

according to the radiologist's report and the surgeon's interpretation of the CT scan. Variables evaluated included age, gender, maximal tumor size (cm) defined as maximum diameter at pathologic analysis, histological differentiation (well, moderate, or poor), margin of resection (positive or negative), node stage (positive nodes; number of examined nodes), and perineural, vascular, and/or lymphatic invasion. Margins assessed included the pancreatic resection margin, biliary margin, posterior margin, retroperitoneal margin, and mesenteric margin. Morbidity, mortality, and length of hospital stay were also determined.

Statistical analysis Data analyses were carried out with GraphPad Prism (GraphPad Software Inc., La Jolla, CA, USA) and Excel 2004 (Microsoft Inc., Seattle, WA, USA). Survival time was measured from the time of PD until

Table 2 Characteristics of RARHA, neoRARHA, and Control Groups

	neoRARHA group	RARHA group	Control (matched) group	*p* value (RARHA group/control group)
n	16	31	31	–
Mean age	59	66	66	ns
Gender (M/F)	1.1	1.3	1.2	ns
Neoadjuvant CRT	16*	0	0	ns
Tumor size (cm)	2.4	3	3.1	ns
Tumor differentiation (%)				ns
Poor	7 (44)	12 (39)	13 (42)	
Moderate	7 (44)	17 (55)	16 (51)	
Well	2 (12)	2 (6)	2 (7)	
RARHA identified by radiologists (%)	5 (31)	9 (29)	–	–
RARHA identified by surgeons alone (%)	8 (50)	16 (51)	–	–
Intraoperative identification of RARHA (%)	8 (50)	15 (49)	–	–
Michels type 1 (normal)	0	0	31	<0.001
Michels type 3 (%)	15 (94)	29 (94)	0	<0.001
Michels type 6 (%)	1 (6)	1 (3)	0	<0.001
Looped hepatic artery (%)	0	1 (3)	0	<0.001

*$p<0.05$ when comparing neoRARHA group and RARHA group

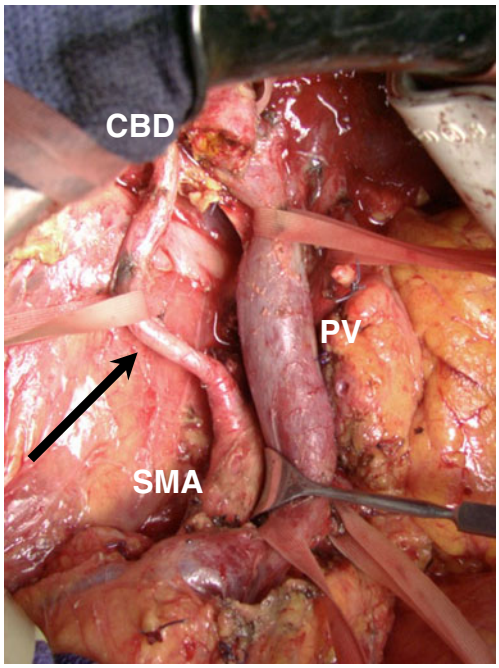


Fig. 2 Operative photograph showing a replaced right hepatic artery Michels type 3 (*black arrow*) preserved during PD and with complete clearance of retroperitoneal soft tissue. *PV* portal vein, *SMA* superior mesenteric artery, *CBD* common bile duct.

death or last follow-up (censor date was December 1, 2008). Statistical associations between categorical factors were assessed using the Fisher exact test. The association of categorical factors with survival was assessed using the Kaplan–Meier method and was tested using the log-rank test. Statistical significance was set at p value<0.05.

Results

RARHA was identified by radiologists in 14 patients (29%) and in 24 patients (51%) by surgeons that analyze the preoperative CT scan; 23 patients (49%) had RARHA identified only during surgery. RARHA identified by radiologists were always detected by surgeons' examination of CT scan. However, surgeons identified 10 patients with RARHA not detected by radiologist's examination of preoperative CT scan. One patient experienced lateral injury of unrecognized RARHA with immediate repair and uneventful postoperative course. Hepatic arterial anatomy was preserved in 44 patients (Fig. 2); three patients had RARHA involved by PA (one Michels type 3 (*RAHRA* group), one Michels type 6 (neoRARHA group), and one "loop" hepatic artery) identified by preoperative staging and confirmed intraoperatively. Michels type 3 patient had splenic-to-hepatic artery bypass using left reverse saphenous vein reconstruction without postoperative complications (Fig. 3). Michels type 6 patient had simple ligation with low right liver perfusion diagnosed on routine follow-up CT scan without related morbidity. Reconstruction of resected "loop" hepatic artery was performed with interposition of inferior mesenteric vein without complications (Fig. 3). Morbidity and mortality of RARHA group were 36% and 2.1% (one patient died of postoperative ventricular fibrillation). Mean tumor size was 3 cm (range 1.2–9.2). No differences were noted in operative duration, blood loss, lymph nodes collected, positives lymph nodes, and involved margins between RARHA group and control

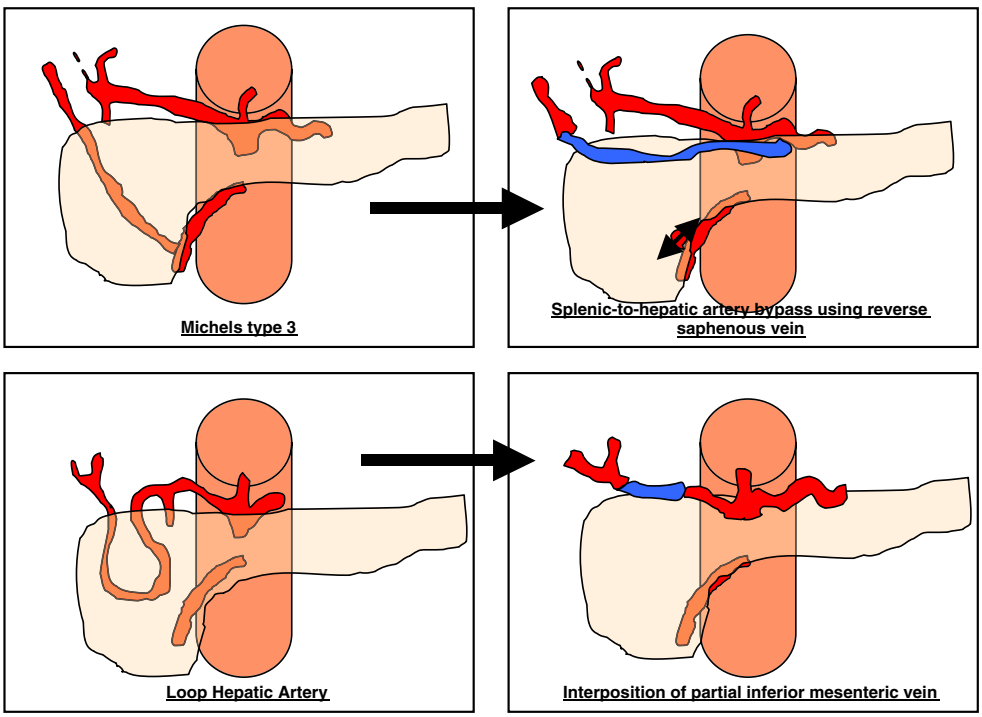


Fig. 3 Reconstruction of involved RARHA.

Table 3 Intraoperative Characteristics, Pathologic Findings, and Survival

	neoRARHA group	RARHA group	Control group	*p* value (RARHA group/control group)
N	16	31	31	–
Operative duration (min)	372	350	310	ns
Blood loss (ml)	482	664	697	ns
Mortality (%)	0	1 (3.2)	1 (3.2)	ns
Morbidity (%)	6 (37.5)	11 (32.3)	11 (35.4)	ns
Tumor size (cm)	2.4	3	3.1	ns
Tumor differentiation (%)				ns
Poor	7 (44)	12 (39)	13 (42)	
Moderate	7 (44)	17 (55)	16 (51)	
Well	2 (12)	2 (6)	2 (7)	
Perineural invasion	9 (56)	24 (77.4)	21 (67.7)	ns
Perivascular invasion	5 (31)	18 (58.1)	20 (64.5)	ns
Mean number of lymph nodes examined	12	11	13	ns
Positive lymph nodes (%)	4 (25)*	25 (80.6)	22 (71)	ns
Involved margins resection (R1) (%)	2 (12.5)	6 (19.3)	5 (16.1)	ns
Median survival (months)	23	23	17	ns
3-Year survival	19%	25%	18%	ns

*$p<0.05$ when comparing neoRARHA group and RARHA group

group (Table 3). Patients of neoRARHA group had lower involved margins rate when compared with patients of RARHA group, but this did not achieve statistical significance (12.5% vs. 19.3%, $p=0.6$). All patients with R1 resection ($n=8$) had tumor size on CT scan or at surgical pathology examination of 3 cm or greater (Table 4). No short- or long-term RARHA-related morbidity was noted. Mean follow-up was 40 months (range 12–95). No differences were noted in median survival time or 1- and 3-year overall survival between RARHA group and control groups (Fig. 4). The two patients of RARHA group with involved RARHA died of disease progression after 6 and 12 months of follow-up. The patient in the neoRARHA group with involved RARHA was still alive without recurrence after 28 months follow-up.

Discussion

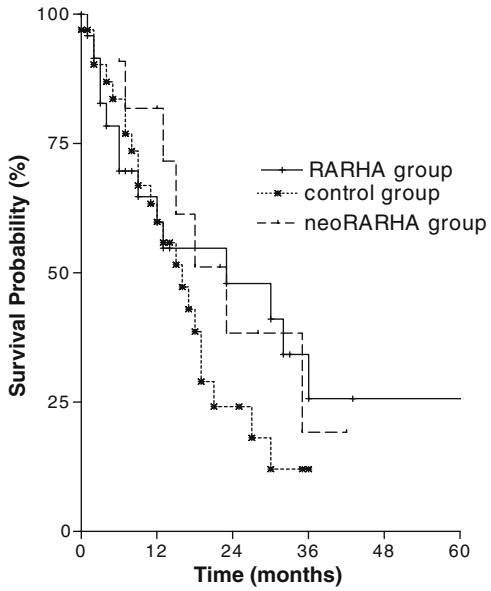
We showed that RARHA was common (10%) and that surgeons were more likely to identify RARHA than radiologists on CT scans. However, nearly 50% of patients

Table 4 Characteristics of Patients with R1 Resection

	Age	Gender	Neoadjuvant CRT	Tumor size (cm)	Lymph nodes	RARHA resected	Michels type	Status	Follow-up (months)
1	79	M	No	3	Involved	No	6	A	14
2	55	F	No	3.4	Involved	Yes	3	D	6
3	49	M	No	4	Involved	No	6	D	33
4	75	M	No	4.4	Involved	Yes	1 (loop)	D	12
5	76	M	No	4.5	Involved	No	6	A	12
6	69	M	No	9.2	Involved	No	6	D	30
7	71	F	Yes	3.5[a]	Negative	No	6	A	32
8	65	F	Yes	3.1[a]	Negative	Yes	3	A	28

A alive, *D* dead

[a] Tumor size on CT scan prior to CRT



log rank test RARHA group vs. control group: 0.29

log rank test neoRARHA group vs. control group: 0.6

Subjects at risk

Time (months)	**0**	**12**	**24**	**36**
RARHA group	31	13	8	4
neoRARHA group	16	13	6	3
Control group	31	17	6	1

Fig. 4 Overall survival of patients undergoing PD with (RARHA group) or without (control group) RARHA.

had unrecognized RARHA on preoperative tumor staging. We suspect that RARHA caliber might be too small to be routinely identified on even thin-cut CT imaging in many patients.

PD remains the gold standard for resectable PA. Free resection margins may be a determinant of improved survival, although this is not universally accepted.[9–12] Optimal tumor clearance is obtained notably by complete removal of pancreatic head and uncinate/retroperitoneal tissue adjacent to the SMA and SMV. However, the presence of RARHA presents a difficult surgical situation: Leaving RARHA might yield incomplete resection whereas arterial ligation or reconstruction might lead to morbidity. Several reports have shown that RARHA resection and reconstruction are feasible and safe.[3,7] In fact, two patients in our series had reconstruction without specific morbidity. Numerous types of reconstruction are available to pancreatic surgeons whereas simple ligation was reserved for a patient with RARHA Michels type 6.[13,14] However, RARHA caliber was not determined in our study, and we did not measure the cut-off caliber above which reconstruction might be required. Preoperative embolization to increase liver blood flow through left hepatic artery has been done, but such a procedure should not be routinely performed.[15] Indeed, tolerance of embolization might signify that intraoperative ligation would be tolerated as well. Thus, we did not recommended preoperative embolization that might lead to a similar set of complications.

We showed that PD for PA in patients with RARHA was safe, and overall survival did not differ from patients without RARHA. We suggest that the presence of RARHA does not impact margin status if no gross tumor involvement is identified by preoperative or intraoperative findings. However, two patients with encased RARHA had poor survival and died 6 and 12 months after surgery. On the other hand, one patient with involved RARHA who received neoadjuvant CRT was still alive after 28 months follow-up. Due to the small number of patients having RARHA involved in this study, definite conclusions cannot be made in regard to management of these patients. Nonetheless, we speculate that RARHA invasion might behave like SMA invasion, and thus, patients with RARHA involvement/encasement might be considered to have locally advanced PA, and a neoadjuvant approach may be considered. Since all patients with involved margins had a tumor size of 3 cm or larger, we recommend a careful preoperative search for RARHA in these patients and consideration of neoadjuvant CRT if involvement/encasement is discovered. We also showed that 49% of patients had only intraoperative RARHA identification, typically after pancreatic neck division. Thus, unsuspected RARHA involvement might be diagnosed at this time and complicate PD, possibly necessitating hepatic artery bypass procedure. In light of this, it makes sense to notify the radiologist preoperatively about the importance of RARHA detection because the repercussions on patient management may be significant.

Conclusions

Based upon this study, RARHA is not rare, but preoperative radiographic identification fails in nearly half of the patients. We recommend that surgeons and radiologists be alerted to the importance of RARHA on preoperative CT scans in patients who are likely to undergo PD for PA. This awareness, in addition to possible adjustments of CT scan images/settings to improve detection of RARHA, may avoid discovery of an unsuspected RARHA at operation. PD for PA in the presence of RARHA appears safe, and reconstruction for RARHA invasion occurred without specific morbidity. Furthermore, preservation of RARHA did not result in increased positive margins or a survival difference in comparison with matched control patients without RARHA. In contrast, the few patients with clear

RARHA involvement seemed to have poor survival. Patients with suspicion of involved RARHA may be considered for neoadjuvant CRT prior to PD for PA.

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Does Body Mass Index/Morbid Obesity Influence Outcome in Patients Who Undergo Pancreatoduodenectomy for Pancreatic Adenocarcinoma?

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Abstract
Introduction The obesity epidemic coupled with epidemiologic evidence of the link between pancreatic cancer and obesity has raised the interest in the impact of body mass index (BMI) on outcomes for resected pancreatic cancer.
Methods All patients who underwent pancreatoduodenectomy (PD) for pancreatic adenocarcinoma from 1981 to 2007 were categorized into four groups according to their BMI (<25, 25 to <30, 30 to <35, and ≥35). Associations of these BMI groups with perioperative (operating time, blood loss, complications, in-hospital mortality), pathologic (tumor diameter, tumor stage, differentiation, lymph node status, R0 status) features and long-term patient outcome were evaluated using Kruskal–Wallis and chi-square tests, logistic regression, and Cox proportional hazards regression. A second set of analyses were performed by dichotomizing patients into morbidly obese (BMI≥35) in comparison to the rest.
Results Of the 586 consecutive patients studied, there were 232 (39.6%) with BMI <25, 232 (39.6%) with BMI 25 to <30, 89 (15.2%) with BMI 30 to <35, and 33 (5.6%) with BMI≥35. Operating time (P=0.003) and intraoperative blood loss (P< 0.001) increased with BMI, although none of the remaining perioperative features differed significantly among the BMI groups. Similarly, there were no significant associations between BMI group and the pathological features studied, particularly lymph node status (P=0.98). BMI was not associated with lymph node status even after adjusting for tumor diameter. All analyses were repeated for the morbidly obese. Cox regression did not demonstrate an impact of BMI or morbid obesity on overall or disease-free survival.
Conclusions BMI (and morbid obesity) does not appear to influence long-term outcomes for patients undergoing PD. Surgeons should be vigilant of the greater risk of perioperative blood loss with increasing BMI.

Keywords Pancreatic cancer · BMI · Pancreatic surgery · Pancreatoduodenectomy · Survival

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Introduction

With the increasingly obvious "epidemic" of obesity, scientists have begun to focus on the contribution of the chronic inflammatory state of morbidly obese patients in an effort to evaluate its correlation to the comorbidities of obesity. Notably, population studies are beginning to show that one of the most serious potential comorbidities of obesity is an increased lifetime risk of developing cancer.[1] Several epidemiologic studies have explored a link between pancreatic cancer and obesity.[2–4] Similar to other sites of malignancy, these studies point to an increased lifetime risk of developing pancreatic cancer in the obese population.

Contemporary data conflict with the notion that obesity predisposes to an increased risk of complications in elective operations[5] or resections for cancer;[6] however, others

disagree[7] and highlight an increased perioperative morbidity. This concept is important because to-date, surgical resection offers the only hope of prolonged survival and possible cure for pancreatic cancer. With the ever-increasing prevalence of obesity,[8] pancreatic surgeons are encountering more and more obese (and morbidly obese) patients for cancer resection.

In this study, we have reviewed the impact of body mass index (BMI) as a surrogate marker for obesity and morbid obesity (BMI≥35 kg/m^2) in a cohort who have undergone pancreatoduodenectomy (PD) for pancreatic adenocarcinoma. The objectives include analysis of perioperative and cancer-related outcomes, as well as disease-free and overall survival in a large, well-studied cohort. We hoped to answer some of the challenging questions about risks and outcome of resection to better inform the clinician and patient alike. Our hypothesis based on previous literature was that obesity would have negative effects on perioperative, pathologic, and long-term outcomes of patients with a pancreatic adenocarcinoma undergoing a potentially curative PD.

Methods

This study was approved by the Mayo Clinic Rochester Institutional Review Board. The medical records of all patients who underwent PD for pancreatic ductal adenocarcinoma at Mayo Clinic Rochester from 1981 through 2007 were analyzed. Patients with unclear site of origin, ampullary, duodenal, distal bile duct, neuroendocrine, and cystic neoplasms were excluded, as were patients who underwent other forms of pancreatic head resection such as total pancreatectomy and those treated with neoadjuvant chemotherapy or radiation. Patient follow-up was obtained through office and hospital records, documents of communication with other health care providers, the Mayo Tumor Registry, and retrieval of death certificates of patients living within the USA. Disease-free survival was defined as the last date the patient was known to be alive and without radiologic evidence of recurrence.

Patients were categorized with respect to their BMI as follows: normal <25, overweight 25 to <30, obese 30 to <35, and morbidly obese ≥35. Data collected for comparison included patient demographics, operative and perioperative outcomes, characteristics of the neoplasm, duration of stay, and disease-free and long-term survival. The lymph node ratio was determined by dividing the total number of lymph nodes harboring a metastasis by the total number of nodes examined. Resections were deemed R1 if there was histopathologic involvement of margin(s). En bloc resections refer to removal of the tumor specimen intact, where no further resection was required to achieve an R0 status. Perioperative complications were stratified according the Clavien's classification.[9]

Subanalyses were performed for those patients with morbid obesity (BMI≥35) versus the rest of the cohort, in particular comparing nodal involvement, disease recurrence, and longevity after PD.

The statistical package JMP® (Version 7, SAS institute inc., Cary, NC, USA) was used for analyses. For descriptive statistics, median (and interquartile range, IQR) was utilized as an expression of central tendency and spread of continuous data. Associations of BMI category with perioperative and pathologic features were evaluated using chi-square, Kruskal–Wallis, and Wilcoxon rank sum tests. Associations of BMI with lymph node involvement were further evaluated using logistic regression models and summarized with odds ratios and 95% confidence intervals (CIs). Patient outcomes were estimated using the Kaplan–Meier method and compared among groups using log-rank tests. Associations of BMI with patient outcomes were further evaluated using stratified Cox proportional hazards regression models with year group (1981–1995, 1996–2000, 2001–2003, 2004–2007) as a stratification effect and summarized with hazard ratios and 95% CIs.

Results

Over the time interval, 586 patients fulfilled the study criteria. The median study follow-up was 18.3 months (IQR 10.4–34.5). Table 1 depicts patient demographics; there were more males in the overweight population ($P<0.001$), and not surprisingly, weight loss was less commonly associated with morbid obesity ($P=0.04$).

Impact of BMI on Perioperative Outcomes

Table 2 depicts the summary perioperative outcomes (operating time, estimated blood loss, duration of stay, number of patients undergoing portal vein resection, in-hospital complications, and mortality) stratified by BMI category. Operating time and blood loss were associated with greater BMI ($P=0.003$ and $P<0.001$). The number of patients suffering a clinically important complication or perioperative mortality did not differ significantly, nor did the proportion of patients undergoing a portal vein resection.

Impact of BMI on Oncologic Outcomes

Table 3 presents the summary oncologic outcomes stratified by BMI category, including tumor diameter, lymph node ratio, total number of lymph nodes resected, tumor differentiation, T stage, lymph node positivity, resection margin status, the ability to perform en bloc resections, and

Table 1 Patient Demographics as per BMI Category

Feature	Median (IQR) or percentage (%)					*P* value[a]	*P* value[b]
	<25 (*N*=232)	25 to <30 (*N*=232)	30 to <35 (*N*=89)	<35 (*N*=553)	≥35 (*N*=33)		
Age (years)	68 (59–74)	67 (59–75)	66 (57–73)	**67 (58–74)**	**64 (57–70)**	0.15	**0.047**
Sex							
Male	**107 (46)**	**156 (67)**	**49 (55)**	312 (56)	**16 (48)**	**<0.001**	0.37
Female	**125 (54)**	**76 (33)**	**40 (45)**	241 (44)	**17 (52)**		
ASA score							
I and II	89 (38)	94 (41)	31 (35)	214 (39)	9 (27)	0.45	0.19
III and IV	143 (62)	138 (59)	58 (65)	339 (61)	24 (73)		
Presentation							
Jaundice	169 (73)	182 (78)	70 (79)	421 (76)	28 (85)	0.29	0.25
Weight loss	**125 (54)**	**108 (47)**	**47 (53)**	280 (51)	**10 (30)**	**0.049**	**0.023**
Abdominal pain	91 (39)	90 (39)	32 (36)	213 (39)	11 (33)	0.88	0.55

[a] *P* value for BMI <25 versus 25 to <30 versus 30 to <35 versus ≥35

[b] *P* value for BMI <35 versus ≥35

proportion of patients undergoing adjuvant chemotherapy. None of these measures was found to be associated with any particular BMI class. There was no difference in the number of patients receiving adjuvant therapy (chemo-radiation) across the BMI spectrum.

Impact of Morbid Obesity (BMI≥35)

Patients were also stratified according to whether they were morbidly obese (BMI≥35) and compared to the rest of the cohort (Tables 1, 2, 3, and 4). Morbidly obese patients were younger in age (P=0.047) and were associated with greater operating times (P=0.017) and blood loss (P=0.001) intra-operatively. Morbidly obese patients were significantly less likely to present with weight loss (P=0.023). All other parameters (as shown in Tables 2 and 3) were comparable, and no significant associations were found. In particular, there was no association between morbid obesity and either tumor diameter, stage, nodal disease, or the extent of lymph node involvement (P>0.6).

A multiple logistic regression model was used to evaluate the association of morbid obesity (BMI≥35 versus <35) with lymph node positivity after adjusting for tumor diameter. In this model, tumor diameter was associated with an increased risk of at least one node being positive (P<0.001), but morbid obesity was not associated node positivity (P=0.91, Table 5).

Long-Term Survival and Disease Recurrence

Overall and disease-free survival were not significantly associated with BMI group or with morbid obesity at presentation (log-rank P=0.49 and P=0.51, respectively, Fig. 1). The likelihood of disease recurrence was unaffected by BMI or morbid obesity at presentation (P=0.63; see Table 4).

Similarly, BMI group was not found to be an independent predictor of overall survival in a Cox proportional hazards

Table 2 Perioperative Outcomes as per BMI Category

Feature	Median (IQR) or percentage (%)					*P* value[a]	*P* value[b]
	<25 (*N*=232)	25 to <30 (*N*=232)	30 to <35 (*N*=89)	<35 (*N*=553)	≥35 (*N*=33)		
Operating time (min)	**342 (290–399)**	**360 (308–418)**	**357 (315–423)**	**354 (300–411)**	**380 (343–455)**	**0.003**	**0.017**
Blood loss (ml)	**500 (300–800)**	**600 (400–1000)**	**600 (500–1000)**	**600 (400–900)**	**800 (650–1300)**	**<0.001**	**0.001**
Duration of stay (days)	11 (9–15)	11 (9–15)	11 (9–18)	11 (9–16)	11 (9–14)	0.59	0.72
Portal vein resection	36 (16)	34 (15)	17 (19)	87 (16)	4 (12)	0.73	0.58
In-hospital complications (Clavien grade II and above)	78 (34)	93 (40)	40 (46)	211 (38)	12 (36)	0.22	0.81
In-hospital mortality	2 (1)	4 (2)	1 (1)	7 (1)	0	0.92	1.0

[a] *P* value for BMI <25 versus 25 to <30 versus 30 to <35 versus ≥35

[b] *P* value for BMI <35 versus ≥35

Table 3 Oncologic Results as per BMI Category

Feature	Median (IQR) or percentage (%)					*P* value[a]	*P* value[b]
	<25 (*N*=232)	25 to <30 (*N*=232)	30 to <35 (*N*=89)	<35 (*N*=553)	≥35 (*N*=33)		
Tumor diameter (cm)	3.0 (2.5–4.0)	3.1 (2.5–4.0)	3.4 (2.5–4.0)	3.0 (2.5–4.0)	3.4 (2.5–4.0)	0.49	0.70
Lymph node ratio	0.07 (0–0.20)	0.07 (0–0.25)	0.09 (0–0.20)	0.07 (0–0.22)	0.12 (0–0.31)	0.53	0.24
Total number of lymph nodes resected	9.5 (6–16)	10 (6–15)	11 (7–17)	10 (6–16)	11 (7–16)	0.97	0.82
Tumor differentiation							
Moderate	41 (18)	41 (18)	17 (19)	99 (18)	5 (15)	0.98	0.70
Poor	150 (65)	146 (63)	54 (61)	350 (64)	20 (61)		
Dedifferentiated	41 (18)	44 (19)	17 (19)	102 (18)	8 (24)		
T stage							
1	21 (9)	17 (7)	6 (7)	44 (8)	1 (3)	0.72	0.65
2	61 (26)	53 (23)	21 (24)	135 (24)	7 (21)		
3	150 (65)	160 (69)	62 (70)	372 (67)	25 (76)		
4	0	2 (1)	0	2 (<1)	0		
Positive lymph nodes (N1)	127 (55)	131 (56)	50 (56)	308 (56)	19 (58)	0.98	0.83
Positive surgical margins	49 (21)	57 (25)	25 (28)	131 (24)	8 (24)	0.59	0.94
En bloc resection	161 (69)	151 (65)	58 (65)	370 (67)	22 (67)	0.77	0.98
Adjuvant chemotherapy (*N*=528)	159 (74)	159 (77)	65 (81)	383 (76)	23 (85)	0.44	0.29

[a] *P* value for BMI <25 versus 25 to <30 versus 30 to <35 versus ≥35

[b] *P* value for BMI <35 versus ≥35

model after adjusting for tumor diameter and lymph node status (*P*=0.56). These results did not change when patients with morbid obesity (BMI≥35) were compared (*P*=0.76). Finally, BMI group (*P*=0.52) or morbid obesity (*P*=0.89) were also not predictive of disease-free survival in a Cox model after adjusting for tumor diameter and lymph node status. These results (Table 6) demonstrate the tumor diameter and lymph nodal positivity as variables with independent prognostic significance.

Discussion

By studying a homogeneous, consecutive cohort of patients undergoing PD for pancreatic ductal adenocarcinoma, we measured the impact of BMI on complex perioperative, tumor-related, and long-term outcomes. We found that there was no difference in the mode of presenting symptoms and ASA grade across the BMI spectrum; although obesity has been linked to a greater risk of other comorbidity,[10] the presence of obesity did not affect the ASA grading, even in the subset of patients with morbid obesity (BMI≥35).

A greater rate of perioperative complications in obese patients have been reported after PD, in particular pancreatic leak[11] and surgical site infections.[12,13] An interesting twist in this debate is the notion of the "obesity paradox". Overweight and moderately obese patients have been reported to have a somewhat better operative mortality for general surgical operations compared to normal/underweight population.[14] We did not find an increase in rate of complications, duration of in-hospital stay, or operative mortality across the BMI spectrum. Importantly, a greater operative blood loss was observed, and this increase was most notable in the morbidly obese group. Somewhat expectedly, the operative time also increased with increasing weight and was especially evident in patients with morbid obesity; similar findings have been reported by

Table 4 Overall and Disease-Free Survival in Months as per BMI Category

	<25 (*N*=232)	25 to <30 (*N*=232)	30 to <35 (*N*=89)	<35 (*N*=553)	≥35 (*N*=33)	*P* value[a]	*P* value[b]
Median overall survival	18.5	17.0	24.7	18.5	22.2	0.49	0.62
Median disease-free survival	20.7	19.1	26.1	20.7	25.3	0.51	0.78
Median recurrence-free survival	15.5	13.2	14.8	14.0	15.9	0.63	0.71

[a] *P* value for BMI <25 versus 25 to <30 versus 30 to <35 versus ≥35

[b] *P* value for BMI <35 versus ≥35

Table 5 Multivariable Logistic Model to Predict Lymph Node Positivity

	Odds ratio (95% CI)	*P* value
Tumor diameter (1-cm increase)	1.60 (1.37–1.88)	<0.001
Morbid obesity	1.05 (0.50–2.19)	0.91

Table 6 Multivariable Cox Proportional Hazards Regression Model to Predict Long-Term Patient Outcome

	Hazard ratio (95% CI)	*P* value
Death from any cause		
Tumor diameter (1-cm increase)	1.19 (1.10–1.28)	<0.001
Positive lymph nodes (N1)	1.30 (1.07–1.56)	0.007
Morbid obesity	0.94 (0.63–1.40)	0.76
Death from disease		
Tumor diameter (1-cm increase)	1.20 (1.10–1.32)	<0.001
Positive lymph nodes (N1)	1.27 (1.03–1.58)	0.028
Morbid obesity	0.97 (0.61–1.55)	0.89
Recurrence		
Tumor diameter (1-cm increase)	1.20 (1.10–1.31)	<0.001
Positive lymph nodes (N1)	1.26 (1.02–1.55)	0.034
Morbid obesity	1.08 (0.70–1.66)	0.75

other investigators.[12,15] Increased blood loss and need for transfusion have been implicated in poor short and long-term results after PD for malignancy;[16,17], hence the need for meticulous technique and appropriate preoperative blood/product scheduling. It is evident that morbid obesity may enhance the technical challenge of PD, but obesity itself does not influence the likelihood of achieving an R0 resection or an en bloc removal of tumor, a finding not reported previously. Furthermore, obesity does not appear to influence the ability to perform a safe portal venous resection, when required.

Two further points should be acknowledged. First, we found that overweight patients were significantly younger at presentation. This observation is intriguing because epidemiologic evidence points to a younger age of onset of pancreatic cancer in the obese population (BMI >25).[2] Second, the association of onset of diabetes (especially type II) and obesity is well known,[10] but recent data from our institution point to the alarming incidence of pancreatic cancer in new onset diabetes.[18–20] Future studies should investigate these issues further.

In addition, we did not find any association between BMI (or morbid obesity) and any of the cancer-related parameters despite a detailed analysis of factors including tumor stage, tumor differentiation (T or N stage), lymph node status, and lymph node ratio. This lack of any association appears to be in contrast to increasing epidemiologic evidence of a link between pancreatic cancer and obesity. Nevertheless, similar findings to our study have been reported.[12]

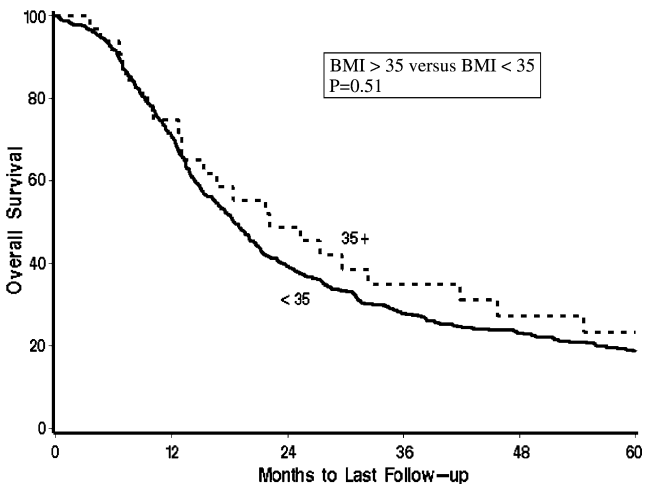

Fig. 1 Long-term overall survival, morbidly obese patients versus the rest of the cohort. Kaplan–Meier plot.

Benns and coworkers found similar results in long-term and disease-free survival for resected pancreatic cancer in the obese patients.[12] In contrast, Fleming and colleagues reported recently an apparent association between morbid obesity and lymph node involvement in patients with pancreatic adenocarcinoma (n=20 patients); consequently, the morbidly obese group in their sample had a lesser overall and disease-free survival.[21] We, however, were unable to demonstrate a similar association either on univariate or multiple regression analysis with a much larger data base of nearly 600 patients who underwent PD. The similarity of our population group to their group makes it difficult to postulate a plausible explanation even after controlling for other potential confounding covariates (neoadjuvant therapy, tumor stage, grade, etc.). Further, there was no impact of BMI or morbid obesity on long-term or disease-free survival; moreover, neither obesity per se nor morbid obesity had independent predictive value of longevity or recurrence.

In summary, our analysis suggests that BMI and morbid obesity have no negative predictive implications concerning surgical outcome in resected pancreatic adenocarcinoma, contrary to our hypothesis. Uniquely, our study found no increase in perioperative, detailed pathologic and long-term outcomes affected by BMI or morbid obesity, in contrast to other reports. The corollary of our findings suggests that, in experienced units, short- and long-term outcomes after PD for pancreatic cancer are not influenced by BMI at presentation. A word of caution is raised against the greater risk of perioperative blood loss which could lead to potentially serious complications.

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Pancreatoduodenectomy for Ductal Adenocarcinoma in the Very Elderly; Is It Safe and Justified?

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Abstract
Background The outcomes of complex major surgery in the elderly are being scrutinized because of the demands on surgical services by an aging population and the concern whether such endeavors are justified. Pancreatoduodenectomy (PD) for pancreatic adenocarcinoma presents special challenges because of the high morbidity of the procedure, dismal prognosis of the disease, and the increasing incidence of pancreatic cancer with age.
Methods All patients who underwent PD for pancreatic adenocarcinoma from 1981 to 2007 were analyzed for perioperative outcomes, tumor-related parameters, use of adjuvant therapy, and long-term survival. Specifically those aged ≥80 years were compared with a control group aged ≤80 years. Continuous variables are displayed as median and interquartile range (IQR); log-rank test and Cox's proportional hazards were used to determine survival and effect of age as an independent marker against other covariates.
Results Fifty-three patients aged ≥80 years underwent PD. Twenty-six (51%) developed complications, including delayed gastric emptying (nine, 17%), pancreatic leak (six, 11%), and postoperative bleeding (five, 9%). There was one in-hospital death (2%). The hospital stay was 13.5 days (IQR 9–19). Forty-one (79%) patients were discharged home; of the 11 (21%) patients who went to an outside health care facility (pancreatic leak/drains and feeding issues—five, delayed gastric emptying/nutritional—four, no home support—one), one died in a nursing home at 5 months while the other ten patients returned to their previous abode (median 4 weeks). The median disease-free and overall survivals were 11.8 (IQR 7.8–18.4) and 13.5 months (IQR 12–21.3). Compared to the non-octogenarians (n=567), the older population had more poor risk patients with respect to ASA status (P<0.0004), stayed longer as in-patients (P<0.04), were more likely to develop complications (P<0.001), and were less likely to receive adjuvant therapy (P<0.0001). There was no difference in long-term disease-free or overall survival (log-rank P<0.30 and P<0.14), and age did not appear to be an independent marker of prognosis when analyzed (Cox's proportional hazards P<0.26; chi-square, 1.25).
Conclusions In experienced institutions, PD for ductal adenocarcinoma is a viable option in the ambulatory octogenarian population who are deemed operative candidates for a PD. The trade off is a greater complication rate and the prospect of discharge (one in five) to a chronic care facility. The majority, however, can be discharged home with a reasonable functional status, and those discharged to temporary health care rehabilitation facilities are likely to make a recovery over a few weeks.

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Keywords Pancreatic cancer · Pancreatic surgery · Pancreatoduodenectomy · Operative risks

Introduction

The burden of cancer in the Western population is expected to increase by 45% between 2010 and 2030, in large part due to an aging population. By 2030, approximately 70% of all cancers will be diagnosed in older adults ≥70 years.[1,2]

Alarmingly, pancreatic cancer is listed among those with the greatest relative increase in incidence (55%). To address the anticipated upsurge in cancer incidence, substantive research resources are needed to better understand not only the biology of the disease but also the outcome of all potential interventions in the older population.

Historically, the morbidity and mortality of a major pancreatic resection and the dismal long-term survival of pancreatic neoplasia have led some investigators to question the rationale for operative resection in the elderly.[3,4] There have been unquestioned advancements in surgical outcomes for pancreatic resection;[5] the reasons for this increase in survival and decrease in overall morbidity are multifactorial and include improvements in patient selection, technique, team work, perioperative care, and management of complications. Recently, evidence has emerged that the long-term survival has also shown consistent improvement after curative resection for pancreatic adenocarcinoma, with one in five patients surviving up to 5 years.[6]

The safety of pancreatoduodenectomy (PD) in the elderly patients (≥70 years) has been reported by several centers.[7–9] PD in patients ≥80 years old (for pancreatic ductal adenocarcinoma) poses special challenges because of the perceived frailty of the patients and the concern that perioperative survival may not translate to a return to functional status or meaningful longevity. Therefore, it is imperative to identify treatment strategies that improve quality of life and are cost-effective in this subset of patients that we are increasingly likely to encounter in the future. Although PD in the octogenarian and older patients has been reported,[10] our study evaluates results of PD specifically for ductal adenocarcinoma and the effect of such complex major surgery in this specific age group both in the short-term (perioperative morbidity/mortality) and in the long-term (survival).

Methods

The study was approved by the Mayo Clinic Rochester Institutional Review Board. The medical records of all patients who underwent PD specifically for pancreatic ductal adenocarcinoma at Mayo Clinic Rochester from 1981 through 2007 were analyzed. Patients with unclear site of origin, ampullary, duodenal, distal bile duct, neuroendocrine, and cystic neoplasms were excluded, as were patients who underwent other forms of pancreatic head resection such as total pancreatectomy. Patient follow-up was obtained through office and hospital records, documents of communication with other health care providers, the Mayo Tumor Registry, and retrieval of death certificates of patients living within the United States. Disease-free survival was defined as the last date the patient was known to be alive and without radiologic evidence of recurrence.

The subgroup of patients aged 80 years and greater was studied with respect to preoperative comorbidities, operative and perioperative outcomes, tumor characteristics, duration of stay, and mode of discharge (return to premorbid state). Comparisons were drawn between the older (aged ≥80) patient population and those less than 80 years of age, assessing rates of complications, hospital stay, and determinants of long-term survival.

For descriptive statistics, median and interquartile range (IQR) were utilized as an expression of central tendency and spread of continuous data. Univariate survival analysis was conducted using Kaplan–Meier curves and the log-rank test. The association between variables was examined by estimating χ^2 test (including the test for trend, where appropriate), and the Wilcoxon test. The Cox regression model was utilized to explore whether age at the time of the operation was an independent prognostic indicator.

Results

During the study period, 617 patients underwent pancreatoduodenectomy for pancreatic ductal adenocarcinoma. Fifty-three (8.5%) patients were aged 80 or above. The details of these patients are represented in Table 1. The patients aged ≥80 years were all ambulatory and either independent in their day-to-day living or required very little

Table 1 Patient demographics

Total (n=53)	
Age	80–84=44 (83%) 85–90=9(17%) including 3 aged 90
Sex	
Male	31 (58%)
Female	22 (42%)
Body Mass Index (BMI)	25.2 (± 3.7)
Comorbidity	
Hypertension	24 (45%)
Diabetes	10 (19%)
Cardiac disease	12 (23%)
Pulmonary disease	2 (4%)
Chronic renal disease	2 (4%)
Other significant	10 (19%)
>2 conditions	27 (51%)
Presentation	
Jaundice	33 (62%)
Weight loss	29 (54%)
Abdominal pain	13 (24%)
Preoperative biliary stent	25 (49%)

support and obviously deemed to be appropriate operative candidates based on comorbidities. All those with a previously treated malignancy had an average interval of 5 years disease-free prior to PD. Preoperative biliary stents were placed in other institutions or when there was a delay in operative treatment in a jaundiced patient. Thirty-four patients underwent pylorus preserving PD, whereas 19 had a classic pancreaticoduodenal resection with distal gastrectomy performed.

Perioperative Outcomes

There was one in-hospital death (2%) secondary to aspiration occurring 4 days after exploration for postoperative bleeding. Twenty-seven patients (51%) developed a complication (Table 2). Four patients had more than one complication.

Two other patients required a re-laparotomy, one for postoperative hemorrhage and the other for abdominal wound dehiscence and pancreatic leak (re-operation rate 6%). Endoscopic control of bleeding was achieved in another patient. Sixteen patients (30%) spent a median of 2 days (IQR 1.25–3) in the intensive care unit; however, the practice pattern has shifted in the last decade of admitting patients to a step-down unit or commonly direct to a regular surgical nursing unit post-operatively.

Hospital Discharge/Ambulatory Status

The median hospital stay was 13.5 days (IQR 9–19 days). Forty-one (79%) patients were discharged directly home; in all cases, the patients had support from a relative or companion. Amongst those who went home, five patients had drains in place. All discharged patients were independent in their activities or required very little support.

Table 2 Complications of pancreatoduodenectomy

Complication type	Frequency (treatment)
Pancreatic leak[33]	6 (11%)
Type A	1
Type B	5 (Four needed interventional radiology)
	Four required parenteral nutrition
Biliary anastomotic leak	1
Delayed gastric emptying	9 (17%—six required parenteral nutrition)
Postoperative hemorrhage	5 (9%)—including two intraluminal and one adrenal
Cardiac dysrhythmia	3 (6%)
Pneumonia	4 (8%)
Clostridium Difficile	2 (4%)

Eleven patients (21%) were discharged to health care facility (nursing home—five, skilled care—five, another hospital—one); the reasons for transfer included (pancreatic leak/drains and feeding issues—five, delayed gastric emptying/nutritional—four, no home support—one). Among these 11 patients, seven returned home after further recovery (median 4 weeks, range 2–16 weeks), two were previous nursing home residents who returned to their previous abode, and one patient failed to improve and died in a nursing home 5 months later (no data were available on the other patient).

Therefore, return to the original preoperative living status occurred in at least 51 of the 52 survivors. Two of three patients aged 90 were discharged home, and the third required a temporary skilled care facility.

Comparison with Patients ≤80 Years (Table 3)

There were no significant differences between the octogenarians and non-octogenarians (n=564, median age=66, IQR 58–72 years) with respect to sex, tumor size, grade of neoplasm, lymph node metastases and resection margin (R0 versus R1), operative blood loss, mean operating time, transfusion requirement, and in-hospital mortality. The older population, however, did have more poor risk patients with respect to ASA status (P<0.0004), a greater postoperative hospital stay (P<0.04), were more likely to develop complications (P<0.001), and were less likely to receive adjuvant therapy (P<0.0001).

Long-Term Survival

Patients were followed up for a median of 18.3 months (IQR 10.4–34.9). Survival data were retrieved on all patients to their last follow-up or death. Five hundred and three patients died during follow-up, while seven out of the 53 elderly octogenarian patients are still alive. Although there was no statistically significant difference in disease-free or overall long-term survivals between the two groups (log-rank P<0.30 and P<0.14—see Fig. 1), the median disease-free and overall survivals for octogenarians were 11.8 (IQR 7.8–18.4) and 13.5 months (IQR 12–21.3), respectively, and for the non-octogenarians 13.9 (IQR 12.4–15.4) and 18.9 (IQR 17.5–20.7)months. Notably, the median survival of all patients undergoing PD for adenocarcinoma since the start of this decade (2001 to date) has improved (median 28 months). Age (≤80 or ≥80 years) was entered in a Cox regression model along with lymph node status[6] and tumor diameter. Age was not found to be an independent marker of prognosis (P<0.26; chi-square, 1.25).

Amongst the three patients aged 90 years, one is still alive at 41 months, while the other two died at 28 and 26.7 months, respectively, from recurrent cancer.

Table 3 Comparison of patients aged ≥80 years with those ≤80 years of age

	Age >80years	Age <80years	*P* value
Number ('n')	53	564	
ASA Grade			
I	0	4	0.0004
II	7	224	
III	44	326	
IV	2	10	
Grade of neoplasm			
Well differentiated	0	0	NS
Moderately	11	97	
Poorly	35	355	
De-differentiated	7	110	
T Stage			
T1	2	47	NS
T2	18	125	
T3	32	389	
T4	1	3	
Nodal status			
N0	20	263	NS
N1	33	301	
Tumor size (mm.)	32 (25–40)	30 (25–40)	NS
Resection margin			
R0	42	426	NS
R1	11	138	
Operative blood loss (ml)	650 (337–995)	600 (400–975)	NS
Blood transfusion (units)	1 (1–2)	0 (0–1)	
Duration of stay (days)	13.5 (9.25–19)	11 (9–15)	0.04
Complications (*n*)	27 (51%)	209 (37%)	0.004
In-hospital mortality	1 (2%)	6 (1%)	NS
Adjuvant therapy			<0.0001
None	26	99	
Chemo/radiotherapy	19	388	
Chemotherapy	3	23	
Unknown	5	53	

Discussion

We believe that it is important to study the outcomes of surgery for pancreatic ductal adenocarcinoma in the very elderly because of increasing incidence of pancreatic cancer in our aging population. Prognosis of this cancer is purportedly poor despite operative resection. Potential cure is possible in the elderly, and we need to be cognizant of the effect on quality of life of such a major operation on potentially frail patients. It is arguably a sign of progress to note that Spencer and colleagues from our institution made a plea for pancreatectomy for adenocarcinoma in the elderly (>70 years) almost two decades ago[11] that we and others have continued. Amongst the 42 patients in that study, seven were older than 80 (with the oldest being 85), the median survival was 19 months. Interestingly, outcomes of all types of surgery (not specific to cancer) in those aged 90 and above have also reported to be encouraging,[12] making the point that chronologic age should not be the sole determinant of operative candidacy. Still, major operative procedures with such a great morbidity (40–50% for PD) should be analyzed critically for acceptable outcomes in a group of patients whose expected survival from all causes other than the underlying pancreatic cancer is limited, in our case, patients greater than 80 years of age.

It is recognized that chronologic age is a poor descriptor of functional status either physically, mentally, or medically. Nevertheless, selecting appropriate therapy for the very elderly pancreatic cancer patient remains challenging because of concerns with regard to their comorbidities, functional and nutritional status, cognitive function, and social support, in addition to expected survival. Patient selection is crucial for optimal outcomes and remains a challenge.[13] Although nomograms[14] have been developed with age as one of the parameters, we found that age alone in our group of patients selected for PD did not contribute significantly to outcome. Candidates selected for PD at the Mayo Clinic were very carefully evaluated preoperatively for cardiopulmonary and anesthetic considerations; however, no specialized preoper-

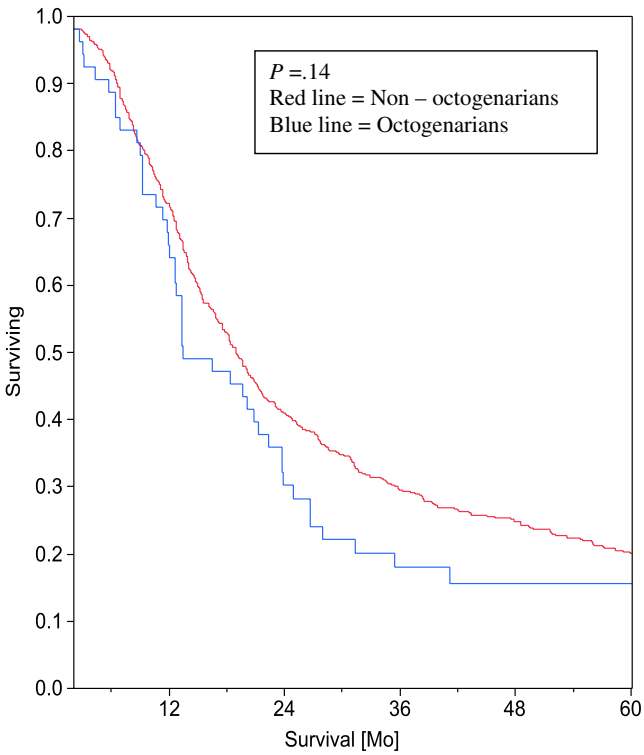

Fig. 1 Survival in months comparing patients aged above 80 (*blue*) versus <80 (*red*)

ative testing was performed unless indicated by history or examination. The decision to offer the older patients PD in general rests on routine testing, independence of lifestyle, and nutritional and general performance status. At times, patients who were candidates for resection were pre-optimized because of a correctable comorbidity or for impaired nutritional status (including biliary stent), despite delaying the operation. The experience of the surgical and medical teams in assessing operative candidates in this scenario should not be under estimated.

There are only a few prior reports on the results of PD in the very elderly,[10,15,16] none of which were specific for ductal adenocarcinoma. These studies in experienced centers demonstrate a similarity in the outcomes. The corollary of these results and other reports of PD in this age group[17–19] attest to the feasibility, safety, and potential for long-term survival of PD in this age group of selected patients deemed on overall medical evaluation to be operative candidates. Importantly, it should be appreciated that this patient subset is likely to have a greater rate of complications, especially delayed gastric emptying (13–17%), and may require longer hospitalization.

Quality of life has been studied in patients following PD and found to be satisfactory,[13,20] while others have concluded that operative intervention for malignancy, whether resection or bypass (as indicated), is of benefit.[21] At least one study reported similar quality of life profiles for those aged <65 years compared to >65 years after PD.[22] Importantly, "palliative" PD in the setting of incurable disease has been shown to have somewhat poorer outcomes compared to a bypass procedure, with a median survival of 7 months (PD) versus 6 months (bypass).[23] Unfortunately very little data exist on post-discharge quality of life specific to this age group. We endeavored to study surrogate markers, such as ambulatory and discharge status (whether to home or a health care facility) and finally whether patients who were discharge to such a facilities regained health to be able to return to their previous abode. It was encouraging to note that about 80% of patients were fit enough for home and independent lifestyle (albeit with companion support). Even amongst those who went to health care facilities, the ambulatory status was not "bed-ridden" but variable. Predictably, complications, such as pancreatic leak, delayed gastric emptying, nutritional support, and in one instance lack of home help, mandated the transfer. It was encouraging that all, but one patient, were able to return to their preoperative residence after several weeks of convalescence. Hardacre and coworkers[15] reported a 59% rate of discharge to a chronic care facility, likely due to the high rate of complications and need for rehabilitation in this age group.

Population-based data of pancreatic resection in the elderly shows poorer short-term results when compared to single institution outcomes. Lightner and colleagues[24] studied patients aged >75 years undergoing pancreatectomy in the state of California (1993–2000, n=515), in particular studying the decline in nutritional and functional status. They reported a 10% in-hospital mortality (for >75 years) and 70% complication rate statewide (cardiac, pancreatic leak, and delayed gastric emptying being the commonest), average postoperative duration of stay 21.4 days and 26% were discharged to an outside health care facility. Interestingly, 24% of the patients required a re-admission, most commonly for malnutrition and dehydration. It is not apparent whether those discharged to a health care facility returned home, and if so, at what time interval. Finlayson and coworkers,[25] using a nationwide in-patient sample (1994–2003, n=2,915 pancreatectomies), found a peri-operative mortality of 15.5% and mean duration of stay 20 days. There is a recent report about a high rate of re-admission after PD (n=2,023 resections, re-admission rate after 30 days—59%).[26] These are sobering results and raise important questions about the provision of specialized services at high and low volume centers and the necessity for audit of results for review and improvement in outcomes.

Not unexpectedly, the very elderly patient population is less likely to be treated with adjuvant therapy (chemotherapy alone or chemoradiotherapy). The reasons that we found in our patient population included a joint decision with oncologist and internist because of potential side effects, concerns about the efficacy, and the delay in recovery from the operation. We found the median survival to be about a year for such patients, which is similar to other reports.[15,16] Although we did not find a statistically significant difference in longevity between the younger and the older patient population, the Kaplan–Meier plot shows a trend toward longer survival for the former, this could be due to the sample size, age at diagnosis, and possibly even selection bias.

The historic concerns associated with PD for cancer not with standing,[27] Vickers and colleagues studied the economic impact for PD in patients aged 70 years and older over a decade ago and concluded that "PD in the elderly can be performed safely without accruing higher cost."[28] Predictably, a greater rate of complications and duration of stay are associated with increased costs,[29–31] underlining the importance of institutional experience and audited outcomes. Encouragingly, recent data with regard to pancreatic resection in the elderly (>75 years) suggest a marginal cost increase in the elderly ($2,202); the authors concluded that "age-related care, including geriatric consultation, supplemental enteral nutrition, and early rehabilitation placement planning, can be designed to mitigate the impact of complications in the elderly and guarantee quality."[32]

Undoubtedly, prospective studies addressing health economics (cost), intervention (whether operative or non-operative) related outcomes, survival, and prospectively evaluated quality of life in patients diagnosed with pancreatic cancer could lead to evidence-based clinical guidelines which will help cancer physicians as they adapt their therapies to the unique functional and physiologic limitations of their older patients.

In conclusion, PD for ductal adenocarcinoma should not be withheld based on age alone. Our experience better informs the clinicians in weighing the odds of such an extensive operation and educates the patient in arriving at a joint decision about the prospect of operative exploration/resection.

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2010 SSAT POSTER PRESENTATION

Intra-abdominal Fat Predicts Survival in Pancreatic Cancer

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Abstract
Background Body mass index (BMI) has proven unreliable in predicting survival following pancreaticoduodenectomy for cancer. While measures of intra-abdominal fat correlate with medical and postoperative complications of obesity, the impact of intra-abdominal fat on pancreatic cancer survival is uncertain. We hypothesized that the quantity of intra-abdominal fat would predict survival following resection of pancreatic cancer.
Methods Preoperative CT imaging was used to measure intra-abdominal fat. Cox regression analyses were used to identify independent predictors of survival.
Results Sixty-one patients from 2000–2009 underwent pancreaticoduodenectomy for exocrine pancreatic adenocarcinoma. After adjusting for age and perineural invasion status, preoperative BMI did not predict overall survival ($p<0.827$). Unlike BMI, quartile of intra-abdominal fat predicted survival. Relative to patients with the least intra-abdominal fat (lowest quartile), those with more intra-abdominal fat demonstrated worse overall survival, but in a non-linear fashion. Individuals in the second quartile showed a fourfold increase in likelihood of death (HR 4.018, 95% CI 1.099–14.687, $p<0.035$) relative to the lowest quartile. Patients in the third (HR 2.124, 95% CI 0.278–16.222, $p<0.468$) and fourth quartile (HR 1.354, 95% CI 0.296–6.190, $p<0.696$) also showed greater risk of death.
Conclusions Measuring intra-abdominal fat identifies a subset of patients with worse prognosis in pancreatic cancer.

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Keywords Obesity · Pancreaticoduodenectomy · Survival

Introduction

The impact of obesity on outcomes following pancreaticoduodenectomy is controversial. Several studies have shown an association between increasing body mass index (BMI) and overall complication rates as well as specific complications including fistula and wound infection.[1–4] However, other groups have shown no association between obesity and short-term outcomes following pancreatic resection.[5,6] Similarly, the effect of obesity on long-term outcomes including overall and disease-free survival is unclear since the limited data available has offered conflicting results.[7,8] Recently, evidence has emerged that BMI is not the most sensitive predictor of outcomes following abdominal surgery and that measures of visceral/intra-abdominal fat better identify high-risk patients.[9–12] The greater sensitivity of these measures may be explained by the fact that BMI is an indirect measure of obesity that does not distinguish between type and distribution of adipose tissue, and these factors may be relevant for cancer growth and development. Indeed, the medical literature has now shown that visceral fat has distinct biologic activity that is important for predicting medical complications of obesity including development of the metabolic syndrome and expression of inflammatory and angiogenic factors.[13–15] Consequently, we hypothesized that quantifying visceral fat would help predict long-term outcomes following pancreaticoduodenectomy for pancreatic adenocarcinoma.

Methods

The analysis was based on data from an IRB-approved prospective database and from review of patient medical records. Patients who underwent pancreaticoduodenectomy for exocrine adenocarcinoma were identified and included in the study. Cases of ampullary adenocarcinoma, neuroendocrine cancer, cholangiocarcinoma, and duodenal carcinoma were not included in the analysis. The prospective database tracks data on patient demographics, clinical history, past medical history, family and social history, pathologic data, and outcomes including perioperative mortality (30-day or in-hospital mortality), and long-term survival. Data were entered into the database in real time by a trained data analyst. All data was backed up by source documents and accuracy of the data entered into the electronic database was periodically reviewed. Mortality was confirmed using the Social Security Death Index.

Preoperative CT imaging was retrospectively reviewed and used to measure a surrogate for visceral fat as described previously.[9] Briefly, the distance from the posterior aspect of the left kidney to the abdominal wall musculature was measured using Adobe Photoshop, and this served as a proxy for quantity of visceral fat. Patients were excluded from measures of visceral fat if the left kidney was atrophic or had large cysts or masses that displaced the parenchyma. Measurement was done by two of the authors (CB and JE) who were blinded to patient outcomes. Interrater reliability was assessed using Pearson's correlation coefficient. Preoperative body mass index was obtained from medical records. The relationship between renal pole distance and body mass index was assessed using ordinary least squares linear regression after assessing the data for heteroscedasticity.

Patients were categorized into four groups or quartiles of visceral fat with the lowest quartile serving as the reference category. Independent predictors of overall survival were then evaluated using Cox proportional hazards regression after adjusting for age (as a continuous variable), perineural invasion status, and body mass index. Missing data points were included in the analysis by assigning a specific category for missing data in order to maximize the number of patients included in the model. Variables for the final model were chosen based on whether they remained significant independent predictors of survival after adjusting for the variables forced into the model (BMI and visceral fat). The proportionality of hazards assumption was evaluated using log-log plots.

Results

Demographics

From 2000–2009, sixty-one patients underwent pancreaticoduodenectomy for exocrine adenocarcinoma of the pancreas and met inclusion criteria for the study. Patients were followed for a total of 77.8 person-years. Mean patient age was 66.3±1.2 years and mean BMI was 25.6±0.76 kg/m^2 (Table 1). Men comprised 62% of the patient cohort and 80% were white, with the remainder being African American or Hispanic. The most common comorbid conditions included smoking (with 67% being current or former smokers), diabetes (23%), and coronary artery disease (15%). Most tumors were either grade II or III, and perineural invasion was present in 72% of resected specimens.

Measuring Visceral Fat

Preoperative CT imaging was used to measure distance from the posterior pole of the left kidney to the abdominal wall

Table 1 Demographics and Tumor Information

Demographics		*N*	Percent (%)
Age (years)		66.3±1.2	
Male		38	62
White		49	80
Current or former smoker		41	67
Diabetes		14	23
Coronary artery disease		9	15
Renal insufficiency		2	3
COPD		1	2
Tumor information			
Tumor stage	I	1	2
	II	43	75
	III	13	23
Tumor grade	I	3	5
	II	33	54
	III	34	39
Perineural invasion		44	72
Vascular invasion		24	39
Obesity measures			
Body mass index (kg/m^2)		25.6±0.8	
Visceral fat (mm)		18.1±1.7	

Total less than 61 reflect missing data

musculature as a surrogate for visceral fat as previously described.[9] Imaging was available for 82% of patients. Mean renal pole distance was 18.1±1.7 mm and ranged from 1.4 to 44 mm. In order to assess interrater reliability, the correlation between two independent raters was assessed on a subset of 20 patients. Interrater correlation was 99.8% which indicates a high degree of reproducibility (Fig. 1). We

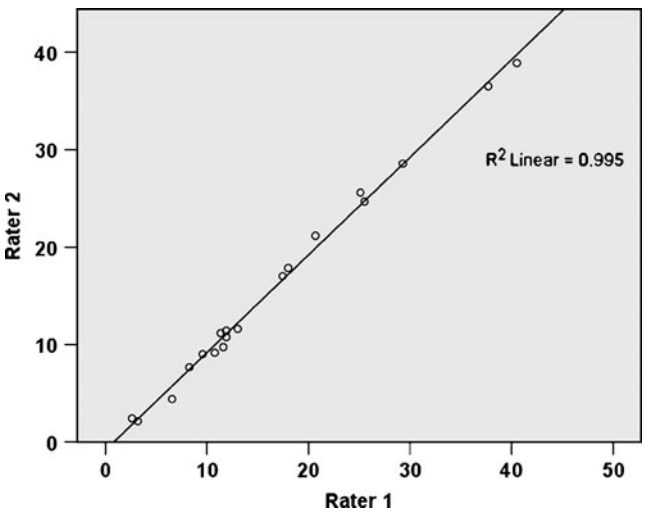

Fig. 1 Interrater reliability for measuring visceral fat. There is highly significant correlation between the two raters evaluating visceral fat by measuring distance from the posterior edge of the kidney to the abdominal wall

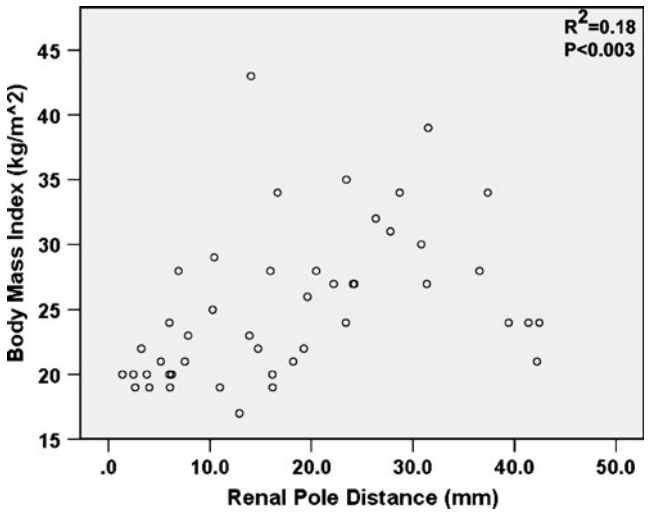

Fig. 2 Correlation between visceral fat and body mass index. There is significant correlation between BMI and visceral fat/renal pole distance, but more than 80% of the variance in BMI is not explained by visceral fat

also evaluated the relationship between visceral fat and BMI in a simple regression model. As shown in Fig. 2, changes in renal pole distance account for approximately 20% of the variance in BMI. While this represents a significant association, 80% of the variance in BMI remains unexplained after measuring visceral fat. This finding indicates that although visceral fat and BMI share a common dimension, they are also measuring different factors as well.

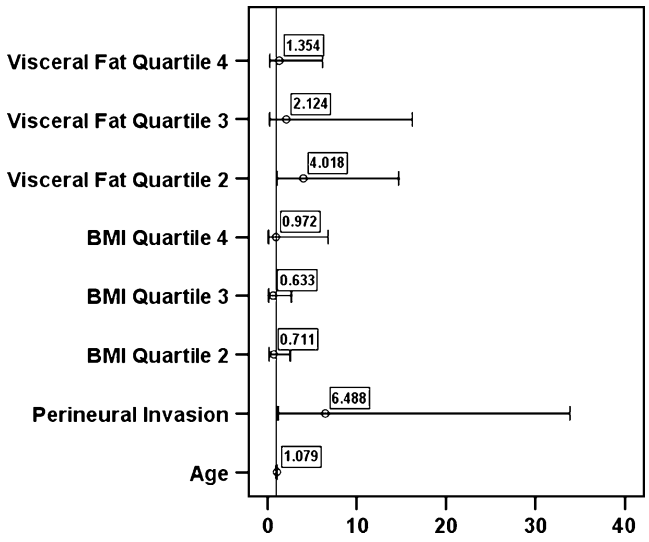

Fig. 3 Visceral fat predicts increased likelihood of death following pancreaticoduodenectomy. Multivariable hazard ratios shown for each quartile of visceral fat and BMI compared to the thinnest patients in quartile 1 (reference category) after adjusting for age and perineural invasion status. *Vertical line* indicates HR of 1

Predicting Survival Following Pancreaticoduodenectomy

Independent predictors of overall survival were evaluated using Cox proportional hazards regression. Patients were divided into four groups or quartiles based on measured quantity of visceral fat. Quartile 1 represents the lowest quantity of visceral fat and serves as the reference category while quartile 4 consists of patients with the most visceral fat. A similar grouping was established for body mass index. After adjusting for age, perineural invasion, and body mass index, visceral fat was a significant predictor of overall survival (Fig. 3). Patients in the second quartile of visceral fat had significantly worse survival than patients with the least amount of visceral fat (HR 4.0, 95% CI 1.1–14.7, $p<0.035$). Individuals in the third (HR 2.1, 95% CI 0.28–16.2, $p<0.468$) and fourth quartile (HR 1.4, 95% CI 0.30–6.2, $p<0.696$) for visceral fat also did worse than those with the least amount of visceral fat, but these differences were not significant. Survival by quartile of visceral fat is also shown graphically in Fig. 4. By contrast, quartile of body mass index did not significantly predict differences in survival. Since not all patients have preoperative imaging available, the possibility of selection bias was examined by comparing patients who had imaging to those without available imaging. No differences in age, BMI, comorbidities, or overall survival were seen between the two groups (data not shown).

Discussion

Obesity has reached epidemic proportions in the US as more than 70 million adults are currently overweight or obese and the US health-care system now spends more than $147 million annually on complications of obesity.[16,17] Additionally, obesity has been associated with increased risk of several cancers including pancreatic, colorectal, and breast.[18] Consequently, as the prevalence of obesity increases, it is important to understand potential implications for care of pancreatic cancer patients. Currently, the evidence regarding the impact of obesity on short-term and long-term outcomes following pancreaticoduodenectomy has been mixed.

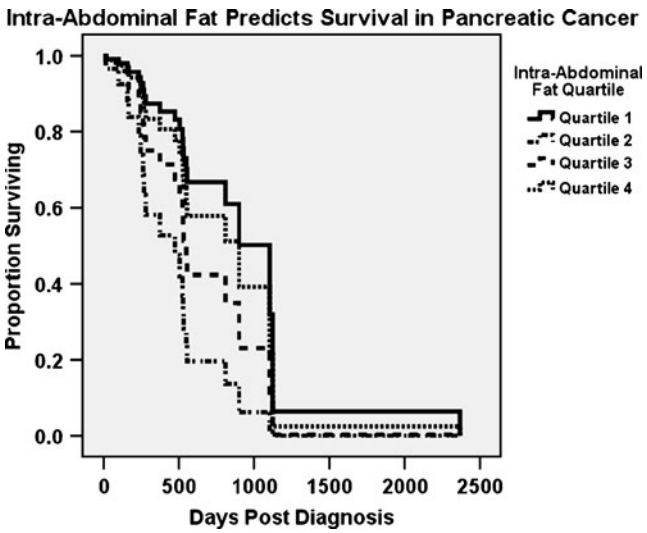

Fig. 4 Survival curves by quartile of visceral fat. Significantly worse survival is seen for quartile 2 relative to quartile 1 (thinnest patients). Worse survival is also seen for quartile 3 and quartile 4 relative to the thinnest patients but these differences are not statistically significant

Gilsdorf and Spanos investigated the prognostic implications of multiple factors at their institution for 88 patients following pancreaticoduodenectomy and found that obesity was associated with a 17% increase in postoperative complications.[4] Noun et al. utilized their institutional prospective database to identify 92 consecutive patients who underwent pancreaticoduodenectomy from 1999 to 2006 and attempted to determine whether obesity predicted postoperative outcomes.[2] They found that BMI≥30 kg/m^2 was associated with increased risk of pancreatic fistula but was not significantly associated with overall morbidity, wound infection, delayed gastric emptying, or mortality. Obesity was associated, however, with prolonged length of stay as obese patients spent an average of 6 days longer in the hospital. Similarly, Rosso et al. examined risk factors for pancreatic fistula and fatty infiltration of the pancreas and found that being overweight (BMI>25 kg/m^2) was associated with greater risk of fatty infiltration and fistula on univariable analysis.[3] Mullen et al. used a larger dataset comprised of ACS NSQIP data for high-risk abdominal surgery including pancreatectomy, gastrectomy, esophagectomy, hepatectomy, and LAR.[1] They found a significantly increased risk of 30-day mortality and wound infection according to BMI. While this study pooled data from multiple surgeries, it does suggest that obesity is associated with poor outcomes for multiple types of high-risk abdominal surgery.

By contrast, other studies have found no significant difference in complications when patients are categorized by BMI. Lermite et al. evaluated predictive factors for developing fistula and delayed gastric emptying and found no association between obesity and either of these complications in 131 consecutive patients undergoing pancreaticuduodenectomy.[5] Williams et al. analyzed their institutional experience with pancreaticoduodenectomy and found that intraoperative bleeding and operative time both increased with greater BMI.[6] Length of hospital stay was also prolonged in obese patients despite no significant differences in complication rate.

When examining long-term outcomes following resection of pancreatic adenocarcinoma, a similarly mixed picture has emerged. Fleming et al. looked at 285 consecutive patients treated at the MD Anderson Cancer Center to determine

predictors of lymph node positivity as well as survival and recurrence.[7] The authors found that morbid obesity (BMI>35 kg/m^2) was associated with an increased probability of positive lymph nodes following resection (OR 12.16, 95% CI 1.58–93.55). The authors also found decreased disease free and overall survival on univariable analysis for patients with BMI>35 kg/m^2 compared to those with BMI≤35 kg/m^2. However, this difference was not significant after adjusting for other factors. Benns et al. undertook a related analysis and found that patients with BMI>30 kg/m^2 had similar survival when compared to those with BMI≤30 kg/m^2.[8]

One potential explanation for these conflicting results is that BMI is an imprecise measure of obesity that does not take into account the actual distribution and quantity of adipose tissue. As our understanding of fat biology has improved, there is an increasing realization that not all adipose tissue is created equal. Visceral/intra-abdominal fat, in particular, has several properties which could promote tumor growth and impact survival. Visceral fat is associated with insulin resistance and the metabolic syndrome which lead to increased serum levels of insulin and insulin-like growth factors that could promote tumor cell growth.[13–15,19] Additionally, visceral fat has been linked to inflammatory cytokines, angiogenic factors, and markers of oxidative stress that help create a microenvironment ripe for tumor expansion and metastasis.[15] Since visceral fat has proven to be an accurate predictor of medical complications of obesity, several groups have evaluated its ability to predict short-term complications following surgery. House et al. examined several measures of visceral fat in addition to BMI to determine which measures of obesity accurately predicted occurrence of postoperative complications.[9] In their series of 356 patients undergoing pancreaticuduodenectomy for adenocarcinoma, the authors found that obesity measured by BMI significantly predicted risk for wound infection but not fistula or overall complication rate. Visceral fat, by contrast, significantly predicted overall complication rate as well as risk of fistula and wound infection. Visceral fat has proven to be a better predictor of complications than BMI in colorectal cancer as well.[10–12] However, to the best of our knowledge, no one has yet evaluated the impact of visceral obesity on long-term outcomes following pancreaticoduodenectomy. Our study represents the first demonstration of an association between visceral fat and survival following resection of pancreatic cancer.

Our initial hypothesis was that greater quantities of visceral fat would be associated with worse outcomes following surgery, but our results did not entirely confirm this hypothesis. Instead, we saw longer survival in patients with the most and the least amounts of visceral fat (first and fourth quartiles). The worst survival was observed in those patients who fell in the middle 50% of visceral fat quantity (second and third quartiles). By contrast, body mass index was not a useful prognostic factor when evaluating survival. There are several potential explanations for this finding. Greater quantities of visceral fat in the setting of pancreatic cancer may represent improved overall health status rather than actual obesity, and this would tend to be reflected by better functional status and prolonged survival seen in quartile 4. The improved survival in those with the least visceral fat might then reflect a balance between overall health and decreasing quantities of any adverse factors secreted by visceral adipose tissue. Diminished survival from patients in the second and third quartiles could represent the biologic impact of factors secreted from adipose tissue (including inflammatory and angiogenic factors) in otherwise moderately healthy individuals.

There are several limitations of the current study. Although patients were analyzed from two separate hospitals, including one private hospital and one Veterans Affairs hospital, all of the patients were still part of a single overall institution so our findings may not generalize to other regions. Additionally, although the majority of patients were tracked in a prospective database, a portion required retrospective chart analysis. Retrospective review can be associated with selection bias as well as increased risk of differential misclassification bias. Additionally, since the visceral fat measurement data was collected retrospectively from preoperative CT scans, the timing of preoperative CT imaging used to quantify visceral fat was not standardized. Consequently, it is difficult to determine whether the quantity of visceral fat measured is a reflection of the pre-cancer state or results from anorexia and cachexia associated with pancreatic cancer. Furthermore, the relatively small number of patients makes it difficult to adequately adjust for all potential confounders which means that residual confounding cannot be completely ruled out. It is also important to note that the findings of a regression model are dependent, at least in part, on the number of cases available for analysis. In our case, the number of available cases limits the number of variables which can be included without over fitting the model and generating spurious results. Consequently, we were forced to balance a need to include relevant variables with the inability to accommodate additional factors which might be considered important. We addressed this problem by limiting our model to only those factors which were most relevant for the primary outcome of survival. Other variables, including stage, grade and nodal status were also considered but did not change the final estimates of hazard ratios (data not shown). The ability to address comorbidities was also limited in our study since the most common comorbidities in our population (diabetes and coronary artery disease) would be expected to have a significant association with obesity regardless of the technique used to measure it. Consequently, we did not specifically include comorbidities in the model because

the correlation increases the likelihood of type II error. A larger study might have been able to compensate for this correlation as well as having the possibility of including more total variables in the final model. Such an analysis might yield different conclusions than the findings outlined in our work.

Conclusions

Despite the above limitations, our findings suggest a relationship between preoperative levels of visceral fat and long-term survival following pancreaticoduodenectomy. This relationship has significant implications for the field of pancreatic cancer surgery. Identifying subsets of patients with improved or worsened outcomes helps both surgeons and medical oncologists to adapt therapy so that more aggressive tumors can receive appropriate therapy. An increasing weight of evidence suggests that direct measures of visceral fat represent a more precise estimate of obesity than the traditional measure of body mass index. Consequently, predictive models based on body mass index will tend to be inaccurate and misleading. As this has already been shown for short-term outcomes, it is important to evaluate how we measure obesity and how it relates to long-term outcomes. Our data suggest that measures of visceral fat merit more study utilizing larger and diverse patient populations in order to establish validity in predicting cancer outcomes.

The views expressed in this article are those of the author(s) and do not necessarily represent the views of the Department of Veterans Affairs.

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2010 SSAT POSTER PRESENTATION

Pancreaticoduodenectomy can be Performed Safely in Patients Aged 80 years and Older

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Abstract
Background Surgery offers the only chance for cure in patients with pancreatic cancer, and a growing number of elderly patients are being offered resection. We examined outcomes after pancreaticoduodenectomy in patients 80 years and older.
Methods We retrospectively collected data on pancreaticoduodenectomy patients from 1992 to 2009 to compare outcomes between patients older and younger than 80 years. Variables were compared using *t*-, Wilcoxon rank-sum, or Fisher's exact tests. Survival was compared using Kaplan–Meier analysis and log-rank test.
Results Patients 80 years and older who underwent pancreaticoduodenectomy were similar with respect to sex, race, blood loss, operative times, reoperation, length of stay, and readmission compared to younger patients. There were no differences in overall complications (47% vs. 51%, $p=0.54$), major complications (19% vs. 25%, $p=0.25$), and mortality (5% vs. 4%, $p=0.53$) when comparing older to younger patients. In a subset who underwent pancreaticoduodenectomy for ductal adenocarcinoma, older patients ($n=45$) had a median survival time of 11.6 months compared to 18.1 months in younger patients ($n=346$; $p<0.01$).
Conclusion Pancreaticoduodenectomy can be performed safely in select patients 80 years and older. Age alone should not dissuade surgeons from offering patients resection, though elderly patients with pancreatic ductal adenocarcinoma appear to have shorter survival than younger patients with the same disease.

Keywords Pancreaticoduodenectomy · Pancreatic resection · Pancreatic ductal adenocarcinoma · Elderly patient · Octogenarian

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Introduction

Pancreatic cancer is the fourth leading cause of cancer-related deaths in the USA with 35,240 estimated deaths in 2009.[1] Age is a risk factor for the development of pancreatic cancer, and the incidence of disease increases with advancing age. In patients aged 60–64 years, the incidence of pancreatic cancer is 29 per 100,000 compared to an incidence of 91 per 100,000 in patients 80–84 years old.[2] Persons older than 70 years represent 9% of the US population and are a rapidly growing group.[3] As the population ages, more elderly patients are diagnosed with pancreatic cancer and referred for treatment of their disease.

Surgery offers the only chance for cure in patients with pancreatic cancer, and a growing number of elderly patients with the disease are being offered resection. Recent reports have found acceptable morbidity and mortality after pancreaticoduodenectomy (PD) performed in patients over 70 years of age.[4–10] However, few reports examine out-

comes after PD in patients aged 80 years and older. We report a single-institution series of PD and compare differences in outcomes between patients older and younger than 80 years of age.

Materials and Methods

We performed a retrospective review of a prospectively maintained database of patients with pancreatic disease. The database is maintained by The Pancreas Center of Columbia University Medical Center (CUMC) and includes the patients of four surgeons (JA, JC, JL, and BS). After approval from the institutional review board and in compliance with Health Insurance Portability and Accountability Act regulations, we queried our database to identify all patients who underwent PD at CUMC from 1992 through 2009.

Descriptive data were collected by review of patients' medical records. Preoperative variables included age, sex, race, neoadjuvant therapy, comorbidity (defined as the presence of any medical or surgical condition), and major comorbidity (defined as the presence of coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), or chronic kidney disease (CKD)). Intraoperative variables were obtained from nurse, anesthesiologist, and surgeon reports. Operating room (OR) time was defined as the time between patient entry into and exit from the OR. Anesthesia time was defined as the time between start of anesthesia care in the OR and patient exit from the OR. Incision time was defined as the time between incision start and incision close. Pathologic diagnosis was determined from final pathology reports. Perioperative complications were gathered from daily progress notes and discharge summaries and graded using the system proposed by De Oliveira et al.[11] Overall morbidity was defined as any complication, and major morbidity was defined as complications grade III and greater. Pancreatic fistula was assessed and graded according to the International Study Group on Pancreatic Fistula recommendations.[12] Length of stay (LOS) was calculated from date of operation to date of hospital discharge. Readmission rate was defined as readmission within 30 days of hospital discharge. Perioperative mortality was defined as death within 30 days of the operation or within the same hospital admission as the operation.

All operations were performed by four pancreatic surgeons (JA, JC, JL, and BS) using our institution's standardized technique. Pancreatic–enteric continuity was restored via pancreaticojejunostomy in all cases. Biases at our institution include pylorus-preserving resections when oncologically appropriate, dissection of peripancreatic lymph nodes only, routine placement of tube gastrostomy, and prophylactic antibiotics. Operative drains are placed at the surgeon's discretion. Pancreatic duct stent, tube jejunostomy, prophylactic octreotide, and total parenteral nutrition are not routinely used.

Patients were grouped by age for comparison. The older group was defined as patients aged 80 years and older; the younger group was defined as patients younger than 80 years. To evaluate disease-specific outcomes, we limited a subset of patients to those who underwent PD for pancreatic ductal adenocarcinoma (n=391). Detailed pathologic data were collected from final pathology reports including tumor differentiation, greatest tumor diameter, lymph node and margin status, and American Joint Committee on Cancer (AJCC) stage.[13] Patients who received neoadjuvant therapy were excluded from the analysis on pathologic characteristics because therapy alters the true pathology (n=89).

Continuous variables were compared using Student's t test or Wilcoxon rank-sum test. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test as appropriate. Continuous variables were reported as median and interquartile range (IQR). Categorical variables were reported as number and percentage (%). Survival probabilities were estimated using Kaplan–Meier methods, and strata were compared using the log-rank test. Univariate analyses were conducted to evaluate the association of clinical variables and risk factors with overall survival. Relative risks (RR) and 95% confidence intervals (CI) were calculated by fitting Cox proportional hazards models. Person-months of follow-up were counted from the time of operation until the date of death or the date of last follow-up, whichever came first. Clinical variables evaluated included age, sex, race, and comorbidity; risk factors evaluated included venous resection, complication, lymph nodes, and stage. A p value of less than 0.05 was considered statistically significant. Statistical analyses were conducted using R and SAS statistical software programs.

Results

From February 5, 1992 through December 31, 2009, a total of 125 patients aged 80 years and older were brought to the operating room for pancreatic resection, with 99 (79.2%) completed and 26 (20.8%) aborted. Attempted pancreatic resections included PD, distal pancreatectomy, total pancreatectomy, partial pancreatectomy, and central pancreatectomy. At our institution, 9.5% of all PDs have been performed on patients aged 80 years and older, with most performed after 2005 (Fig. 1). Of the patients brought to the operating room for PD, a total of 85 were attempted with 74 (87.1%) completed and 11 (12.9%) aborted. Reasons for aborting PD included the presence of metastatic disease in

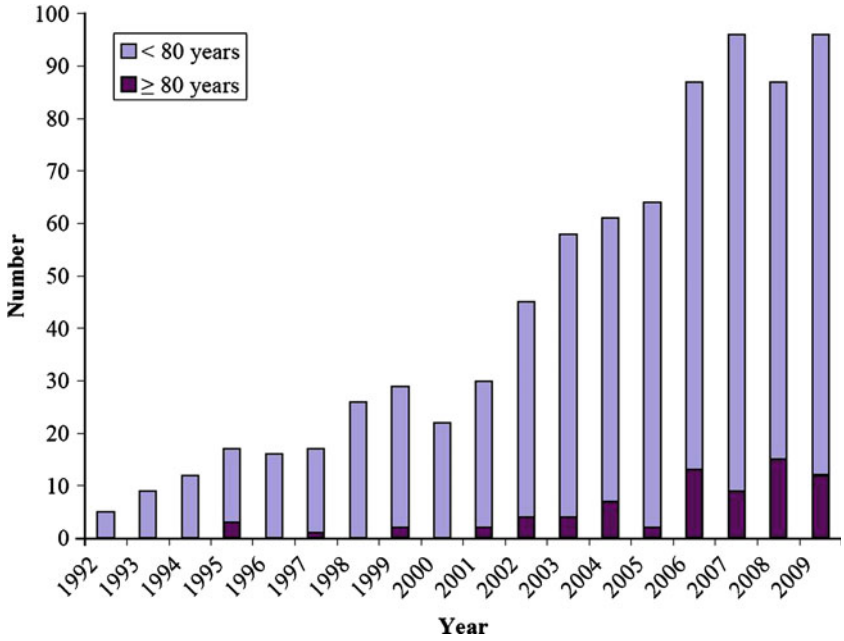

Fig. 1 Annual distribution of pancreaticoduodenectomy performed in patients aged 80 years and older over the study period

seven patients and locally advanced disease involving major vessels in four patients. During the same time period, 703 PDs were completed in patients younger than 80 years of age.

Patient Characteristics and Outcomes for All PD Patients

There were no statistically significant differences in preoperative variables between the older and younger groups. The median age was 82.6 years (IQR 81.4–84.4 years) in the older group and 64.1 years (IQR 55.2–71.2 years) in the younger group. There were 29 (39.2%) men and 45 (60.8%) women in the older group and 349 (49.6%) men and 354 (50.4%) women in the younger group (p=0.09), with the majority being Caucasian in both groups (p=0.25). Sixty-nine (93.2%) older patients had a comorbidity versus 552 (78.5%) younger patients (p<0.01). The incidences of CAD (10.8% vs. 11.9%, p>0.99), COPD (1.4% vs. 3.7%, p=0.50), DM (24.3% vs. 18.3%, p=0.21), and CKD (5.4% vs. 2.1%, p=0.10) were similar between the older and younger groups (Table 1).

Of the 74 PDs performed in the older group, 58 (78.4%) were for malignant disease. The most common malignancies included pancreatic ductal adenocarcinoma in 45 (60.8%), ampullary adenocarcinoma in four (5.4%), and cholangiocarcinoma in two (2.7%) patients. Of the 703 PDs performed in the younger group, 520 (74.0%) were for malignant disease and included pancreatic ductal adenocarcinoma in 346

Table 1 Demographics and preoperative comorbidities of patients undergoing pancreaticoduodenectomy

Variable	≥80years (n=74)	<80years (n=703)	p value
Demographics			
Age, median (IQR)	82.6 (81.4–84.4)	64.1 (55.2–71.2)	
Sex, M/F	29/45	349/354	0.09
Race (%)[a]			
Caucasian	60 (81.1)	528 (75.1)	0.25
Hispanic	3 (4.0)	55 (7.8)	
Black	2 (2.7)	47 (6.7)	
Asian	2 (2.7)	24 (3.4)	
Other	7 (9.5)	49 (7.0)	
Any comorbidity (%)	69 (93.2)	552 (78.5)	<0.01
Major comorbidity (%)[b]			
CAD	8 (10.8)	84 (11.9)	>0.99
COPD	1 (1.4)	26 (3.7)	0.50
DM	18 (24.3)	129 (18.3)	0.21
CKD	4 (5.4)	15 (2.1)	0.10

IQR interquartile range, *CAD* coronary artery disease, *COPD* chronic obstructive pulmonary disease, *DM* diabetes mellitus, *CKD* chronic kidney disease (CKD)

[a] Statistical analysis was performed on Caucasian versus all other races

[b] Some patients had more than one major comorbidity

Table 2 Pathologic characteristics of patients undergoing pancreaticoduodenectomy

Variable	≥80years (n=74)	<80years (n=703)	p value
Benign (%)	16 (21.6)	183 (26.0)	0.41
Malignant (%)	58 (78.4)	520 (74.0)	
Specific pathology (%)			
Pancreatic adenocarcinoma	45 (60.8)	346 (49.2)	0.06
Ampullary adenocarcinoma	4 (5.4)	71 (10.1)	
Duodenal adenocarcinoma	1 (1.4)	22 (3.1)	
Cholangiocarcinoma	2 (2.7)	25 (3.6)	
Cystadenocarcinoma	0 (0)	3 (0.4)	
Pancreatic neuroendocrine tumor	4 (5.4)	44 (6.3)	
Mucinous cystic neoplasm	1 (1.4)	10 (1.4)	
Serous cystadenoma	2 (2.7)	15 (2.1)	
IPMN	5 (6.8)	48 (6.8)	
Pseudocyst	0 (0)	2 (0.3)	
Simple cyst	0 (0)	4 (0.6)	
Ampullary adenoma	5 (6.8)	19 (2.7)	
Duodenal adenoma	1 (1.4)	18 (2.6)	
Pancreatitis	0 (0)	36 (5.1)	
Solid pseudopapillary neoplasm	0 (0)	6 (0.9)	
Other	4 (5.4)	34 (4.8)	

IPMN intraductal papillary mucinous neoplasm

(49.2%), ampullary adenocarcinoma in 71 (10.1%), and cholangiocarcinoma in 25 (3.6%) patients (Table 2).

Forty-nine (66.2%) older patients underwent pylorus-preserving PD and 25 (33.8%) underwent classic PD compared to 440 (62.6%) younger patients who underwent pylorus-preserving PD and 263 (37.4%) who underwent classic PD (p=0.54). Eleven (14.9%) older patients underwent venous resection and reconstruction compared to 131 (18.6%) younger patients (p=0.42). There were no differences in median OR time (399 min, IQR 356–451 min vs. 430 min, IQR 375–521 min; p=0.07), anesthesia time (360 min, IQR 306–404 min vs. 377 min, IQR 325–460 min; p=0.12), or incision time (315 min, IQR 262–369 min vs. 329 min, IQR 283–400 min; p=0.16) between the older and younger groups. Older patients had similar median intraoperative blood loss compared to younger patients (800 mL, IQR 500–1,325 mL vs. 1m000 mL, IQR 500–1,500 mL; p=0.15; Table 3).

Patients in the older group had similar overall (47.3% vs. 51.1%, p=0.54) and major complication rates (18.9% vs. 24.9%, p=0.25) compared to younger patients. There were no statistically significant differences in pancreatic fistula rate (4.1% vs. 7.4%, p=0.47). Of the patients who developed pancreatic fistulae, two (66.7%) were clinically significant in the older group compared to 42 (80.8%) in the younger group (p=0.50). The groups were similar with respect to rates of reoperation (5.4% vs. 8.7%, p=0.38) and readmission (2.7% vs. 7.8%, p=0.16). Patients in the older group had similar

Table 3 Intraoperative characteristics of patient undergoing pancreaticoduodenectomy

Variable	≥80years (n=74)	<80years (n=703)	p value
Type of resection (%)			
Classic	49 (66.2)	440 (62.6)	0.54
Pylorus-preserving	25 (33.8)	263 (37.4)	
Venous resection (%)	11 (14.9)	131 (18.6)	0.42
Operating room time, minutes			
Median (IQR)	399 (356–451)	430 (375–521)	0.07
Anesthesia time, minutes			
Median (IQR)	360 (306–404)	377 (325–460)	0.12
Incision time, minutes			
Median (IQR)	315 (262–369)	329 (283–400)	0.16
Intraoperative blood loss, mL			
Median (IQR)	800 (500–1,325)	1,000 (500–1,500)	0.15

IQR interquartile range

Table 4 Postoperative characteristics of patients undergoing pancreaticoduodenectomy

Variable	≥80years (n=74)	<80years (n=703)	p value
Overall morbidity (%)	35 (47.3)	359 (51.1)	0.54
Major morbidity (%)	14 (18.9)	175 (24.9)	0.25
Pancreatic fistula (%)	3 (4.1)	52 (7.4)	0.47
Grade A	1	10	
Grade B	1	24	
Grade C	1	18	
Reoperation (%)	4 (5.4)	61 (8.7)	0.38
Readmission (%)	2 (2.7)	55 (7.8)	0.16
Mortality (%)	4 (5.4)	27 (3.8)	0.53
Length of stay, days			
Median (IQR)	10.5 (8–13)	11.0 (8–16)	0.41

IQR interquartile range

median LOS compared to those in the younger group (10.5 days, IQR 8–13 days vs. 11 days, IQR 8–16 days; p=0.41). There was no difference in mortality between the older and younger groups (5.4% vs. 3.8%, p=0.53; Table 4).

Subset Analysis of Patients with Pancreatic Ductal Adenocarcinoma

PD was performed for pancreatic ductal adenocarcinoma in 45 (60.8%) patients aged 80 years and older and in 346 (49.2%) patients younger than 80 years. The median age in the older group was 82.1 years (IQR 81.3–83.9 years) years and 64.5 years (IQR 58.0–70.1 years) in the younger group. There was no difference in sex or race between groups. Forty-two (93.3%) older patients had any comorbidity versus 267 (77.2%) younger patients (p=0.01). The incidences of CAD, COPD, DM, and CKD were similar between the older and younger groups. Six (13.3%) older patients received neoadjuvant therapy compared to 89 (25.7%) younger patients (p=0.09; Table 5).

A similar proportion of patients in each group had pylorus-preserving PDs (28.9% vs. 28.0%, p=0.90). Older patients underwent venous resection and reconstruction less frequently compared to younger patients (15.6% vs. 31.8%, p=0.02). There were no differences in median OR time, anesthesia time, incision time, and intraoperative blood loss between the older and younger groups (Table 6).

On final pathology, AJCC staging was similar between groups with the majority of patients having stage II disease in both groups (92.3% vs. 93.4%, p=0.20). The median lesion size was 3.0 cm in both groups (p=0.72). Twelve (30.8%) older patients had positive resection margins compared to 58 (22.6%) younger patients (p=0.31). The groups had similar rates of positive lymph nodes (74.4% vs. 73.2%, p>0.99). The groups also had a similar distribution of tumor differentiation with the majority of patients having

Table 5 Pancreaticoduodenectomy for ductal adenocarcinoma: demographics and preoperative comorbidities

Variable	≥80years (n=45)	<80years (n=346)	p value
Demographics			
Age, median (IQR)	82.1 (81.3–83.9)	64.5 (58.0–71.0)	
Sex, M/F	18/27	179/167	0.14
Race (%)[a]			
Caucasian	38 (84.4)	276 (79.8)	0.34
Hispanic	1 (2.2)	15 (4.3)	
Black	0 (0)	19 (5.5)	
Asian	0 (0)	6 (1.7)	
Other	6 (13.3)	30 (8.7)	
Any comorbidity (%)	42 (93.3)	267 (77.2)	0.01
Major comorbidity (%)			
CAD	5 (10.9)	40 (11.6)	>0.99
COPD	0 (0)	11 (3.2)	0.62
DM	15 (33.3)	86 (24.9)	0.22
CKD	2 (4.4)	13 (3.8)	0.69
Neoadjuvant therapy (%)	6 (13.3)	89 (25.7)	0.09

IQR interquartile range, *CAD* coronary artery disease, *COPD* chronic obstructive pulmonary disease, *DM* diabetes mellitus, *CKD* chronic kidney disease

[a] Statistical analysis was performed on Caucasian versus all other races

[b] Some patients had more than one major comorbidity

Table 6 Pancreaticoduodenectomy for ductal adenocarcinoma: intraoperative characteristics

Variable	≥80years (n=45)	<80years (n=346)	p value
Type of resection (%)			
Classic	32 (71.1)	249 (72.0)	0.90
Pylorus-preserving	13 (28.9)	97 (28.0)	
Venous resection (%)	7 (15.6)	110 (31.8)	0.02
Operating room time, minutes			
Median (IQR)	420 (385–510)	475 (391–571)	0.09
Anesthesia time, minutes			
Median (IQR)	370 (344–445)	408 (330–476)	0.35
Incision time, minutes			
Median (IQR)	337 (309–393)	349 (290–425)	0.44
Intraoperative blood loss, mL			
Median (IQR)	900 (500–1,500)	1,000 (700–2,000)	0.07

IQR interquartile range

poorly differentiated tumors (64.1% vs. 50.6%, p=0.13). Patients who received neoadjuvant therapy were excluded from this analysis (Table 7).

Compared to the younger group, patients in the older group had similar rates of overall (48.9% vs. 49.4%, p=0.95) and major complications (22.2% vs. 24.6%, p=0.85), and overall (2.3% vs. 4.6%, p=0.43) and clinically significant pancreatic fistulae (100% vs. 87.5%, p>0.99). There were no differences in rates of reoperation (6.7% vs. 9.2%, p=0.78) and readmission (2.2% vs. 7.5%, p=0.34). Patients in the older group had similar median LOS compared to those in the younger group (11 days, IQR 8–14 days vs. 10 days, IQR 8–16 days; p=0.63). There was no difference in mortality between the older and younger groups (4.4% vs. 4.3%, p=0.71; Table 8). Median survival time for patients in the older group was 11.6 months versus 18.1 months for patients in the younger group (p<0.01). Estimated 5-year survival was less than 5% in the older group versus 14% in the younger group (Fig. 2).

Table 7 Pancreaticoduodenectomy for ductal adenocarcinoma: pathologic characteristics[a]

Variable	≥80years (n=39)	<80years (n=257)	p value
Stage (AJCC[b]) (%)			
Stage I	0 (0)	8 (3.1)	0.20
Stage II	36 (92.3)	240 (93.4)	
Stage III	2 (5.1)	9 (3.5)	
Stage IV	1 (2.6)	0 (0)	
Lesion size, cm			
Median (IQR)	3.0 (2.5–3.8)	3.0 (2.2–4.0)	0.72
Resection margins (%)			
Positive	12 (30.8)	58 (22.6)	0.31
Negative	27 (39.2)	199 (77.4)	
Lymph nodes (%)			
Positive	29 (74.4)	188 (73.2)	>0.99
Negative	10 (25.6)	69 (26.8)	
Differentiation (%)[c]			
Well	1 (2.6)	15 (5.8)	0.13
Moderate	13 (33.3)	109 (42.4)	
Poor	25 (64.1)	130 (50.6)	

IQR interquartile range

[a] Patients who received neoadjuvant therapy were excluded from this analysis as data were not available on all patients

[b] American Joint Committee on Cancer (AJCC). Statistical analysis performed on early stage (0, I, and II) versus late stage (III and IV)

[c] Statistical analysis performed on low-grade (well and moderate differentiation) versus high-grade (poor differentiation)

As median survival time among patients with pancreatic ductal adenocarcinoma was slightly shorter for those in the older compared to younger group, we examined clinical variables and risk factors that may be associated with poorer survival in patients aged 80 years and older. In univariate analysis, only non-Caucasian race (RR=6.14, 95%CI=2.22–16.96) and positive lymph nodes (RR=2.54, 95% CI=1.09–5.93) were associated with shorter survival time among elderly patients. Risk was slightly stronger when mutually adjusted. In the multivariate model, being female (RR=3.20, 95%CI=1.08–9.50), non-Caucasian (RR=8.98, 95%CI=2.19–36.87) or having positive lymph nodes (RR=6.18, 95%CI=1.49–25.6) were associated with shorter survival time. However, due to small case numbers, we had limited power to examine these factors.

Discussion

Advancing age is a risk factor for the development of pancreatic cancer. As the US' population ages, more elderly patients are being diagnosed with the disease and referred for surgery. Many recent series have evaluated outcomes after PD in patients older than 70 years and have

Table 8 Pancreaticoduodenectomy for ductal adenocarcinoma: postoperative characteristics

Variable	≥80years (n=45)	<80years (n=346)	p value
Overall morbidity (%)	22 (48.9)	171 (49.4)	0.95
Major morbidity (%)	10 (22.2)	85 (24.6)	0.85
Pancreatic fistula (%)	1 (2.3)	16 (4.6)	0.43
Grade A	0	2	
Grade B	1	4	
Grade C	0	10	
Reoperation (%)	3 (6.7)	32 (9.2)	0.78
Readmission (%)	1 (2.2)	26 (7.5)	0.34
Mortality (%)	2 (4.4)	15 (4.3)	0.71
Length of stay, days			
Median (IQR)	11 (8–14)	10 (8–16)	0.63

Interquartile range (IQR)

demonstrated acceptable morbidity and mortality. These series also have found prolonged survival in select elderly patients.[4,10] Three series to date examined pancreatic resection in patients older than 80 years, with only two evaluating outcomes after PD.[14–16] The aim of this study was to assess a single institution's experience with PD in patients aged 80 years and older.

The majority of older patients who underwent PD were women, which mirrors the predominantly female demographic of the aging US population.[3] Although more patients had a coexistent medical condition in the older group, the incidence of a major comorbidity, such as CAD, COPD, DM, and CKD, was similar to that in the younger group. There were no significant differences in operative characteristics and final pathology between groups. Patients aged 80 years and older had remarkably similar outcomes compared to younger patients with no differences in morbidity, pancreatic fistula, and mortality. Older patients also had similar lengths of stay compared to younger patients. Together, these data suggest that PD can be performed safely in patients aged 80 years and older.

Results in the literature differ with respect to morbidity and mortality. Chen et al.[15] compared patients over 80 years of age to patients 70–80 years old and found similar morbidity (51.0% vs. 56.0%) and mortality (13.0% vs. 12.0%) between age groups. This study, however, had a limited sample size with only 16 patients in the older group. In contrast, Makary et al.[14] updated the series of Sohn et al.[17] to examine outcomes after PD in 207 patients aged 80 years and older. Comparing 80–89-year-old patients to those younger than 80 years, the authors found significant differences in preoperative comorbidity and postoperative morbidity (52.8% vs. 41.6%) and mortality (4.1% vs. 1.7%). In their multivariate logistic regression analysis, they found that CAD and COPD were associated with increased morbidity and mortality and concluded that major comorbidity impacted perioperative outcomes more so than age alone. Our data showed no significant differences in preoperative comorbidity and postoperative morbidity and mortality between older and younger PD patients. As the criteria used to select elderly patients for PD are institution specific, these differences in comorbid medical conditions

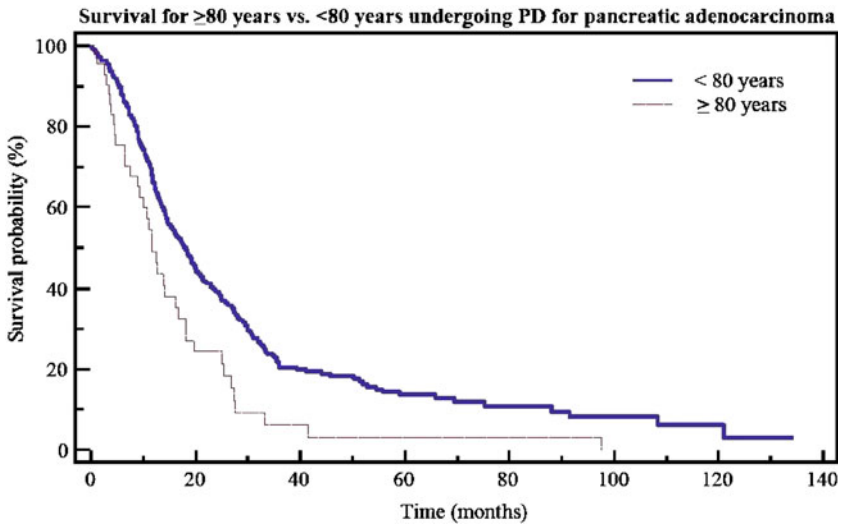

Fig. 2 Kaplan–Meier survival curves of patients who underwent pancreaticoduodenectomy for pancreatic ductal adenocarcinoma aged 80 years and older compared to younger patients with the same disease show decreased survival (p<0.01)

and postoperative outcomes likely reflect inherent selection biases. Moreover, the use of different systems to classify comorbidities and complications make it difficult to compare certain outcomes across the literature.

Pancreatic fistula is one of the most serious complications following PD, but also one of the most problematic to compare across retrospective studies. In the literature, rates of pancreatic fistula after PD range from 3% to 22% in patients over 70 years of age, and from 10% to 13% in patients over 80 years of age.[4] Despite retrospective grading by ISGPF guidelines, the 4.1% pancreatic fistula rate in older PD patients in this series likely underestimates the true rate. We do not routinely place operative drains during PD and, in patients with drains, do not routinely monitor serum and drain amylase levels. Only patients who manifest clinical (e.g., abdominal pain) or subclinical (e.g., change in the character of drain fluid) signs that prompt work-up and treatment for pancreatic fistula are captured. Hence, our pancreatic fistula rate likely misses grade A fistulae as evidenced by the disproportionate incidence of grade B and C fistulae (80% of all pancreatic fistulae in this series).

Survival after PD differs significantly according to pathology. Five-year relative survival rates after PD for duodenal carcinoma, for example, range from 25% to 60%[18] whereas those for cholangiocarcinoma range from 15% to 25%.[19,20] Thus, for an analysis of disease-specific outcomes after PD, we examined a subset of patients with pancreatic ductal adenocarcinoma only. Operative characteristics were similar between age groups. Postoperative outcomes also were similar with no differences in morbidity, pancreatic fistula, and mortality. Finally, patients aged 80 years and older who underwent PD for ductal adenocarcinoma had decreased median survival time (11.6 months) compared to younger patients with the same disease (18.6 months). These median survival times are similar to those reported by Makary et al. (11 and 18 months, respectively). Other series in the literature also demonstrated decreased survival time after PD in older versus younger patients, but these series examined survival of all periampullary carcinoma.[10,21] It is difficult to determine if decreased life expectancy or the disease itself diminishes survival without comparing elderly patients with the same disease who are eligible for resection and have surgery to those who are eligible for resection and do not have surgery. In addition, the comparison is difficult because those individuals who have and do not have surgery may be different based on other non-measured confounders.

In our analysis, we examined survival time of patients using Kaplan–Meier and Cox proportional hazard models. In the elderly group, being female, non-Caucasian, or having positive lymph nodes correlated with poorer survival, though we had limited power due to small case numbers. Other unmeasured clinical variables and risk factors may affect survival. Furthermore, these unmeasured factors may differ by age and thus, differentially affect survival of patients with pancreatic ductal adenocarcinoma who undergo PD.

Conclusion

PD can be performed safely in select patients aged 80 years and older. As our data demonstrate, careful patient selection can lead to acceptable morbidity and mortality after PD and age alone should not dissuade surgeons from offering elderly patients surgery. Surgical resection offers patients with pancreatic ductal adenocarcinoma the only chance for cure, though older patients appear to have shorter survival time than younger patients with the same disease.

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2010 SSAT QUICK SHOT PRESENTATION

Prophylactic Pancreatectomy for Intraductal Papillary Mucinous Neoplasm Does Not Negatively Impact Quality of Life: A Preliminary Study

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Abstract
Background Uncertainties remain over whether prophylactic surgery or surveillance is the better management option for intraductal papillary mucinous neoplasm of the pancreas. The aim of this preliminary study was to determine if differences in anxiety and quality of life exist between patients who have surgery or undergo surveillance.
Methods Recruited patients were given the Hospital Anxiety and Depression Scale, a general survey that evaluates anxiety, and the Functional Assessment of Cancer Therapy-Pancreas, a disease-specific survey that assesses quality of life. Questionnaires were scored by standardized algorithms and compared using Student's *t* test or Wilcoxon rank-sum test.
Results Sixteen patients had surgery and 16 patients were undergoing surveillance. Mean age was 66.8±19.9 years. Responses from both groups were remarkably similar. Surgery patients scored higher on the anxiety questionnaire than surveillance patients, although not statistically significant (p=0.09). Surgery patients scored lower on the functional well-being domain of the quality-of-life instrument (p=0.03), though there were no differences in overall quality of life.
Conclusion Prophylactic surgery does not reduce quality of life, and a protocol of surveillance does not appear to generate undue anxiety in this select patient group. Further investigation with more patients is required to validate these findings.

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Keywords Intraductal papillary mucinous neoplasm · IPMN · Quality of life · Prophylactic surgery · Pancreatectomy

Introduction

The recent increased access to high-resolution cross-sectional abdominal imaging has enabled clinicians to identify a growing number of patients with cystic lesions of the pancreas. A majority of these patients have intraductal papillary mucinous neoplasm (IPMN), a well-characterized, mucin-producing cystic lesion of the pancreas with clear malignant potential. Similar to the adenoma–carcinoma sequence seen in colon[1] and pancreatic[2] cancer, the indolent course of IPMN follows a defined pattern, progressing from intraductal papillary mucinous adenoma to IPMN with dysplasia to IPMN with carcinoma in situ and eventually to invasive carcinoma. A review of the

literature reveals that the incidence of malignancy associated with IPMN ranges from 19% to 46% with a mean incidence of 37%. Survival for patients with noninvasive resected disease is excellent; however, once invasive disease develops, the 5-year survival ranges from 31% to 58%.[3–7]

Although international guidelines have been established,[8–10] the management of patients with IPMN remains controversial. Prophylactic surgical resection decreases the potential for developing pancreatic cancer but carries certain risks such as postoperative complications, the development of diabetes and pancreatic exocrine insufficiency, and a small chance of mortality. Surveillance avoids the risks of surgery but leaves the lesion and requires yearly radiographic and endoscopic abdominal imaging that may heighten patient anxiety. Of paramount concerns to patients and their physicians are the expected anxiety, functional impairment, and overall quality of life (QoL) associated with each pathway. To date, there are little data in the literature to help patients and physicians anticipate these outcomes. The aim of this preliminary study was to evaluate the differences in anxiety and QoL between patients with IPMN who have prophylactic surgery and who undergo surveillance.

Materials and Methods

After approval from the institutional review board and in compliance with Health Insurance Portability and Accountability Act regulations, patients with a diagnosis of IPMN were identified retrospectively and recruited into the study through The Pancreas Center of Columbia University Medical Center (CUMC) via mail, telephone, or office visit. All patients provided informed consent and were recruited between June 1, 2009, and March 15, 2010.

At our institution, patients and their physicians choose either surgery or surveillance following a standard protocol (Fig. 1). For the surgery group, we recruited patients who had undergone pancreatic resection for IPMN as documented on final pathology. We did not recruit patients who had undergone total pancreatectomy for IPMN because the operation is associated with a 100% incidence of postoperative diabetes and pancreatic exocrine insufficiency, sequelae that impact patient quality of life. Time since operation was defined as the number of months between the date of operation and the date of recruitment. For the surveillance group, we recruited patients who were undergoing surveillance for a diagnosis of IPMN as documented by radiography (computed tomography (CT), magnetic resonance

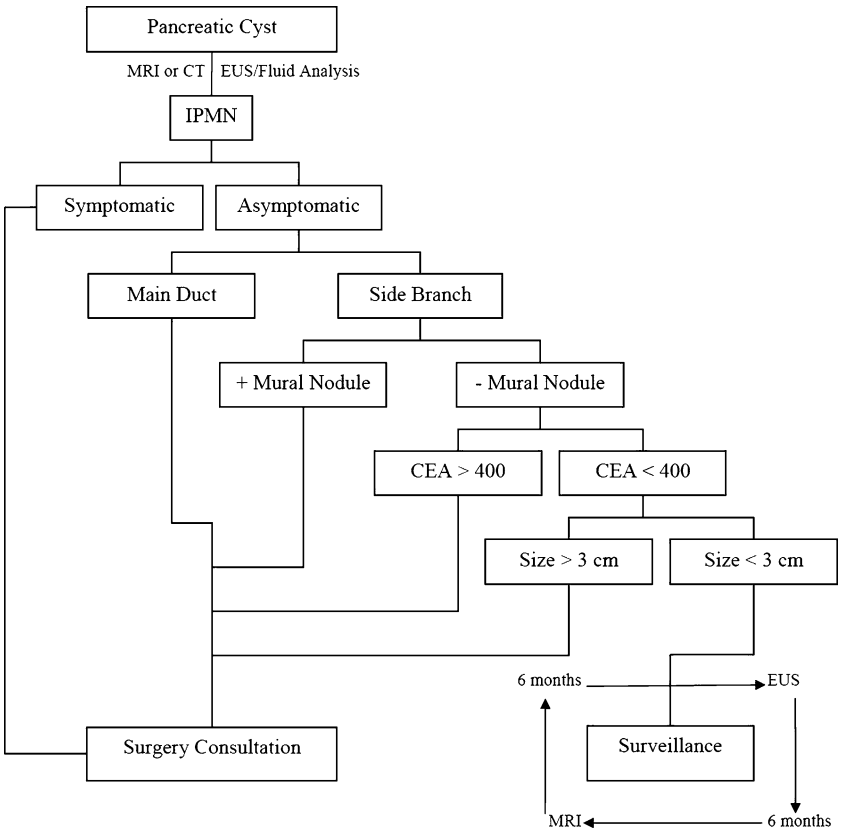

Fig. 1 Decision-making algorithm outlining the clinical management of pancreatic cysts at our institution. *MRI* Magnetic resonance imaging, *CT* computed tomography, *EUS* endoscopic ultrasound

imaging (MRI), endoscopic ultrasound (EUS)), or cytology (fine-needle aspiration). Our institutional protocol of surveillance includes MRI and EUS, alternating every 6 months. Time since diagnosis was defined as the number of months between start of surveillance and the date of recruitment.

We retrospectively reviewed the medical records of all patients in the study. For the surgery group, pathologic diagnosis was determined from final pathology reports. Perioperative complications were gathered from daily progress notes and discharge summaries and graded using the system proposed by DeOliveira and colleagues.[11] Overall morbidity was defined as any complication, and major morbidity was defined as complications grade III and greater. Pancreatic fistula was assessed according to the International Study Group on Pancreatic Fistula recommendations.[12] Length of stay (LOS) was calculated from date of operation to date of hospital discharge. Readmission was defined as readmission within 30 days of hospital discharge. For the surveillance group, presumed pathologic diagnosis of IPMN was determined from final radiology and cytology reports, where applicable.

All patients in both groups received three questionnaires at the time of recruitment into the study: our non-validated, institutional general health survey, the Hospital Anxiety and Depression Scale (HADS), and the Functional Assessment of Cancer Therapy-Pancreas (FACT-Pa). Questionnaires were administered one time only. Our institutional general health survey evaluates demographics, presenting symptoms, comorbidities, and postoperative pancreatic endocrine, and exocrine insufficiency, where applicable. Major comorbidity was defined as the presence of diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), or coronary artery disease (CAD).

The HADS questionnaire identifies caseness of (i.e., possible and probable) anxiety disorders and depression among patients in non-psychiatric clinical settings. To eliminate the possible confusion introduced by somatic disorders, all symptoms of anxiety that overlap with physical disorders such as dizziness, headaches, and insomnia are excluded from the instrument. The HADS is divided into an anxiety subscale (HADS-A) and a depression subscale (HADS-D). For the purposes of this study, we evaluated the HADS-A only. The HADS-A contains seven items, scored 0 to 3, for total scores that range from 0 to 21. A score greater than 8 indicates increased levels of anxiety.[13]

The FACT-Pa is a generic and pancreatic disease-specific health status questionnaire that evaluates patient QoL during the last 7 days. Subjects are scored against age- and gender-matched controls, allowing comparisons of disease burden against the norm.[14] The questionnaire evaluates four separate domains of QoL including physical well-being, social well-being, emotional well-being, and functional well-being. These domains can be evaluated together for an overall composite score and separately for individual domain scores. The adjusted composite score is expressed in logits and transformed into a 0 to 144 scale, with 0 representing worst QoL and 144 representing best QoL.

Categorical variables were compared using Pearson's chi-squared test or Fisher's exact test when appropriate. Continuous variables were compared using Student's t test or Wilcoxon rank-sum test. The validated instruments were scored according to their respective algorithms and compared using Student's t test or Wilcoxon rank-sum test based on the normalcy of the distribution. A p value of less than 0.05 was considered statistically significant.

Results

Sixteen patients who had pancreatic resection for IPMN between May 20, 2002, and April 27, 2009, were recruited to the surgery group. Sixteen patients who were undergoing surveillance for IPMN diagnosed between March 1, 2003, and February 9, 2010, were recruited to the surveillance group. The median time since operation was 17.1 months in the surgery group, and the median time since diagnosis was 24.9 months in the surveillance group ($p=0.37$). The mean age in the surgery group was 68.0±13.0 versus 73.4± 10.6 years in the surveillance group ($p=0.21$). There were 11 (68.7%) women and five (31.3%) men in the surgery group and seven (43.7%) women and nine (56.3%) men in the surveillance group ($p=0.29$). Fifteen patients were Caucasian and one was Hispanic in the surgery group whereas all of the patients were Caucasian in the surveillance group.

In the surgery group, seven (43.7%) patients were found to have IPMN incidentally, three (18.7%) presented with abdominal symptoms, one (6.3%) presented with an episode of pancreatitis, and five (31.3%) were undergoing surveillance for IPMN when a change in cyst character initiated surgical evaluation. In the surveillance group, 13 (81.3%) patients were found to have IPMN incidentally, two (12.5%) presented with abdominal symptoms, and one (6.2%) presented with an episode of pancreatitis. Seven (43.7%) patients in the surgery group had a major comorbidity, including four patients with DM, one patient with COPD, and two patients with CAD. Nine (56.3%) patients in the surveillance group had a major comorbidity, including five patients with DM and four patients with CAD. There was no difference in incidence of major comorbidity between the groups ($p=0.72$), and no patient in the surveillance group had a comorbidity that would preclude surgical resection of IPMN (Table 1).

The types of pancreatic resection performed in the surgery group included seven (43.7%) pancreaticoduodenectomies, seven (43.7%) distal pancreatectomies, and two (12.6%) central pancreatectomies. Seven (43.7%) patients had postoperative complications, three (18.7%) of whom had major

Table 1 Demographics and preoperative characteristics of IPMN patients in the surgery and surveillance groups

Variable	Surgery (n=16)	Surveillance (n=16)	p value
Demographics			
Mean age, year (SD)	68.0 (13.0)	73.4 (10.6)	0.21
Gender, F/M	11/5	7/9	0.29
Race			
Caucasian	15	16	1.00
Hispanic	1	0	
Presenting symptoms			
Incidental (%)	7 (43.7)	13 (81.3)	0.07
Abdominal symptoms	3	2	
Pancreatitis	1	1	
Change in cyst	5	0	
Comorbidities (%)	7 (43.7)	9 (56.3)	0.72
DM	4	5	
COPD	1	0	
CAD	2	4	

SD standard deviation, *DM* diabetes mellitus, *COPD* chronic obstructive pulmonary disease, *CAD* coronary artery disease

complications. All of the major complications were grade C pancreatic fistulae requiring endoscopic retrograde cholangiopancreatography with pancreatic duct stent placement in two patients and CT-guided drain placement in one patient. Two fistulae occurred after distal pancreatectomy and one fistula occurred after central pancreatectomy. The minor complications included two patients with delayed gastric emptying, one patient with a urinary tract infection and wound infection, and one patient with an episode of atrial fibrillation. No patient required reoperation. The median LOS was 7 days. Two (12.6%) patients required readmission. Four (25%) patients developed pancreatic endocrine insufficiency, with one patient who developed new-onset diabetes and three preoperative diabetics who required an escalation of blood glucose control regimen from oral hypoglycemic medication to insulin injection. Three (18.7%) patients developed pancreatic exocrine insufficiency requiring postoperative pancreatic enzyme supplementation (Table 2).

Table 2 Perioperative characteristics of IPMN patients in the surgery group

Variable	Surgery (n=16)
Resection (%)	
Pancreaticoduodenectomy	7 (43.7)
Distal pancreatectomy	7 (43.7)
Central pancreatectomy	2 (12.6)
Any complication (%)	7 (43.7)
Major complication (%)	3 (18.7)
Pancreatic fistula (%)	3 (18.7)
Reoperation (%)	0 (0)
Readmission (%)	2 (12.6)
Endocrine insufficiency (%)	4 (25.0)
Exocrine insufficiency (%)	3 (18.7)

Final pathologic examination after pancreatectomy revealed side-branch IPMN in 10 (62.5%) patients and main duct IPMN in six (37.5%) patients. No patient with side-branch IPMN had evidence of invasive carcinoma whereas one patient with main duct IPMN had a microscopic focus of invasive carcinoma. Four (25%) patients had evidence of IPMN on the surgical margin, three with low-grade dysplasia and one with moderate-grade dysplasia. All patients in the surveillance group had side-branch IPMN by radiographic and/or cytologic evaluation (Table 3).

The surgery group scored higher on the HADS-A questionnaire with a mean score of 9.4 versus a mean score of 7.4 in the surveillance group, though these scores were not statistically different (p=0.09) (Fig. 2). Results for the FACT-Pa questionnaire were similar between the surgery and surveillance groups, with median composite scores of 113 in the surgery group versus 123 in the surveillance group (p=0.27). The individual median domain scores also were similar in terms of physical well-being (25 vs. 27, p=0.08), social well-being (24 vs. 24, p=0.83), and emotional well-being (21 vs. 22, p=0.32). The surgery group scored significantly lower on the functional well-being domain compared to the surveil-

Table 3 Pathologic characteristics of IPMN in patients in the surgery and surveillance groups

Variable	Surgery (n=16)	Surveillance (n=16)
Main duct IPMN (%)	6 (37.5)	0 (0)
Invasive carcinoma	1	0
Side-branch IPMN (%)	10 (62.5)	16 (100)
Invasive carcinoma	0	0
Positive margin (%)	4 (25.0)	NA

Fig. 2 Mean score on the Hospital Anxiety and Depression Scale-Anxiety (*HADS-A*) for the surgery versus surveillance groups (9.4 vs. 7.4, $p=0.09$)

lance group with a mean score of 19 versus 23.5 ($p=0.03$) (Fig. 3).

Discussion

The growing number of incidentally identified IPMN coupled with the indolent course of the disease offers a unique opportunity for early and aggressive management of these premalignant pancreatic lesions. A growing body of literature evaluates factors that predict malignancy to provide better guidelines for surgery or surveillance in IPMN patients, yet no literature to date examines outcomes from the patient's perspective. Surgery removes the focus of disease and provides patients with a definitive pathologic diagnosis. However, surgical patients are subject to potential perioperative complications and pancreatic endocrine and exocrine insufficiency. Surveillance spares patients' surgical morbidity, yet these patients may harbor invasive disease and require vigilant follow-up. The aim of this preliminary study was to use validated instruments to determine differences in patient anxiety and QoL following surgery or surveillance for IPMN.

The patients recruited to the surgery and surveillance groups were similar with respect to demographics, coexistent comorbidity, and median time since operation or diagnosis. It was important for comparison that patients in both groups had equivalent elapsed time between their operation or diagnosis and recruitment for this study. Despite similarities, the groups were inherently different because of their management of IPMN. The surgical patients had real morbidity with an overall complication rate of 43.7%, a major complication rate of 18.7%, and postoperative pancreatic endocrine and exocrine insufficiency in 25% and 18.7%, respectively. In the surgery group, 37.5% of patients had main duct IPMN while no patient in the surveillance group was suspected to have main duct IPMN. Furthermore, 25% of patients in the surgery group had IPMN on the final surgical margin. These differences likely influenced patient responses on the anxiety and QoL questionnaires.

The psychological impact of prophylactic pancreatic resection for IPMN shares some similarities to that of prophylactic mastectomy in women at increased risk of developing breast cancer. Hatcher and colleagues[15] reported that bilateral prophylactic mastectomy may reduce anxiety whereas surveillance may perpetuate anxiety in high-risk women. Our data demonstrate an opposite result in patients with IPMN. The results of the HADS-A showed that surgical patients scored higher on measures of anxiety compared to their surveillance counterparts. With a median score greater than 8, the surgery group met the threshold for high anxiety, whereas with a score of 7.4, the surveillance group did not. It is possible that patients in the surgery group had higher baseline anxiety levels and therefore may

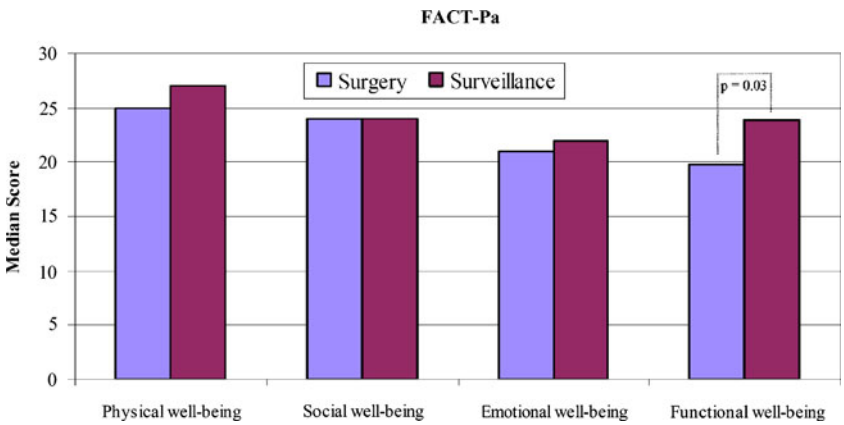

Fig. 3 Median scores on the four domains of the Functional Assessment of Cancer Therapy-Pancreas (*FACT-Pa*) for the surgery versus surveillance groups. Physical well-being 25 vs. 27, $p=0.08$; social well-being 24 vs. 24, $p=0.83$; emotional well-being 21 vs. 22, $p=0.32$; functional well-being 19 vs. 23.5, $p=0.03$

have chosen the more definitive intervention. Additionally, final pathologic characteristics in our surgery patients, such as the presence of main duct IPMN and positive surgical margins, may have induced higher anxiety levels.

The results of the FACT-Pa demonstrate no difference in overall QoL between surgery and surveillance patients with IPMN. Furthermore, there were no significant differences between the groups in measures of physical, social, and emotional well-being. Surgery negatively impacted only the functional well-being domain ($p=0.03$). The functional well-being domain included questions such as "I am able to work" and "I am enjoying the things I usually do for fun." Given that the median time since operation in the surgery group was 17.1 months, short-term sequelae such as pain likely did not influence these results. However, long-term sequelae such as diabetes requiring insulin injection and diarrhea requiring pancreatic enzyme supplementation potentially did affect patient perceptions of functional well-being.

With 16 patients per group, this study is limited by small sample size. A larger sample size may reveal clinically relevant differences between the surgery and surveillance groups. Another limitation is that questionnaires were administered only once at the time of recruitment, which varied between patients. Future work should involve prospective recruitment of patients and administration of the questionnaires at multiple, standardized time points (e.g., at the time of operation or diagnosis and at 6 and 12 months after) to better characterize patient QoL in surgery and surveillance pathways.

Conclusion

From these preliminary data, a protocol of surveillance does not appear to generate undue anxiety in patients with IPMN. Furthermore, prophylactic surgery does not reduce QoL in this select patient population. Despite limitations, this study provides an important foundation for a more comprehensive investigation with a larger patient population.

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2010 SSAT POSTER PRESENTATION MANUSCRIPT

HPB Surgery Can Be Safely Performed in a Community Teaching Hospital

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Abstract
Introduction There is ongoing debate about feasibility of performing hepatobiliopancreatic (HPB) cases in low-volume, community hospitals. We decided to analyze outcomes of HPB surgical cases done in our community hospital and compare it with published data from academic centers and/or national data.
Materials and Methods We reviewed all HPB cases (liver, pancreas, and bile duct cases) performed in an 8-year-period (2001–2009) by HPB-fellowship-trained general surgeon (P.F.S.) at the Danbury Hospital, CT, USA. All electronic files of the patients, who underwent HPB surgery, were reviewed, and all pertinent clinical information was retrieved. Complications and mortality were recorded for length of hospital stay and 30 days after discharge. All complications were graded according to Clavien classification. Pancreatic specific complications—pancreatic fistula/leak and delayed gastric emptying—were graded using International Study Group on Pancreatic Fistula and International Study Group of Pancreatic Surgery definitions.
Results There were 140 HPB cases. These included 33 pancreatoduodenectomies, 29 distal pancreatectomies, 52 hepatic cases, and 26 cases of other cases involving pancreas and biliary tract. Overall complication rate was 36.4%. Using Clavien classifications, there were 26 grade 1 complications, 21 grade 2 complications, and four grade 3 complications. Two patients underwent reoperation for postoperative complications. Overall mortality was 0.7% (one patient). Pancreas-specific complications included 6% pancreatic leak rate after pancreatoduodenectomy and 24.1% leak rate for distal pancreatectomy.
Conclusion HPB surgery could be safely performed in community setting, with morbidity and mortality comparable to high-volume centers.

Keywords Hepatobiliopancreatic surgery · Community hospital · ISGFP

There is an ongoing debate about the feasibility of performing hepatobiliopancreatic (HPB) cases in low-volume, community hospitals.[1–3] Better results in terms of morbidity, mortality, and oncological outcomes were found to be achieved in high-volume, academic centers by some studies.[1] We decided to analyze outcomes of HPB surgical cases done in our community teaching hospital and compare it with the published data from academic centers and/or national data.

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Materials and Methods

We retrospectively reviewed all liver, pancreas, and bile duct cases performed in an 8-year-period (2001–2009) by a HPB-fellowship-trained surgeon (P.F.S.) at the Danbury Hospital, CT, USA. Danbury Hospital is a 371-bed community hospital with interventional and endoscopic services available 24/7 and capable to provide diagnostic and therapeutic options necessary to perform complex surgery. All HPB cases were unselected, initially referred for potential surgery to Danbury Hospital. There were no cases referred to tertiary centers due

to their complexity. All procedures were performed by a single surgeon (P.F.S) assisted by resident house staff. The electronic files of the patients who underwent HPB surgery were reviewed, and pertinent clinical information was retrieved. Morbidity and mortality were recorded for 30 days after surgery date. All complications were graded according to Clavien classification (Table 1).[4] Pancreatic specific complications—pancreatic fistula/leak and delayed gastric emptying—were graded using International Study Group on Pancreatic Fistula and International Study Group of Pancreatic Surgery definitions.[5,6]

Results

There were 140 HPB cases performed. These included 33 pancreatoduodenectomies, 29 distal pancreatectomies, 52 hepatic cases, and 26 other cases involving pancreas and biliary tract. The mean patient age was 61.5 years (range, 19–86 years). There were 65 females and 75 males. Mean length of stay was 8.9 days (range, 1–60). Majority of the patients were in the ASA class 2 (66%). The overall complication rate was 36.4%. Using Clavien classification, there were 26 grade 1 complications, 13 grade 2 complications, and four grade 3 complications. Two patients underwent reoperation for postoperative complications. The overall mortality was 0.7% (one patient). Pancreas-specific complications included 6% pancreatic leak rate after pancreatoduodenectomy group and 24.1% leak rate for distal pancreatectomy group (Table 2).

Pancreatoduodenectomy Group There were 33 pancreatoduodenectomies. All pancreatoduodenectomies were done as classic, nonpylorus-preserving resection and included partial gastric resection. Pancreatojejunal anastomosis was performed according to Blumgart technique, described in details elsewhere.[7] One JP drain was routinely left intra-abdominally near the pancreatojejunostomy anastomosis. Drainage fluid from the drain was not routinely sent for amylase and performed only when a pancreatic leak was suspected on clinical or radiological grounds.

The mean patient age was 68 years (range, 53–86 years). There were 18 males and 15 females. Mean length of stay was 11 days (range, 6–28 days). Indications for PD were as follows: pancreatic adenocarcinoma in 15 cases, ampullary cancer in four, distal common bile duct cancer in three, duodenal villous adenoma with dysplasia in three, duodenal cancer in two, mucinous cystic neoplasm in two, and intraductal pancreatic mucinous neoplasm in one case. Three pancreatoduodenectomies were initially performed for suspected malignancy, but ultimately proved to be benign on pathology evaluation and included one benign pancreatic cyst, one case of sclerosing pancreatitis, and one benign distal common bile duct stricture.

The overall complication rate for the whole group was 51.5% (17) and included two cases of grade B pancreatic leak which were resolved with conservative treatment and percutaneous drainage (6%), three cases of delayed gastric emptying (two grade A and one grade B—in total 9%), one case of hepatojejunostomy leak (3%), seven infectious complications (21.2%), and two intra-abdominal abscesses requiring percutaneous drainage (6%). One patient developed enterocutaneous fistula, managed conservatively, and one patient was reoperated for an afferent loop obstruction and hepatojejunostomy blowout. None of the patients died, resulting in a zero mortality.

Distal Pancreatectomy Group Twenty-nine distal pancreatectomies, including three laparoscopic distal pancreatectomies, were performed. Mean patient age was 58.8 years (range, 25–80 years). There were 11 males and 18 females, majority in ASA class 2. Mean length of stay was 7.7 days (range, 4–30 days). All of distal pancreatectomies included splenectomy and were performed in standard fashion. The pancreas was transected with a stapler or oversewn. JP drain was routinely left in proximity of the pancreatic stump. Drainage fluid was not routinely checked for amylase levels unless pancreatic leak was suspected. Indications for distal pancreatectomy were as follows: pancreatic adenocarcinoma in six cases, neuroendocrine tumors in ten, mucinous cystic adenoma in five, solid papillary tumor in one, intraductal papillary mucinous tumor in one, serous cystic adenoma in

Table 1 Clavien Classification of Postoperative Complications

Complication grade	Description
Grade 1	No specific intervention needed. Certain medications (antiemetics, antipyretics, diuretics, analgetics, electrolytes) are included. Include wound infections opened at bedside and physiotherapy.
Grade 2	Specific measures, such as TPN/blood transfusion and medications not related to approved in Grade 1 situation are needed
Grade 3	Surgical, endoscopic, or radiologic intervention with or without use of general anesthesia
Grade 4	Life-threatening complications, including ICU admission
Grade 5	Patient's death

Table 2 Summary of HPB Cases

Procedure type	Number of cases	Age (mean, years)	Male/ female	Length of stay (days)	Morbidity	Mortality
Pancreatoduodenectomy	33	68 (53–86)	18/15	11 (6–28)	51.5%	0
Distal pancreatectomy and splenectomy	29	58.8 (25–80)	11/18	7.7 (4–30)	51.7%	0
Hepatic cases	52	57.6 (91.9–80)	31/21	6.9 (1–36)	21.1%	0
Miscellaneous HPB	26	58.2 (25–83)	15/16	13 (4–60)	31.5%	3.8% (one patient)
Overall	140	61.5 (19–86)	75/65	8.9 (1–60)	36.4%	0.7%

one, pancreatic schwannoma in one, and benign pancreatic cysts (lymphoepithelial and simple cyst) in three cases. Overall, there were 15 complications, representing a 51.7% complication rate. Most common complication was pancreatic leak which occurred in seven patients (24.1%), being grade B in two cases (needed percutaneous drainage) or 28.5%, and five grade A leaks treated by maintaining JP drain. Intra-abdominal fluid collections, requiring percutaneous drainage, developed in four patients (13.79%). Eight patients developed infectious complications, other than intra-abdominally (wound infections, pneumonia, and *Clostridium difficile* colitis) for a total complication rate of 27.5%. There was zero intraoperative or postoperative 30-days mortality.

Hepatic Surgery Group There were 52 hepatic surgery cases recorded for specified period. Mean patients age was 57.6 years (range, 19–80 years) and there were 21 females and 31 males in this group. Mean length of stay was 6.9 days (range, 1–36 days). Surgery was performed for malignant metastatic disease in 53.8% of all hepatic cases: 21 cases of metastatic colorectal cancer, five cases of metastatic carcinoid, one case of metastatic neuroendocrine tumor, and one case of metastatic squamous cancer. Eleven resections were done for primary liver cancer—seven for cholangiocarcinoma, three for hepatocellular carcinoma, and one for oncocytic papillary tumor. Eleven cases were performed for benign disease—three resections for giant hemangioma, three cases for simple liver cysts, one for focal nodular hyperplasia, one for nodular fibrosis, one for isolated intrahepatic biliary duct dilatation, one for hepatolithiasis, and one open radiofrequency ablation case. This group included 16 major hepatectomies (six right, four right extended, four left, two left extended) and 30 minor hepatectomies, defined as removal of less than three segments of the liver (five left lateral sectionectomies, ten segmentectomies, six bisegmentectomies, and nine wedge resections, combined in nine cases with hepatic artery pump placement). Nonresectional liver cases included two hepatic cyst cystectomies with unroofing, three hepatic pump placement cases, and one open radiofrequency ablation case. All liver resections were without routine inflow occlusion. Hepatic parenchyma was transected with the use of CUSA device or stapler. Overall mortality was zero. Complication rate was 21.1% and included four cases of biliary leak from hepatojejunostomy requiring percutaneous or transhepatic drainage (7.6%). Two patients developed intra-abdominal abscesses and were drained by interventional radiology. Other infections developed in 9.6% of cases (five patients).

Miscellaneous HPB Procedures This group included 26 HPB procedures other than pancreatoduodenectomy, distal pancreatectomy, and liver cases. The group included the following procedures: Frey procedure for pleuropancreatic fistula, one; completion pancreatectomy for recurrent cancer, one; total pancreatectomy for IPMN, one; laparoscopic pancreatic cystectomy for benign cyst, one; enucleation of pancreatic insulinoma, one; Roux-en-Y cystojejunostomy for pancreatic pseudocyst, three, cystogastrostomy for pancreatic pseudocyst, three; choledochal cyst resection, two; Roux-en-Y hepatojejunostomy with or without gastrojejunostomy as a bypass procedure in unresectable pancreatic cancer, 12; and duodenal ampullectomy for tubulovillous adenoma, one. The mean patient age was 58.2 years (range, 25–83) with 11 females and 15 males. Mean length of stay was 13 days (range, 4–60). There was 31.5% overall complication rate. Complications included grade A delayed gastric emptying in one case, one intra-abdominal abscess, requiring percutaneous drainage, one duodenal leak, treated conservatively with TPN, two episodes of ileus, one postoperative pneumonia, one *C. difficile* colitis requiring subtotal colectomy, and one postoperative bleeding requiring angioembolization and prolonged ICU stay. One patient succumbed as a result of perioperative stroke resulting in overall mortality of 3.8%. Group-specific morbidity is reflected in Table 3.

Discussion

HPB surgery is associated with significant morbidity and mortality. And if mortality is improving, postoperative morbidity is still substantial. Recent analysis of NSQIP database revealed 20.1–32.4% morbidity and 2.3–2.7%

Table 3 Group-Specific Morbidity

Complication	PD group (33 cases)	DPS group (29 cases)	Hepatic group (52 cases)	Misc. HPB (16 cases)
Pancreatic leak	6% (2)	24.1% (7)		
Grade A	–	71.4% (5)		
Grade B	100% (2)	28.6% (2)		
Delayed gastric emptying	9% (3)			5.2% (1)
Grade A	66.6% (2)			
Grade B	33.4% (1)			
Hepatojejunostomy leak	3% (1)		7.6% (4)	
Duodenal leak				5.2% (1)
Intra-abdominal abscess	6% (2)	13.7% (4)		5.2% (1)
Infections other than intra-abdominal	21.2% (7)	27.5% (8)	9.6% (5)	
Ileus				10.4% (2)
Pulmonary embolism	3% (1)			
Stroke				5.2% (1)
Enterocutaneous fistula	3% (1)			
Postoperative bleeding				5.2% (1)
Fluid overload	3% (1)			

PD pancreatoduodenectomy, *DPS* distal pancreatectomy and splenectomy, *Misc. HPB* miscellaneous HPB cases

mortality rates following elective HPB procedures.[8,9] As overall mortality was reduced to below 5% level in many recent series from high-volume institutions, many publications suggested the need to regionalize HPB surgery in order to decrease mortality and complications. However, there is still controversy regarding volume–outcome relationships in HPB surgery as some studies reported comparable results from low-volume community hospitals.[2,3] It was pointed out that low mortality at the high-volume centers could be in fact reflection of the high volume and not necessary improved outcome.[10] Allocations of clinical resources, local surgical expertise, and individual volume have been found to predict outcomes in HPB surgery.[11,12]

We hypothesized that general HPB surgery could be safely performed in a low-volume, community teaching hospital. Our overall 36.4% morbidity rate is comparable with the majority of published data as well as 0.7% mortality. Major HPB-specific morbidity—6% pancreatic leak rate after pancreatoduodenectomy and 24.1% pancreatic leak rate after distal pancreatectomy—is in line with the current results from high-volume institutions.[5,13,14] We attribute these results to the presence of fellowship-trained surgeon, availability of the clinical resources to perform complex HPB surgery, and careful patient selection.

There are several limitations of this study. First, a retrospective analysis is prone to bias and confounding. Second, there is the possibility of incomplete data, despite the fact that all major morbidity and mortality are carefully reported, and effort was made by the authors of this article to provide as accurate information as possible. And third, there is no policy of routine evaluation of the drain fluid for amylase and as a consequence, reported rates of pancreatic leak may not reflect the true incidence.

Based on our study, we believe that general HPB surgery can be safely performed in a low-volume, community hospital. Majority of HPB surgery in USA is done by surgeons without HPB training.[15] In certain population, such as Medicare patients, more than 50% of some HPB cases (pancreatic resection) are done in hospitals performing less than two procedures per year.[1] Presence of a fellowship-trained surgeons, appropriate clinical resources and ancillary services can contribute to the outcomes improvement in low-volume institutions.

Conclusion

HPB surgery can be safely performed in community teaching hospital, with results comparable to high-volume centers. Appropriate surgical expertise and clinical resources are necessary to provide satisfactory outcomes.

Disclosure section Dr. Andrei Cocieru, MD and Pierre F. Saldinger, MD, FACS have no conflicts of interest or financial ties to report.

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