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2010 SSAT QUICK SHOT PRESENTATION

Improvement of Respiratory Symptoms Following Heller Myotomy for Achalasia

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Abstract
Introduction Although patients with achalasia complain mainly of dysphagia, we have observed that they also have a high rate of respiratory problems. We hypothesized that the latter may be due to poor esophageal clearance leading to aspiration. This study examines the effect of Heller myotomy on these symptoms.
Methods We studied the course of 111 patients with achalasia who underwent Heller myotomy between 1994 and 2008 and who agreed to participate in this study. All patients completed a questionnaire postoperatively assessing the preoperative and postoperative prevalence and severity of symptoms using visual analog scales. Patients were divided into two groups: one that included all those with respiratory symptoms (dyspnea, hoarseness, cough, wheezing, sore throat, and/or a history of asthma or pneumonia) prior to myotomy and one that included those without those symptoms.
Results All patients presented with dysphagia as their primary complaint, and 63 (57%) reported respiratory symptoms or disease prior to surgery. There were no significant differences in preoperative characteristics between those with and without respiratory manifestations. After a median follow-up of 71 months (range 9–186 months), 55 (87%) patients reported durable improvement of dysphagia. The frequency and severity of all respiratory symptoms decreased significantly. Twenty-four of the 29 patients (82%) who reported a history of pneumonia prior to surgery did not experience recurrent episodes after Heller myotomy.
Conclusions A Heller myotomy is effective in improving esophageal emptying in patients with achalasia. This results in sustained improvement of dysphagia and associated respiratory symptoms/diseases. This suggests that respiratory symptoms/diseases in these patients are likely caused by esophageal retention of food and secretions, and then aspiration.

Keywords Achalasia · Respiratory disease · Heller myotomy · Surgical · Esophageal

Introduction

Achalasia is an esophageal motility disorder characterized by aperistalsis of the esophageal body and failure of relaxation of the lower esophageal sphincter (LES). As a result, the most common manifestation is severe, progressive dysphagia, regurgitation, and occasional chest pain. Several previous case reports have suggested a connection between acquired respiratory conditions and achalasia.[1–7] More recently, we carried out a systematic investigation of the prevalence of respiratory symptoms and diseases in patients with achalasia[8] and reported a relatively high prevalence of patients with cough, hoarseness, wheezing, dyspnea, sore throat, and episodes of pneumonia. Although the pathophysiology is now known, it has been postulated that impaired esophageal emptying from achalasia may result not only in dysphagia but also that the retained food and secretions pooled in the esophagus may give rise to episodes of micro- and macro-aspiration, leading to symptoms or airway and pulmonary disease.[9,10]

Treatment of achalasia, whether surgical or non-surgical, is palliative and focuses on ablation of the LES to relieve

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distal esophageal obstruction and improve esophageal emptying. Surgical myotomy has so far demonstrated the best long-term outcome with regard to improvement in upper digestive symptoms and relief of dysphagia.[11–14] Surgical treatment, first described by Ernst Heller in 1913,[15] consists, today, of a single, long esophageal myotomy of the longitudinal and circular layers with a 3-cm extension on to the gastric cardia to completely obliterate the LES and allow for better esophageal emptying.

The aim of this study was to determine the effect of a laparoscopic Heller myotomy on associated respiratory symptoms in patients with achalasia. We postulated that if they were related to aspiration of retained esophageal contents, the symptoms and the associated pulmonary disease should be relieved in parallel with dysphagia.

Methods

All patients with achalasia who underwent Heller myotomy (either laparoscopic or thoracoscopic) at the University of Washington between September 1994 and July 2009 were identified from our prospectively collected database. We mailed a follow-up questionnaire and made at least three phone calls per patient in an attempt to find as many patients as possible. Those that were contacted and who consented to participate in this study completed a postoperative questionnaire via phone or mail assessing preoperative and postoperative respiratory and digestive symptoms using visual analog scales.

Patients were asked to indicate both preoperative and postoperative frequency and severity of respiratory symptoms, including dyspnea, hoarseness, cough, wheezing, pneumonia, and/or sore throat, as well as more typical esophageal symptoms such as dysphagia, regurgitation, chest pain, and heartburn on a five-point scale, with 0 = "never," 1 = "once a month," 2 = "once a week," 3 = "once a day," and 4 = "several times daily." Severity of symptoms was rated on a ten-point visual analog scale ranging from 0 (absent) to 10 (worst). Baseline demographics including prior history of respiratory diseases, manometric and radiologic data, in addition to perioperative and long-term follow-up data, were abstracted from our database and clinical records. Patients reporting respiratory symptoms (dyspnea, hoarseness, cough, wheezing, or sore throat) occurring at least once per week prior to myotomy and/or a history of asthma or pneumonia were considered to have respiratory symptoms or diseases and included in our analysis.

To investigate the potential for recall bias with respect to symptoms patients were experiencing prior to the Heller myotomy, we separately analyzed a subset of 28 patients. These 28 patients, besides participating in this study, had also been enrolled in a separate prospective achalasia study where a questionnaire inquiring about respiratory symptoms was administered prior to surgery. The responses of patients in both surveys were compared to examine concordance and evaluate the precision of patient symptom recollection for this study with prospectively collected symptoms.

All operations were performed laparoscopically or thoracoscopically and an esophagogastric myotomy was carried out as previously described by our group.[14,16–18] In almost all cases (unless there was a sigmoid esophagus and potential for angulation), a partial posterior (Toupet) or anterior (Dor) fundoplication was added.

Continuous variables are described as mean ± standard deviation, and categorical variables are described as percentages of the study population. Symptom severity and frequency scores before and after myotomy were compared using a Wilcoxon matched-pairs test. Fisher's exact test and the Wilcoxon rank-sum test were used to compare categorical and continuous data where appropriate, respectively. Data were analyzed using Stata SE version 11.0 (College Station, Texas), and a p value$\leq$0.05 was considered statistically significant.

This study was approved by the University of Washington Institutional Review Board (University of Washington HSD: 35459).

Results

A total of 395 patients who underwent Heller myotomy for achalasia at the University of Washington between 1994 and 2009 were identified. We were able to contact 118 patients via mail or phone, and six patients had died. Seven patients declined participation in the study. Among these 111 patients, the median follow-up after myotomy was 71 months (range 9–186 months). All patients presented with dysphagia as the primary complaint. Sixty-three of the 111 patients in the study (57%) reported at least one clinically significant baseline respiratory symptom or respiratory disease prior to undergoing Heller myotomy (Table 1).

The group of patients reporting clinically significant respiratory symptoms (n=63) were compared to those who did not (n=48) to determine if there were differences that might explain their risk for developing respiratory manifestations. No significant differences existed between these two groups in baseline characteristics, with the exception that those with respiratory disease presented with a shorter duration of dysphagia compared to those without respiratory disease; however, this was not statistically significant (87±99 versus 122±129 months, p=0.14; Table 2).

Table 1 Incidence of baseline respiratory symptoms

Demographic	n=111 (%)
Respiratory symptoms ≥ once/week	
Dyspnea	15 (14)
Hoarseness	17 (15)
Cough	33 (30)
Wheezing	17 (15)
Sore throat	15 (14)
Pneumonia	29 (26)
Asthma	16 (14)
Any respiratory symptoms ≥ once/week or prior history of pneumonia/asthma	63 (57)

All patients underwent a Heller myotomy. Of the 63 patients reporting baseline respiratory symptoms, 50 underwent laparoscopic Heller myotomy combined with an antireflux procedure (Dor or Toupet fundoplication), five underwent laparoscopic Heller myotomy alone, one underwent thoracoscopic Heller myotomy alone, and seven patients had a laparoscopic redo myotomy with or without fundoplication. There were no significant differences between those patients with or without respiratory symptoms in regards to length of stay [1 day (range 1–3) versus 1 day (range 1–6), p=0.3] or overall improvement in dysphagia (97% versus 94%) following surgery. There was no perioperative mortality (90-day) in either group. There were no significant differences in morbidity between the two groups (Table 3).

Fifty-five of the 63 (87%) patients with preoperative respiratory symptoms experienced durable improvement in their dysphagia. The frequency and severity of all respiratory symptoms decreased significantly following surgery (Figs. 1 and 2). Twenty-four of the 29 patients (82%) who reported a history of pneumonia prior to surgery did not experience recurrent episodes for up to 5 years following Heller myotomy.

When comparing the responses regarding respiratory symptoms for the 28 patients who were enrolled in both the prospective and this retrospective study, we found a concordance of 96%. In other words, 27 of the 28 patients reported a similar incidence of respiratory symptoms in the prospectively collected data as they did in the questionnaire they answered in response to our request for this study.

Discussion

In a previous study, we found a high prevalence of pulmonary symptoms/disease in patients with achalasia (Tatum et al., under review). In this study, we demonstrated significant improvement in these symptoms following successful surgical treatment of achalasia with Heller myotomy, and these improvements parallel improvements in dysphagia. The most logical causal link between esophageal obstruction and the presence of respiratory symptoms in the setting of achalasia is esophageal non-emptying and aspiration of retained food and secretions from the esophagus into the upper and lower respiratory tracts.

Several previous studies have looked at the natural history of untreated achalasia and offered conflicting reports of severity and prevalence of respiratory symptoms. As early as 1960, Ellis[19] examined the natural history of untreated achalasia and reported a 33% incidence of chronic pulmonary infection in patients with at least a 10-year history

Table 2 Baseline patient demographics comparing patients with and without respiratory symptoms

Demographic	Respiratory symptoms (n=63)	No respiratory symptoms (n=48)	p value
Age (years)			
Mean±SD	52±15	53±14	0.83
Median (min–max)	54 (21–83)	52 (18–79)	
Male (%)	31 (49)	29 (60)	0.34
Duration of dysphagia (months)			
Mean±SD	87±99	122±129	0.14
Median (min–max)	36 (6–432)	60 (1–468)	
LESP (mmHg)	37±21	37±21	0.96
Sigmoid esophagus (%)	4 (6)	5 (10)	0.49

Table 3 Postoperative surgical outcomes

Demographic	Respiratory symptoms (n=63)	No respiratory symptoms (n=48)	p value
Length of stay (days)			
Median (min–max)	1 (1–3)	1 (1–6)	0.3
30-day mortality (%)	0 (0)	0 (0)	1.0
Morbidity (%)			
Intraoperative aspiration	0 (0)	1 (2)	0.4
Pneumonia	1 (1)	0 (0)	0.4
Improved dysphagia (%)	61 (97)	45 (94)	0.65

of untreated achalasia, which he attributed to repeated aspiration. Although we found one study that did not mention the presence of respiratory manifestations,[20] other small series and case reports have described such a connection. Not all respiratory pathology reported has been attributed to aspiration, but instead presumably resulting from "mass effect" from a dilated esophagus. These include case reports of atypical infections, hoarseness resulting from recurrent laryngeal nerve compression, and more serious and life-threatening complications such as stridor and tracheal obstruction from airway compression.[3,21–28]

To our knowledge, no prior studies have examined what effect surgical treatment with Heller myotomy has on respiratory disorders associated with achalasia. In this study, we set up to systematically examine the effect of this operation on these symptoms. Furthermore, we were able to do so in a relatively large group of patients, operated with the same technique by a single group of surgeons. In addition, our observations provide data on the durability of the results with relatively long-term follow-up. Importantly, our study also includes a population that previously did *not* suffer from respiratory symptoms that underwent myotomy. We were not able to find any substantial demographic or clinical differences between this group and that of patients with respiratory symptoms. We are left to believe that among patients who suffer from achalasia for several years (as was the case in our 111 patients), some tend to protect their airway better than others. Although the mechanisms underlying this special ability (or the lack thereof) remain obscure.

Of the 48 patients who did not report respiratory symptoms prior to myotomy, six (13%) went on to develop at least one respiratory symptom after myotomy, which included hoarseness, wheezing, cough, shortness of breath, or sore throat. None of these six reported pneumonia in the 5-year time period after myotomy. It is important to analyze the possible causes in this small subset, even though the group (n=6) is too small to make any conclusions. Of these six patients, two patients did not have improvement in dysphagia after surgery and had complex problems that were difficult to manage. One had a history of prior subtotal gastrectomy before Heller myotomy and had a small Dor fundoplication done at the time of the myotomy. This eventually required reoperation and takedown of this fundoplication due to persistent dysphagia. The other patient only underwent myotomy without an anti-reflux procedure because of an end-stage, sigmoid distal esophagus. Of course it is also possible that some of these patients may have developed more typical GERD (and aspiration) as a result of the myotomy.

While these data are compelling, this study has several limitations. This study is retrospective and relies upon relatively subjective outcome measures. Therefore, recall bias may influence patients' reporting of severity and

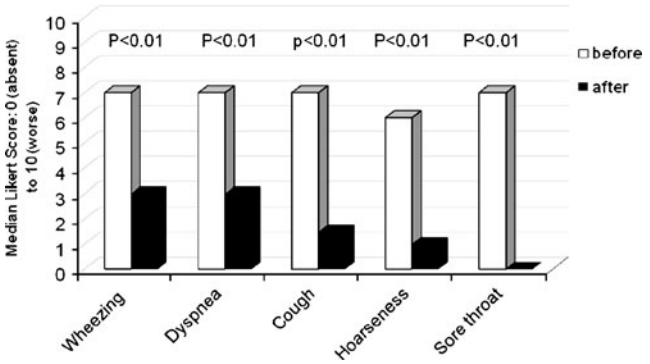

Fig. 1 Comparison of preoperative and postoperative severity of respiratory symptoms

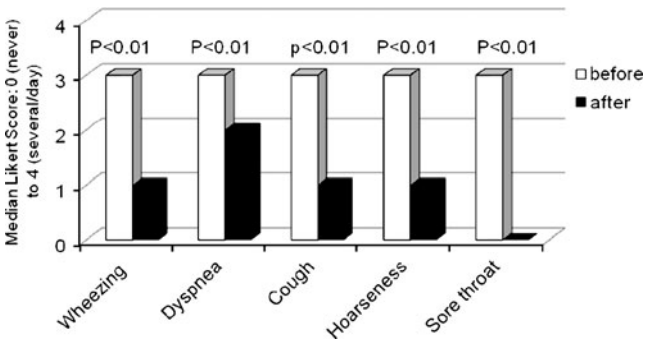

Fig. 2 Comparison of preoperative and postoperative frequency of respiratory symptoms

frequency of their symptoms. This could be further compounded by long follow-up periods in some cases. When comparing the responses regarding respiratory symptoms for the 28 patients who were enrolled in both the prospective and retrospective study, we found a concordance of 96%. This finding suggests that there was consistent reporting between the same population in the two studies and that patients were able to accurately recall their symptoms when asked retrospectively, indicating that the effect of recall bias is likely minimal. Future studies to better characterize the relationship of respiratory disease with achalasia, as well as the effect of Heller myotomy, should ideally include prospectively collected data.

Despite these limitations, these findings present a compelling case that highlights the presence of and explains the pathophysiology of respiratory disease in patients with achalasia. Delayed esophageal emptying is certainly the most likely reason for these respiratory symptoms, and the improvement after performance of Heller myotomy strengthens the likelihood of this association. Moreover, the substantial improvement in respiratory symptoms and disease after Heller myotomy, which was heretofore not appreciated, is yet another benefit of surgical therapy for this disease.

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2010 SSAT PLENARY PRESENTATION

Intestinal Adaptation for Oligopeptide Absorption via PepT1 After Massive (70%) Mid-Small Bowel Resection

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Abstract
Introduction Proteins are absorbed primarily as short peptides via peptide transporter 1 (PepT1).
Hypothesis Intestinal adaptation for peptide absorption after massive mid-small intestinal resection occurs by increased expression of PepT1 in the remnant small intestine and colon.
Methods Peptide uptake was measured in duodenum, jejunum, ileum, and colon using glycyl-sarcosine 1 week (n=9) and 4 weeks (n=11) after 70% mid-small bowel resection and in corresponding segments from unoperated rats (n=12) and after transection and reanastomosis of jejunum and ileum (n=8). Expression of PepT1 (mRNA, protein) and villus height were measured.
Results Intestinal transection/reanastomosis did not alter gene expression. Compared to non-operated controls, 70% mid-small bowel resection increased jejunal peptide uptake (p<0.05) associated with increased villus height (1.13 vs 1.77 and 1.50 mm, respectively, p<0.01). In ileum although villus height increased at 1 and 4 weeks (1.03 vs 1.21 and 1.35 mm, respectively; p<0.01), peptide uptake was not altered. PepT1 mRNA and protein were decreased at 1 week, and PepT1 protein continued low at 4 weeks. Gene expression, peptide uptake, and histomorphology were unchanged in the colon.
Conclusions Jejunal adaptation for peptide absorption occurs by hyperplasia. Distal ileum and colon do not have a substantive role in adaptation for peptide absorption.

Keywords Peptide absorption · Short bowel syndrome · PepT1 · Intestinal adaptation · Protein absorption · Malabsorption

Introduction

Short bowel syndrome arises from malabsorption of nutrients in response to a marked decrease in the intestinal absorptive area after intestinal resection/loss for a multitude of reasons. The current treatment options for this condition include intestinal rehabilitation, chronic parenteral nutrition, intestinal transplantation, and intestine lengthening procedures, all of which carry a variable prognosis and outcome.[1,2] A better understanding of the etiology of the pathophysiologic changes occurring in short bowel syndrome may engender novel methods for improving the absorptive potential of the remnant small intestine in these patients.

Because the small intestine demonstrates a remarkable ability to adapt its absorptive capacity for nutrient absorption after a marked decrease in effective absorptive surface, many approaches have been directed at augmenting this adaptive mechanism(s).[3,4] Prior experiments from our laboratory have investigated the adaptive mechanisms mediated by brush border transporters for glucose and peptide absorption in the ileum after 70% proximal intestinal resection[5]; however, the adaptive changes in the jejunum and duodenum have not been well characterized

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for the transport proteins that regulate the uptake of peptides by epithelial cells. The role of terminal ileum and colon in improving survival in patients with short bowel syndrome is well established.[6] Recent studies have suggested an increase in expression of Peptide Transporter 1 (PepT1) mRNA in the colon of patients with short bowel syndrome[7,8]; however, the absorptive function of the colon for peptides has not been studied.

The current study was designed to determine the effects of a marked, mid-small bowel resection (70%) on the expression and function of the peptide transporter PepT1 in the duodenum, proximal jejunum, distal ileum, and proximal colon. Our hypothesis was that the remnant small bowel adapts to this marked loss of absorptive area by increasing expression and function of PepT1 per enterocyte in addition to the expected mucosal/epithelial cell hyperplasia.

Methods

This study was approved by our Institutional Animal Care and Use Committee, and all experiments were carried out in accordance with the NIH guidelines for the humane use and care of laboratory animals.

Design

Male Lewis rats (Harlan Laboratories, Indianapolis, IN, USA) weighing approximately 200 g were maintained in a 12-h light–dark cycle (6 A.M. lights on, 6 P.M. lights off) and were allowed free access to water and standard rat chow (5001 Rodent Diet, PMI Nutrition International, LLC, Brentwood, MO, USA). They were first allowed a week to acclimatize to the housing conditions, after which a 70% mid-segmental, jejunoileal resection was performed; the rats were studied subsequently at 1 week ($n=8$) and at 4 weeks ($n=11$) after intestinal resection. An additional group of rats ($n=9$) that underwent transection and immediate primary reanastomosis of their small intestine at points corresponding to the sites of transection in the resection groups were studied 1 week postoperatively and served as "operated control" for the non-specific effects of anesthesia, celiotomy, and disruption of the enteric nervous system. Another group of 12 rats served as non-operated controls. A final group of eight rats were maintained in similar conditions to determine weight changes over 4 weeks in non-operated control rats.

Intestinal Resection Mid-ventral celiotomy was performed after anesthetizing the rats with pentobarbital (50 mg/kg). The ligament of Treitz was identified and the length of the jejunoileum measured. A 70% mid-segmental, jejunoileal resection was performed with primary end-to-end anastomosis of the remnant jejunum and ileum using a single-layer anastomosis with 6–0 silk sutures. The ventral abdominal wall muscles were reapproximated with a running 6–0 silk suture, and the skin was closed with subcuticular 5–0 vicryl sutures. Buprenorphine (0.05–0.1 mg/kg) was administered subcutaneously for analgesia every 12 h for 1 day. The rats were maintained on water for 24 h before being given free access to rat chow.

Operated Control These rats underwent celiotomy under anesthesia as in the resection group. After measuring the length of the jejunoileum, the intestine was transected and reanastomosed as above at the two places corresponding to the transections in the resection groups; however, the intervening intestine was not resected. The abdomen was closed and analgesia provided as above.

Tissue Harvest Tissue from all rats was harvested consistently at 9 A.M. due to known diurnal variations in gene expression of PepT1.[9,10] The rats were anesthetized as described previously and a secondary mid-ventral celiotomy performed. The duodenum was cannulated just distal to the pylorus, and the small and large intestines were flushed with cold (4°C) Ringers solution. The duodenum, remnant jejunum, ileum, and proximal colon were harvested from the rats that had undergone intestinal resection 1 and 4 weeks prior to harvest. In the non-operated controls and the operated controls, the proximal jejunum and distal ileum, which corresponded to the remnant segments in the resection group, along with the duodenum and colon were harvested at 0 and 1 week, respectively. The mucosa of the jejunum, ileum, and colon was scraped using a glass slide and stored in a RNA stabilizing solution (RNALater, Qiagen, Valencia, CA, USA) for mRNA analysis and in RIPA buffer containing protease inhibitors (Halt protease, Pierce, Rockford, IL, USA) and phenylmethanesulfonyl fluoride solution (PMSF; Sigma Aldrich, St. Louis, MO, USA) for protein analysis. There was not enough duodenal tissue to harvest mucosa. The mucosal tissues were frozen in liquid nitrogen and stored at −80°C for later batch analysis. A piece of intestine was pinned carefully onto a silicon elastomer support and fixed in 10% formalin for histomorphologic analysis after staining with hematoxylin and eosin.

In Vitro Peptide Uptake/Everted Sleeve Technique The harvested segments of gut were placed in cold (4°C) Ringers solution oxygenated with 95% O_2/5% CO_2. Rate of transport of the non-hydrolyzable dipeptide glycyl-sarcosine (Gly-Sar; Sigma Aldrich, St. Louis, MO, USA) was measured using the everted sleeve technique using 1-cm segments of bowel everted over steel rod as described previously.[5,9,11,12]

The sleeves were incubated initially for 3 min in a warm (38°C) buffer solution (129 mM NaCl, 5.1 mM KCl, 1.4 mM $CaCl_2$, 1.3 mM NaH_2PO_4, 1.3 mM Na_2HPO_4 adjusted to a pH of 6). The sleeves were then incubated for 1 min in 8 ml of test solution containing Gly-Sar at various concentrations (0.02–40 mM). Test solutions were prepared by isosmolar replacement of NaCl with Gly-Sar in the buffer solution. To each test tube, 1 mCi of ^{14}C-labeled Gly-Sar (Moravek Biochemicals, Brea, CA, USA) was added. After incubating for 1 min, the intestinal sleeves were dissolved in 1 ml of tissue solvent (Solvable, Perkin Elmer, MA, USA), mixed in 15 ml of scintillation cocktail (Optiflour, Perkin Elmer, MA, USA), and ^{14}C radioactivity was measured in a Beckman LS6000SC counter (Beckman Coulter, Brea, CA, USA). Carrier-mediated (active) transport was calculated as nanomoles per centimeter per minute as described previously.[9,12]

Protein Analysis The mucosal samples were thawed on ice and homogenized in RIPA buffer containing protease inhibitor and PMSF using a Kontes pestle (Fischer Scientific, Pittsburg, PA, USA). The protein content was estimated by bicinchoninic acid method (Pierce, Rockford, IL, USA). Protein (200 μg) from each sample was resolved on 10% sodium dodecyl sulfate polyacrylamide gel electrophoresis (Bio-Rad, Hercules, CA, USA) and transferred electrically onto polyvinylidene fluoride membranes (Millipore, Bedford, MA). PepT1 was detected using IgG antibodies raised in rabbits (Santa Cruz Biotechnology, Santa Cruz, CA, USA). Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was detected using IgG antibody raised in mice (US Biological, Swampscott, MA, USA). Corresponding secondary antibodies conjugated with horseradish peroxidase (Sigma Aldrich, St. Louis, MO, USA) were used to identify the protein bands using Opti-4CN calorimetric substrate kits (Bio-Rad). The PepT1 band was enhanced with Amplified Opti-4CN substrate kit band intensity and measured using ImageJ 1.42 (NIH, Bethesda, MD, USA). The amount of PepT1 was normalized to levels of the stably expressed housekeeper gene GAPDH. Values are represented relative to protein expression levels in non-operated control rats.

mRNA Analysis Mucosal scrapings frozen in RNALater at −80°C were thawed on ice and homogenized. RNA was extracted using a RNAeasy Midi Kit (Qiagen) according to the manufacturer's instruction. RNA concentration was estimated by spectrophotometry. From this RNA, cDNA was reverse transcribed with Superscript II kit (Invitrogen, Carlsbad, CA, USA) and random hexamer primers. The cDNA was stored at −80°C. PepT1 mRNA was quantified by real-time reverse transcriptase polymerase chain reaction (PCR) using a 7500 Thermocycler and Taqman® chemistries with primers and fluorescently labeled probes in assay mixes according to the manufacturer's instructions (Applied Biosystems, San Francisco, CA, USA). All samples were run as duplicates with 2 μl of sample cDNA (or known standard) added to 23 μl of master mix for a total sample volume of 25 μl. Real-time PCR was carried out at 95°C for 10 min followed by 40 cycles of 15 s at 95°C and 1 min at 60°C during which fluorescence was measured. mRNA levels were normalized to levels of GAPDH, a housekeeper gene. Values are represented relative to mRNA expression levels in non-operated control rats.

Histomorphometry The formalin-fixed tissues from the duodenum, jejunum, ileum, and colon from six rats in each group were embedded in paraffin and sectioned along the villus axis. A minimum of eight sections were cut from each tissue sample, and hematoxylin-and-eosin staining was performed. Maximum villus height and crypt depth was measured from the top of the crypt to the tip of the villus at ×10 magnification. A minimum of six sections were reviewed per each segment with at least three measurements of villus height per section so that at least 18 measurements were made for each segment per rat.

Data Analysis

Data are represented as median (interquartile range). Data were analyzed by Kruskal–Wallis test and Wilcoxon test using JMP 8.0 (SAS Institute Inc., Cary, NC, USA). p value of <0.05 was considered significant. Bonferroni correction was performed where applicable.

Results

Body Weight

All animals appeared healthy and ate normally. At 1 week postoperatively, the rats that underwent 70% resection lost more weight than the control group and the operated control group (−6% vs 8% and 1%, $p<0.05$; Fig. 1). By 4 weeks, the resection group had gained 29% (22%, 31%) of their initial weight; however, this weight gain was less than the weight gained by non-operated control rats over 4 weeks of 33% (30%, 37%; $p<0.05$) pointing to the establishment of a transient malabsorptive state. In the resection group, both proximal and distal small intestine were found to have undergone progressive dilation along with an increase in wall thickness at time of tissue harvest. The small intestine of the operated control rats appeared normal without apparent dilation.

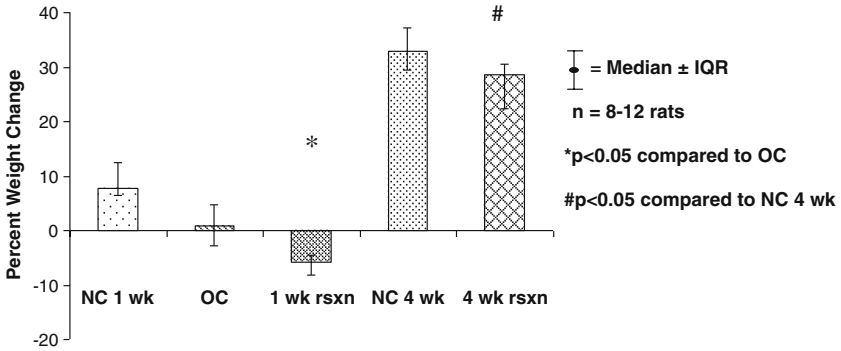

Fig. 1 Weight change expressed as percentage change in initial weight in non-operated control rats at 1 week (*NC 1 wk*), operated controls at 1 week (*OC*) and 1 week postresection rats (*1 wk rsxn*), and weight change in non-operated control rats at 4 weeks (*NC 4 wk*) compared to resection rats at 4 weeks (*4 wk rsxn*). Weight change in resection group is less that OC at 1 week and less than non-operated controls over 4 weeks

Peptide Transport

No difference was observed in the rate of peptide uptake between the non-operated and operated control groups when expressed as uptake per centimeter ($p>0.05$; Fig. 2a, b), suggesting that the anesthesia and operative procedure did not affect peptide uptake measured at 1 week postoperatively. In contrast, at 1 and 4 weeks after 70% mid-small bowel resection, peptide uptake in the remnant segments was altered.

In the duodenum, compared to non-operated controls, the mean Gly-Sar uptake (nanomoles per centimeter per minute) was increased at 1 week postresection to 6.6 (3.8, 16.2) vs 22.0 (7.8, 22.2), but at 4 weeks postresection, Gly-Sar uptake decreased to levels not different from the non-operated control group 8.2 (−0.7, 12.8); these changes were not statistically significant.

In the jejunum, Kruskal–Wallis rank sum showed a change in peptide uptakes after intestinal resection ($p<0.05$), and uptake at 1 and 4 weeks was greater than in the control

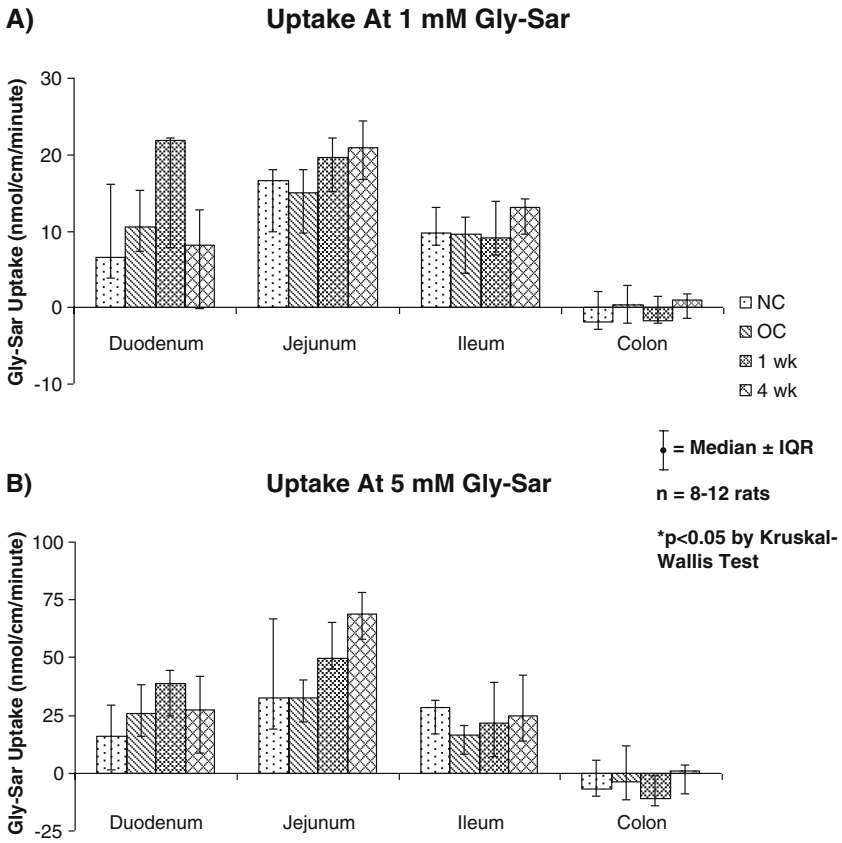

Fig. 2 Carrier-mediated Gly-Sar uptake at **a** 1 mM and **b** 5 mM Gly-Sar concentrations in the four anatomic segments of the intestine in non-operated control (*NC*), operated control (*OC*), 1 week post resection group (*1 wk rsxn*), and 4 weeks postresection group (*4 wk rsxn*). Gly-Sar uptake is increased significantly 4 weeks after resection in the jejunum

group (32.5 vs 49.5 and 69.0, respectively, Fig. 2a, b). In the remnant (distal) ileum, there were no changes in rate of peptide uptake after resection compared to the distal ileum in the non-operated control group. We could not measure any substantive Gly-Sar uptake in the colon in non-operated control, operated control, and postresection groups (Fig. 2a, b).

Protein Expression

Protein levels of PepT1 were normalized to levels of GAPDH, a stably expressed housekeeper gene, to estimate relative expression levels per enterocyte in the four groups. Non-operated controls had similar PepT1 protein levels in the proximal jejunum and distal ileum compared to the operated controls. After 70% mid-small intestinal resection, no differences were seen in expression levels of PepT1 protein in the remnant jejunum at 1 and 4 weeks post-resection when compared to non-operated and operated control rats ($p>0.05$; Fig. 3a). In contrast, in the ileum, the amount of PepT1 was decreased at both 1- and 4-week time points at 0.50 (0.46, 0.86) and 0.65 (0.53, 0.72) vs 1.00 (0.89, 1.07), respectively ($p<0.01$). In the colon, although PepT1 was measurable in all groups, no changes were noted in PepT1 protein content in operated controls and after small intestine resection (Fig. 3b).

mRNA Analysis

PepT1 mRNA levels were also normalized to levels of GAPDH, a stably expressed housekeeper gene, to estimate relative expression level per enterocyte in the four groups. Operated controls had similar PepT1 mRNA levels in all segments of the intestine compared to the non-operated controls. In contrast, in the remnant distal ileum, PepT1 mRNA was decreased at 1 week after intestinal resection compared to non-operated controls ($p<0.01$; Fig. 4). However, no differences were observed at 4 weeks after resection. PepT1 mRNA levels were not altered in the jejunum and colon in all groups.

Histomorphometry

In the duodenum, there were no significant changes in the height of villi in operated control and postresection groups when compared to non-operated control group. The villus height of the jejunum after intestinal resection was increased at both 1 and 4 weeks ($p<0.01$: Fig. 5). Villus height was also greater in the operated control group also ($p<0.02$). In the ileum, no difference was noted between the non-operated and operated control groups. After intestinal resection, however, when compared to the non-operated controls, the villus height was increased at 1 and at 4 weeks

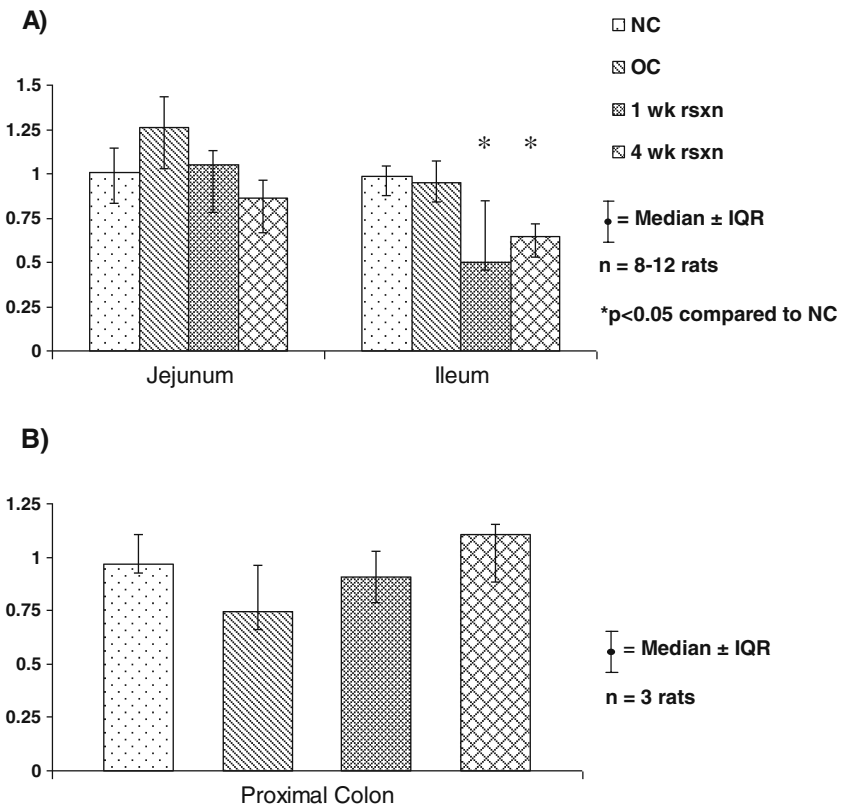

Fig. 3 Variations in relative cellular levels of PepT1 protein in **a** proximal jejunum and distal ileum and **b** proximal colon in non-operated control (*NC*), operated control (*OC*), 1 week postresection group (*1 wk rsxn*), and 4 weeks postresection group (*4 wk rsxn*). PepT1 protein levels are decreased in ileum after resection. No change noted in colon

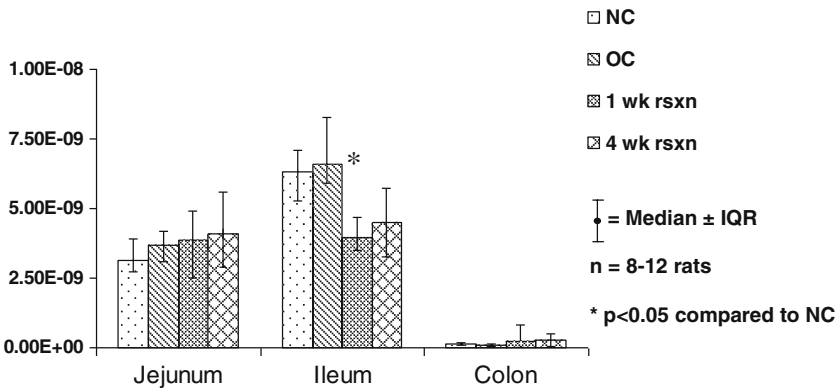

Fig. 4 Variations in relative cellular levels of PepT1 mRNA in proximal jejunum, distal ileum, and proximal colon in non-operated control (*NC*), operated control (*OC*), 1 week postresection group (*1 wk rsxn*), and 4 weeks postresection group (*4 wk rsxn*). PepT1 mRNA levels are decreased in ileum 1 week after resection. No change noted in colon

($p<0.01$). There were no changes observed in the colon across the groups.

Discussion

Our study was designed specifically to evaluate the ability of the duodenum, proximal jejunum, distal ileum, and proximal colon to adapt its capacity for peptide absorption after a massive mid-small bowel resection. This study showed that in rats, the jejunum increased its absorptive capacity for peptides not by upregulating the gene expression of peptide transporter PepT1 but rather by mucosal hyperplasia and intestinal dilatation. In contrast, the distal ileum did not increase its capacity for peptide uptake despite the hyperplasia that occurred, suggesting a different adaptive process than in the jejunum. These findings may have important clinical implications after massive intestinal loss/resection.

Recent interest in the intestinal peptide transporter PepT1 arises from its ability to transport a variety of peptide-like drugs, including β lactams,[13] angiotensin converting enzyme inhibitors,[14] and several antiviral drugs[15–17]; indeed, the literature on PepT1 is dominated by its pharmacologic investigation. The importance of peptide transport in health and disease, as well as the limited understanding of the physiology of PepT1 expression and function, captured our interest as we have studied hexose transport. Because PepT1 is capable of transporting all dietary di- and tripeptides,[18,19] it serves as the primary pathway for absorption of the ingested protein after luminal digestion into di- and tripeptides.[20] Hence, understanding the regulatory mechanism(s) of the transporter could provide newer treatment options for improving nutrient absorption in short bowel syndrome.

Our interest focused on mechanisms by which the gut can adapt to loss of absorptive surface area. Intestinal adaptation to increase absorption after resection can occur by epithelial hyperplasia with an increase in number of enterocytes through an increase in villous height resulting in an increase in absorptive surface area, or by cellular upregulation of gene expression of selective transporters resulting in an increase in (absolute or functional) number of transport proteins per enterocyte. In this study, we investigated the adaptive changes occurring in the rat duodenum, proximal jejunum, distal ileum, and colon after a 70% mid-small intestinal resection that led to a "short bowel" syndrome. The jejunum appears to be the principle site of peptide absorption in the non-operated control rats. After 70% resection, we showed that there was an increase in rate of peptide uptake per centimeter of proximal jejunum of about 40%. The proximal jejunum underwent a rapid increase in villus height combined with dilation of the intestine, both of which serve to increase mucosal absorptive area. The villus height was increased as early as

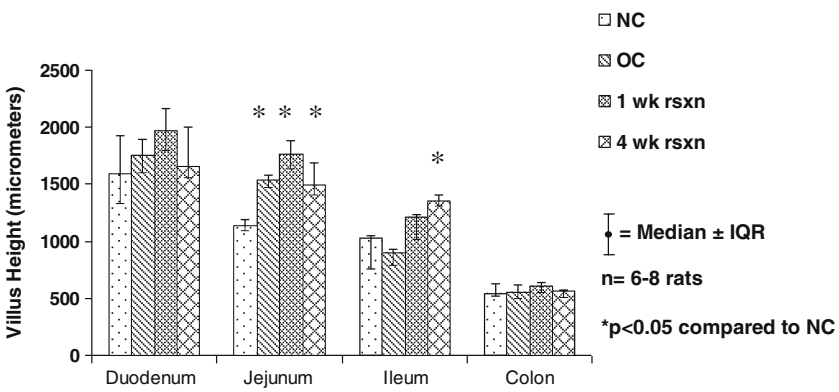

Fig. 5 Change in villous height/colonic crypt depth in the four anatomic segments of the intestines in non-operated control (*NC*), operated control (*OC*), 1 week postresection group (*1 wk rsxn*), and 4 weeks postresection group (*4 wk rsxn*). Villus height is increased in jejunum and ileum after resection

1 week postoperatively and did not show any further change 4 weeks postresection, suggesting that the epithelial proliferation reached its adaptive change by 1 week. In contrast, PepT1 mRNA and PepT1 protein per enterocyte at 1 and 4 weeks postresection as estimated by the PepT1 expression levels normalized to the stably expressed housekeeper gene GAPDH were comparable to the non-operated rats. These findings of an apparent lack of an increase (upregulation) in gene expression (mRNA and transport protein per cell) suggest that the jejunal adaptation to an acute operative loss of 70% of the mid-small intestine occurs primarily by hyperplasia. These findings refute our study hypothesis but are consistent with our prior work with hexose transporters (SGLT1 and GLUT2) where the increase in glucose uptake per centimeter of intestine after massive small bowel resection appeared to occur solely by increased mucosal surface area (villus hyperplasia, intestinal dilation) and not via increase in gene expression per enterocyte for these two hexose transporters.[5]

The distal most ileum (terminal 10 cm) also demonstrates progressive villous hyperplasia after resection. Unlike in the jejunum, however, the processes promoting hyperplasia continue beyond 1 week, and the villi were taller at 4 weeks postresection compared to the 1-week time point. Interestingly, this increase in effective ileal absorptive surface area did not increase functional peptide uptake after resection as measured by everted sleeve technique. Furthermore, the amount of PepT1 protein per enterocyte was decreased at both 1 and 4 weeks postresection, and PepT1 mRNA content was also decreased at 1 week postresection. These findings suggest, potentially, a more immature, undifferentiated epithelium. These data differ from previous studies from our lab (unpublished data) where we measured adaptation in the mid-ileum for peptide and hexose transport[11] in rats that had undergone a 70% proximal jejunoileal resection with the entire jejunum being resected. Adaptive regulation of PepT1 gene expression has been shown to occur in response to substrate concentration in the lumen.[21–23] The presence of proximal jejunum with an increased capacity for peptide absorption might decrease the amount of dietary peptides reaching the terminal ileum and thereby alter ileal adaptation; other possibilities, of course, might include an inability of the distal ileum, in contrast to the mid-ileum, to undergo a rapid adaptation to increase absorption. We have no data on long-term adaptive potential of distal ileum that might occur later than 4 weeks after this 70% mid-small bowel resection.

The changes occurring in the colon of people with short bowel syndrome have received considerable interest in terms of the role of proximal colon in adapting its functional absorption of luminal nutrients. Of note, we were unable to show any substantive uptake of dipeptides into everted sleeves of proximal rat colon or any changes in PepT1 mRNA and protein levels, or histomorphometry. These findings appear to be in contrast to studies in humans with short bowel syndrome that demonstrated an increase in PepT1 mRNA and colonic absorptive surface.[7,8] The presence of a large functional cecum in rats may prevent a meaningful comparison of colonic adaptation in rats and humans.

Our study has several limitations. First, we could not estimate PepT1 expression in the duodenum due to the limited length of the duodenal segment; the rat duodenum is only about 6 to 7 cm, and most the duodenum was used to measure peptide uptake by everted sleeves. In addition, rats have a very large functional cecum which may affect adaptive need. Also, our technique for protein analysis cannot distinguish membrane-bound PepT1 transporter (functional protein) from the intracytoplasmic pool of PepT1 protein (non-functional protein). Cellular regulatory processes might alter intracellular translocation of PepT1 into and out from the apical membrane to increase peptide absorption without altering total cellular PepT1 content as occurring with other transport proteins such as GLUT2.[24]

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Discussant

Dr. Tien C. Ko (Houston, TX): I want to congratulate the authors on a very careful and important study on looking at adaptive response after massive small bowel resection.

It was surprising that you found no change in PepT1 transporter, which is a major transporter for the oligopeptides; however, this lack of a change is based on standardization against GAPDH and you equate that to cell number. I think you have to be a little bit careful because GAPDH may also change, even though it is a housekeeping gene. In many circumstances, housekeeping genes actually do change. Have you analyzed the expression of your mRNA and protein for PepT1 normalized to total DNA or total protein content?

Closing Discussant

Dr. Srivats Madhavan: We have not compared protein and mRNA to total DNA. We will consider normalizing PepT1 expression to DNA in our future study designs; we are less interested in normalizing PepT1 to total protein.

Discussant

Dr. Tien Ko (Houston, TX): You demonstrated that there is an increase in the transport of oligopeptide. How can we take advantage of that to help our patients? Are there things that we can do to augment that response, based on your study and your laboratory's other studies previously published?

Closing Discussant

Dr. Srivats Madhavan: In our model, the jejunum appears to be primarily involved in adaptation to peptide absorption, at least within the first month postoperatively. From a nutritional point, patients undergoing massive intestinal resection might benefit from conserving as much jejunum as possible. Second, considerable data demonstrate the influence of the type of diet on protein absorption. Peptides are absorbed faster and more efficiently compared to complete proteins and individual amino acids. Patients with short bowel syndrome might benefit from including short peptides, not amino acids, in their diet rather than complex proteins, although synthesis of di- and tripeptides is difficult and expensive.

Discussant

Dr. Emina H. Huang (Gainesville, FL): You document that the rats are between 200 and 250 g, which I presume is an adult rat. Since this type of situation, where you might lose a lot of small bowel might be more apropos to a neonate with necrotizing enterocolitis, for example, have you looked in a younger population, a neonate rat or a rat that is less than 4 weeks of age?

Closing Discussant

Dr. Srivats Madhavan: In young rats, there are physiologic fluctuations in intestinal PepT1 expression. We used middle-aged rats because PepT1 expression is stable.

Discussant

Dr. Jeffrey B. Matthews (Chicago, IL): A number of groups, including your own, have looked at various sodium-coupled transporters after massive small bowel resection and found different patterns of adaptation. Can you speculate on the basis of why some sodium-coupled transporters would adapt and PepT1 does not?

Discussant

Dr. Jeffrey B. Matthews (Chicago, IL): After massive small bowel resection, there are transporters that show strikingly different patterns of changes of adaptation—some go up, some go down, and here you show that PepT1 under? goes minimal adaptation. What accounts for the differences?

Closing Discussant

Dr. Srivats Madhavan: Our data are consistent with previous studies from our lab on the intestinal hexose transporter, Glut2 and SGLT1, the archetype sodium-coupled transporter. No changes in gene expression per enterocyte were noticed in this rat model of acute intestinal loss despite a marked increase in rate of glucose absorption after resection. The adaptive mechanism appears to be exclusively by proliferation and an increase in villus height. There was no increase in the amount of transporters per enterocyte after resection.

Discussant

Dr. Charles Yeo (Philadelphia, PA): I want to congratulate you on a wonderful experiment. You set out to test the hypothesis. You set the experiment up perfectly to prove the hypothesis. Your results did not turn out to prove the hypothesis, which, I must say, probably 90% of the experiments I ever set up, exactly this is the outcome. And then you always ask yourself, is there any way to salvage the data? In molecular genetics, we can use TMAs to probe for different molecules—expression of various different proteins, etc. Is there any way that you can salvage this experiment, by somehow probing it again, or probing the effluent from your transporter studies. I am just trying to think what more can we learn from an experiment like this, beyond the fact we just did not prove our hypothesis?

Closing Discussant

Dr. Srivats Madhavan: That is a great question. Right now, we have a technique that can determine peptide uptake into the intestinal epithelium. The result from this study gives us a basic understanding of the physiologic changes, i.e., which part of the intestine demonstrates an adaptive change and how that adaptation occurs. This finding may help direct further studies using an in vivo model to measure nutrient absorption from the intestine which will yield more physiologic data on absorption. It is also be possible to further probe the samples collected to identify the signaling mechanism for the adaptive changes observed.

Discussant

Dr. Margot Fijlstra (Amsterdam): You took out part of the small intestine to study absorption from the remaining small intestine. Do you have any idea if you would test absorption in vivo, how much normal absorption would still be there if you stabilized the nutrient, for instance? Do you have any clue how much of normal absorption is still present in vivo?

Closing Discussant

Dr. Srivats Madhavan: We did not do a metabolic study. We have no data on the fraction of the total caloric intake that was absorbed.

Discussant

Dr. Richard Hodin (Boston, MA): Do I understand correctly that another group has previously shown PepT1 expression increases after small bowel resection? And, if so, do you have an explanation for why your results are different than that?

Closing Discussant

Dr. Srivats Madhavan: There are studies in patients with short bowel syndrome that have demonstrated increased

PepT1 expression in the colon; however, these patients have had their pathology for several years and represent a long-term adaptation. Our study focused on the acute and sub-acute changes occurring in the intestine. The adaptive changes in the colon might be occurring much later in time. Some investigators have also used massive intestinal resection as a mechanism to induce colonic PepT1 expression. We could not, however, measure any change in colonic PepT1 expression. This difference between studies could be due to differences in length of the resected segment and the part of the intestine being resected, proximal versus middle versus distal intestine.

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2010 SSAT PLENARY PRESENTATION

Risk Stratification for Distal Pancreatectomy Utilizing ACS-NSQIP: Preoperative Factors Predict Morbidity and Mortality

Kaitlyn Jane Kelly · David Yu Greenblatt · Yin Wan · Robert J. Rettammel · Emily Winslow · Clifford S. Cho · Sharon M. Weber

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Abstract
Background Evaluation of risk factors for adverse outcomes following distal pancreatectomy (DP) has been limited to data collected from retrospective, primarily single-institution studies. Using a large, multi-institutional prospectively collected dataset, we sought to define the incidence of complications after DP, identify the preoperative and operative risk factors for the development of complications, and develop a risk score that can be utilized preoperatively.
Methods The American College of Surgeons National Surgical Quality Improvement Program participant use file was utilized to identify patients who underwent DP from 2005 to 2008 by Current Procedural Terminology codes. Multivariate logistic regression analysis was performed to identify variables associated with 30-day morbidity and mortality. A scoring system was developed to allow for preoperative risk stratification.
Results In 2,322 patients who underwent DP, overall 30-day complication and mortality were 28.1% and 1.2%, respectively. Serious complication occurred in 22.2%, and the most common complications included sepsis (8.7%), surgical site infection (5.9%), and pneumonia (4.7%). On multivariate analysis, preoperative variables associated with morbidity included male gender, high BMI, smoking, steroid use, neurologic disease, preoperative SIRS/sepsis, hypoalbuminemia, elevated creatinine, and abnormal platelet count. Preoperative variables associated with 30-day mortality included esophageal varices, neurologic disease, dependent functional status, recent weight loss, elevated alkaline phosphatase, and elevated blood urea nitrogen. Operative variables associated with both morbidity and mortality included high intraoperative transfusion requirement (≥3 U) and prolonged operation time (>360 min). Weighted risk scores were created based on the preoperatively determined factors that predicted both morbidity ($p<0.001$) and mortality ($p<0.001$) after DP.
Discussion The rate of serious complication after DP is 22%. The DP-specific preoperative risk scoring system described in this paper may be utilized for patient counseling and informed consent discussions, identifying high-risk patients who would benefit from disease optimization, and risk adjustment when comparing outcomes between institutions.

This work was presented at the S.S.A.T. Residents and Fellows Conference, New Orleans, Louisiana, 1 May 2010, and at the S.S.A.T. Annual Meeting (D.D.W.), New Orleans, Louisiana, 3 May 2010.

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Introduction

Historically, tumors of the distal pancreas have been diagnosed late due to lack of symptoms from lesions in this portion of the gland. With recent advances in radiographic modalities such as ultrasound and cross-

sectional imaging, however, there has been an increase in incidental diagnosis of distal pancreas lesions.[1–3] Distal pancreatectomy (DP) is therefore being performed more frequently and is being performed in an increasingly elderly population.[1,4]

DP is reliably performed with low perioperative mortality, ranging from 0% to 4% in recent series. Perioperative morbidity associated with this procedure, however, remains high, ranging from 22% to 57%.[1,5–8] Many investigators have attempted to identify risk factors for perioperative complications, but most have focused largely on operative variables such as the technique of closure of the pancreatic stump, concomitant resection of other organs, and operative time.[4,9–11] A few studies have attempted to identify preoperative factors that may increase the risk of perioperative complications, but these have been primarily single-institution series or have been limited by small sample sizes.[5–7,12–14]

The goal of the current study was to use a large, multi-institutional dataset to identify preoperative factors that increase the risk of perioperative complications after DP and to create a simple risk score that can be determined prior to surgery. This risk score can be utilized clinically for obtaining informed consent, for comparing risk-adjusted outcomes between different institutions, and for optimizing patient status prior to surgery to potentially decrease the incidence of perioperative morbidity.

Methods

Data Acquisition and Patient Selection

The American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) provides risk-adjusted outcome data to participating hospitals for the purpose of quality improvement. The program focuses on 30-day postoperative outcomes, including mortality and 21 categories of morbidity. Data collection at each of the 211 participating institutions is performed by a dedicated surgical clinical reviewer (SCR), with support and oversight from a nurse coordinator. The SCR, using medical chart extraction, 30-day interviews, and other methods, collects detailed data on patient demographics, comorbidities, laboratory values, operative variables, and postoperative outcomes including 30-day complications, 30-day mortality, reoperation, and length of stay. Descriptions of the qualifications, training, and auditing of data collection personnel, case inclusion criteria, sampling and data collection strategy, and variable and outcome definitions are available online in the ACS NSQIP participant user guide.[15]

Patients who underwent DP were identified from the 2005 to 2008 ACS NSQIP Participant Use Data Files. DPs were identified using the Current Procedural Terminology codes 48140, 48145, and 48146. Patients undergoing pancreaticoduodenectomy or total pancreatectomy were not included. Because our goal was to make the study group representative of patients undergoing DP in the elective setting, we excluded high-risk patients with any of the following characteristics: American Society of Anesthesiologists (ASA) class 5 (moribund), preoperative ventilator dependence, current pneumonia, open wound or wound infection, acute renal failure, coma, and septic shock. We also excluded patients undergoing DP emergently for trauma as this indication has been shown to significantly increase the risk for perioperative complications.[10]

Outcomes

Thirty-day outcomes included overall complications, serious complications, and mortality. We defined serious complication, or morbidity, as the diagnosis of any of the following in the 30 days after DP: sepsis (sepsis and septic shock); surgical site infection (deep surgical site infection, organ/space infection, and dehiscence); respiratory complication (pneumonia, ventilator dependence for >48 h, and unplanned reintubation); thromboembolism (pulmonary embolism and deep vein thrombosis); cardiac complication (acute myocardial infarction and cardiac arrest requiring resuscitation); neurologic complication (stroke and coma); renal complication (postoperative progressive renal insufficiency and acute renal failure); hemorrhage (bleeding requiring transfusion of at least 4 U of packed red blood cells); and graft/prosthesis/flap failure (mechanical failure of an extracardiac graft or prosthesis including myocutenous flaps and skin grafts requiring return to the operating room, interventional radiology, or a balloon angioplasty within 30 days of the operation). We did not consider superficial surgical site infection, urinary tract infection, or peripheral nerve injury to be serious complications and excluded them from the definition of morbidity.

Variables

Independent variables included demographics, preoperative health status and comorbidities, preoperative laboratory values, operative variables, and postoperative diagnosis. Demographics consisted of age, gender, and race (white, black, or other). Variables related to preoperative health included functional status (independent versus partially or totally dependent), body mass index (BMI), weight loss (10% of total body weight in 6 months), smoking (in the last year), alcohol use (more than two drinks per day in the 2 weeks prior to surgery), corticosteroid use, preoperative systemic sepsis (systemic inflammatory response syndrome or sepsis), and recent blood transfusion or operation.

Comorbidities included diabetes mellitus; chronic obstructive pulmonary disease (COPD); coronary artery disease (CAD; history of angina, myocardial infarction, previous percutaneous cardiac intervention, or previous cardiac surgery); peripheral vascular disease (PVD; history of revascularization or amputation for peripheral vascular disease, claudication, rest pain, or gangrene); neurological disease (history of stroke with or without residual deficit, transient ischemic attack, hemiplegia, paraplegia, or quadriplegia, central nervous system tumor, or impaired sensorium); dyspnea; pneumonia; congestive heart failure (CHF); disseminated cancer; and bleeding disorder. Variables related to neoadjuvant therapy included chemotherapy (within 30 days prior to surgery) and radiation therapy (within 90 days prior to surgery). Operative variables included wound class, ASA class, amount of blood transfused, and length of operation.

Preoperative laboratory values consisted of white blood cell (WBC) count, hematocrit, platelet count, international normalized ratio (INR), sodium, blood urea nitrogen (BUN), creatinine, serum glutamic oxaloacetic transaminase (SGOT), alkaline phosphatase, and albumin. Each preoperative laboratory value with missing values was handled with multiple imputation, an approach recommended by several studies on the handling of missing data in ACS NSQIP.[16–19]

Statistical Analyses

The total population of 2,322 patients was randomly divided into an 80% sample for model development and a 20% sample for model validation. The frequencies of the independent and dependent variables were determined in the 80% analysis sample. Continuous variables were compared using the Wilcoxon rank sum test or Mann–Whitney *U* test, a non-parametric version of the *t* test, and categorical variables with chi-square tests. All variables with p values<0.10 were eligible for inclusion in the multivariate models for morbidity and mortality. Multivariate stepwise logistic regression was utilized to calculate adjusted odds ratios and 90% confidence intervals (CIs) for 30-day morbidity and mortality.

Development of a Risk Score Model

Bootstrapping was then used to generate 200 samples. The median beta coefficients from the multivariable regression model were used to develop an integer-based weighted scoring system for the determination of 30-day morbidity and mortality risk as described previously. The referent category for each variable was assigned a score of 0. The remaining categories for each variable were assigned scores proportional to the lowest beta coefficient. A risk score was then calculated for each individual patient by summing the scores from each variable. Risk scores were then stratified into groups according to the estimated morbidity and mortality. This method of risk score development has been described previously.[18, 20–22] Separate risk scores were developed for both 30-day morbidity and mortality after DP.

Morbidity and mortality risk scores were calculated for each patient in the data development set. Discrimination was assessed with the area under the receiver operating characteristic curve. Validity of the scores was assessed by the same method for each record within the previously randomly isolated validation cohort. Concordance indices (*C* indices) were calculated to quantify the predictive accuracy of the final multivariate models of morbidity and mortality in the 20% validation sample. Analyses were performed using SAS 9.1.3 for Windows (SAS Institute, Cary, NC, USA). All tests of significance were at the $p<0.10$ level, and p values were two-tailed.

Results

Patient Characteristics

A total of 2,322 patients who underwent DP were captured in the ACS NSQIP database between 2005 and 2008. The majority (59%) of the patients were women. Approximately one half of the patients (49%) were <60 years old, whereas 46% were between the ages of 60 and 79, and 5% were ≥80 years old. Seventy-eight percent of the patients were white and the remaining 22% were non-white or had race data missing. Forty-three percent of patients had a final histopathologic diagnosis of malignancy while the remainder had benign disease.

Overall Complication Rate

Among 2,322 patients who underwent DP, 30-day morbidity and mortality were 22.2% and 1.2%, respectively. The overall complication rate was 28.1%. All complications are listed in Table 1. Patients who experienced a serious complication had a mean length of stay of 14.7 days versus 7.6 days for those who did not ($p<0.0001$).

Predictors of Morbidity and Mortality

A random sample of 80% of the cohort ($n=1,797$) was selected for the model development set and the remaining 20% of patients used for the validation of the model. Table 2 summarizes the results of univariate analysis of preoperative and operative variables with the combined outcome of morbidity or mortality in the 80% cohort.

Table 1 Frequency of complications in 2,322 patients who underwent DP

Complication	Frequency	Percentage
Infectious	568	24.5
Organ space SSI	214	9.2
Sepsis	203	8.7
Superficial SSI	137	5.9
Pneumonia	111	4.7
Urinary tract infection	96	4.1
Septic shock	53	2.3
Deep incisional SSI	31	1.3
Wound disruption	18	0.8
Hematologic	108	4.7
DVT/thrombophlebitis	48	2.1
Pulmonary embolism	40	1.7
Bleeding	28	1.2
Respiratory	100	4.3
Ventilator >48h	79	3.4
Unplanned intubation	58	2.5
Renal	20	0.9
Progressive renal insufficiency	12	0.5
Acute renal failure	10	0.4
Cardiovascular	19	0.8
Cardiac arrest requiring CPR	13	0.6
Myocardial infarction	6	0.3
Neurologic	9	0.4
Stroke/CVA with neurological deficit	5	0.2
Coma >24h	2	0.1
Peripheral nerve injury	2	0.1
Other	3	0.1
Graft/prosthesis/flap failure	3	0.1
Overall complications	653	28.1
Serious complications	516	22.2

SSI surgical site infection, *DVT* deep vein thrombosis, *CPR* cardiopulmonary resuscitation

Morbidity Modeling

When performed specifically for morbidity, univariate analysis demonstrated that the following preoperative variables were significantly associated at the $p<0.10$ level: low (<18.5 kg/m^2) or high (≥30 kg/m^2) BMI, male gender, smoking, ASA classification, dependent functional status, elevated INR (>1.3), chronic steroid use, leukocytosis (>11,000 cells/mm^3), low hematocrit (<38.0%), abnormal platelet count (<50,000 or >400,000 platelets/mm^3), elevated serum creatinine (>1.4 mg/dL), low serum albumin (<3.4 g/dL), CAD, PVD, neurologic disease, dyspnea, ascites, bleeding disorders, and SIRS/sepsis. Operative variables associated with morbidity were prolonged operation time and high transfusion requirement (>3 U of packed red blood cells).

Multivariable logistic regression analysis was performed incorporating all variables that were found to be significantly associated with morbidity on univariate analysis. Preoperative variables found to be independent multivariate predictors of morbidity included male gender, low or high BMI, CAD, smoking, chronic steroid use, SIRS/sepsis, hypoalbuminemia, thrombocytosis, and elevated serum creatinine (Table 3).

Morbidity Risk Score

Preoperative factors associated with morbidity on multivariable analysis were incorporated into a simple complication risk score (Table 4). The score for each individual patient was determined by simply summing the integer values assigned for each variable in the model. This preoperatively determinable risk score predicted the incidence of perioperative morbidity after DP. The range in morbidity risk score was 0–40. The highest score of any patient in this cohort was 23. Possible risk scores were stratified into three clinically useful groups based on these data. A low-risk group defined as a score of 0–5 had a 17% morbidity rate. A moderate-risk group with scores of 6–10 had a morbidity rate of 25%. A high-risk group with scores of 11–15 had a morbidity rate of 41%, and a very high-risk group defined as a score of >15 had a 67% morbidity rate (Fig. 1). The model demonstrated good discrimination with a *C* index of 0.64 in the validation dataset.

Mortality Modeling

When performed specifically for 30-day mortality, univariate analysis demonstrated that the following preoperative variables were significantly associated at the $p<0.10$ level: high BMI (>30 kg/m^2), ASA classification, dependent functional status, CHF, recent weight loss (>10% body weight), low hematocrit (<38.0%), hyponatremia (<135 mmol/L), high BUN (>40 mg/dL), elevated serum creatinine (>1.4 mg/dL), elevated alkaline phosphatase (>125 U/L), low serum albumin (<3.4 gm/dL), neurologic disease, alcohol consumption (more than two drinks daily), esophageal varices, and SIRS/sepsis. Operative variables associated with mortality included prolonged operation time and high transfusion requirement (>3 U of packed red blood cells).

Preoperative variables significantly associated with mortality on stepwise logistic regression analysis included esophageal varices, neurologic disease, recent weight loss, elevated alkaline phosphatase, elevated BUN, and dependent functional status (Table 5).

Mortality Risk Score

Preoperative variables that were independent predictors of mortality were similarly incorporated into a mortality risk

Table 2 Characteristics of patients who underwent DP in the 80% development set (n=1,797) who experienced 30-day morbidity or mortality

Characteristic	No morbidity or mortality (n=1396)%	Morbidity or mortality (n=401)%	p value
Demographics			
Age (years), mean (SD)	59.2 (14.7)	58.4 (14.5)	0.351
Gender			0.001
Female	61	52	
Male	39	48	
Race/ethnicity			0.978
White	78	78	
Black	9	8	
Other	13	13	
Preoperative health and comorbidities			
BMI (kg/m^2), mean (SD)	28.5 (7.0)	27.7 (6.1)	0.110
Recent weight loss	9	10	0.439
Diabetes mellitus	19	21	0.249
Current smoker within last year	21	27	0.013
Alcohol use (>2 drinks per day)	3	2	0.764
Functional status: partially or totally dependent	2	5	0.001
Dyspnea	8	13	0.009
COPD	4	5	0.255
Coronary artery disease	9	13	0.009
CHF	0	0	0.183
Hypertension	47	48	0.821
Peripheral vascular disease	1	1	0.064
Neurologic disease	4	8	0.0001
Ascites	1	2	0.014
Esophageal varices	0	1	0.110
SIRS/sepsis	1	4	<0.0001
Steroids	2	4	0.007
Bleeding disorder	3	4	0.088
Hemodialysis	0	0	0.901
Preoperative chemotherapy	1	1	0.303
Preoperative radiation therapy	1	0	0.251
Preoperative laboratory values			
Sodium (mmol/L)			0.308
<135	5	6	
135–145	93	93	
>145	2	1	
BUN (>40 mg/dL)	1	1	0.227
Creatinine (>1.4 mg/dL)	5	10	0.0006
Albumin (<3.4 g/dL)	12	21	<0.0001
Total bilirubin (>3.0 mg/dL)	8	13	0.002
SGOT (>40 U/L)	15	16	0.451
Alkaline phosphatase (>125 U/L)	14	17	0.108
WBC count (thousand cells/mm^3)	0		0.010
<4.5	10	6	
4.5–11.0	83	84	
>11.0	7	9	
Hematocrit (<38.0%)	35	41	0.029
Platelet count (thousand cells/mm^3)			0.001
<50	1	1	

Table 2 (continued)

Characteristic	No morbidity or mortality (n=1396)%	Morbidity or mortality (n=401)%	p value
50–400	95	89	
>400	5	9	
INR >1.3	5	8	0.028
Operative variables			
Wound class			0.236
Clean or clean-contaminated	93	91	
Contaminated	5	7	
Dirty or infected	2	2	
ASA class			0.0004
No or mild disturbance	45	35	
Severe disturbance	53	60	
Life threatening disturbance	2	4	
Blood transfusions			>0.0001
None	80	66	
1–2 U	13	16	
>2 U	7	18	
Length of operation			>0.0001
<4 h	64	53	
4–6 h	27	27	
>6 h	9	20	
Postoperative diagnosis			0.319
Malignant	43	46	
Benign	57	54	

Age and BMI are reported as continuous variables with means in years and kilograms per square meter, respectively, for each cohort of patients. The remainder of the variables are categorized with the percentage of patients in each group reported

BMI body mass index, *COPD* chronic obstructive pulmonary disease, *CHF* congestive heart failure, *WBC* white blood cell, *BUN* blood urea nitrogen, *SGOT* serum glutamic oxaloacetic transaminase, *INR* international normalized ratio, *ASA* American Society of Anesthesiologists

score (Table 6). This preoperatively determinable risk score successfully predicted the incidence of mortality after DP. The possible mortality risk score for any given patient ranged from 0 to 13. The highest score of any patient in this cohort was 6. Based on this scale, scores were stratified into three clinically useful groups. A low-risk group with scores ranging from 0 to 2 had a mortality rate of 0.9%. A moderate-risk group defined as a risk score of 3 or 4 had a mortality rate of 4.5%. A high-risk group defined as a score of >4 had a mortality rate of 44% (Fig. 2). The model demonstrated good discrimination with a *C* index of 0.79 in the validation dataset. The final morbidity and mortality multivariate models, based solely on preoperative factors, were used to create an online prediction tool, which will be accessible at the following web address: https://www.surgery.wisc.edu.

Discussion

In the current study, a large, multi-institutional database was used to identify preoperative factors that predict perioperative morbidity and 30-day mortality after DP. Based on this analysis, a weighted, integer-based preoperative risk score was designed and validated.

Multiple investigators have reported on the effects of operative factors, such as method of closure of the pancreatic stump and gland texture, on perioperative morbidity after DP, but few have assessed the association of preoperative factors with outcome.[4,9–11] Those studies that have assessed preoperative factors have been limited by small sample sizes and single-institution series and have found a correlation of increased risk for morbidity and higher BMI,[12] higher ASA score, lower hemoglobin, lower serum albumin, and elevated creatinine.[6] Poor nutritional status (defined as low albumin and/or recent weight loss),[14] advanced age, male gender, and higher BMI have been correlated with an increased risk of pancreatic fistula (PF) after DP.[7,23] Overall, the disparities in these findings between studies, low overall sample sizes, and differences in the methodology of analysis make it difficult to make meaningful conclusions from these data.

ACS NSQIP has several features that make it well equipped to enhance preoperative risk stratification. It

Table 3 Multivariable logistic regression to model risk of 30-day morbidity in the development set

Risk factor	Adjusted odds ratio (90% CI)	*p* value
Gender		
Female	Referent	
Male	1.37 (1.12–1.67)	0.010
BMI (kg/m^2)		
Underweight (<18.5)	1.68 (0.10–2.84)	0.103
Normal (18.5–24.9)	Referent	
Overweight (25.0–29.9)	1.19 (0.93–1.53)	0.256
Obese (≥30.0)	1.44 (1.12–1.85)	0.017
Neurologic disease		
No	Referent	
Yes	2.05 (1.37–3.06)	0.004
Current smoking		
No	Referent	
Yes	1.30 (1.04–1.63)	0.055
Chronic steroid use		
No	Referent	
Yes	2.29 (1.32–3.98)	0.013
Preoperative sepsis		
No	Referent	
Yes	3.09 (1.65–5.82)	0.003
Albumin (g/dL)		
<3.4	1.54 (1.18–2.00)	0.008
≥3.4	Referent	
Creatinine (mg/dL)		
<1.4	1.66 (1.16–2.36)	0.019
≥1.4	Referent	
Platelet count (10^3/mm^3)		
Low (<50)	3.05 (1.15–8.12)	0.061
Normal (50–400)	Referent	
High (>400)	1.79 (1.24–2.59)	0.010

Table 4 Preoperative risk score for morbidity based on beta coefficients from regression model

Risk factor	Risk score
Gender	
Female	0
Male	2
BMI (kg/m^2)	
Underweight (<18.5)	3
Normal (18.5–24.9)	0
Overweight (25.0–29.9)	1
Obese (≥30.0)	2
Neurologic disease	
No	0
Yes	4
Current smoking	
No	0
Yes	2
Chronic steroid use	
No	0
Yes	5
Preoperative sepsis	
No	0
Yes	7
Albumin (g/dL)	
<3.4	2
≥3.4	0
Creatinine (mg/dL)	
<1.4	0
≥1.4	3
Platelet count (10^3/mm^3)	
Low (<50)	6
Normal (50–400)	0
High (>400)	3

The risk score for each individual patient is determined by summing the value for each of the nine variables at the time of preoperative evaluation. The total score may range from 0 to 40

contains an expansive amount of preoperative patient information including medical comorbidities, social habits (i.e., smoking and alcohol use), functional status, steroid and chemotherapy use, and preoperative laboratory values. Furthermore, because ACS NSQIP contains data from >250 different institutions (both academic and community centers), the findings based on these data are likely to be widely applicable as opposed to findings based on data from single-institution studies. Lastly, the large size of this database allows rapid accumulation of large sample sizes. Our sample consisted of 2,322 patients, all of whom underwent DP between 2005 and 2008, by far the largest dataset on which risk factors for morbidity and mortality after DP have been studied. Confining the study dates to a short interval also improves the consistency of the perioperative care delivered and therefore enhances meaningful interpretation of the data.

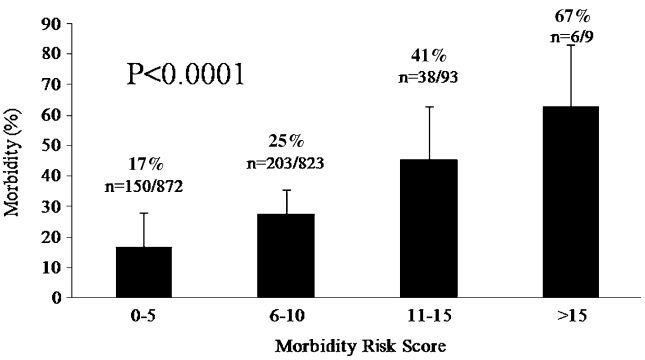

Fig. 1 Integer morbidity risk score (derived from Table 4) correlates with 30-day morbidity

Table 5 Multivariable stepwise logistic regression to model risk of 30-day mortality in the development set

Risk factor	Adjusted odds ratio (90% CI)	*p* value
Esophageal varices		
No	Referent	0.003
Yes	15.43 (3.41–69.90)	
Neurologic disease		
No	Referent	0.023
Yes	4.10 (1.48–11.33)	
Functional status		
Independent	Referent	
Partially or totally dependent	5.42 (1.87–15.72)	0.009
Recent weight loss		
No	Referent	
Yes	2.53 (1.02–6.24)	0.091
Alkaline phosphatase (U/L)		
Low/normal (≤125)	Referent	0.039
High (>125)	2.81 (1.23–6.40)	
BUN (mg/dL)		
Low/normal (≤40)	Referent	<0.001
High (>40)	20.16 (5.08–79.99)	

Table 6 Preoperative risk score for 30-day mortality based on beta coefficients from regression model

Risk factor	Risk score
Esophageal varices	
No	0
Yes	3
Neurologic disease	
No	0
Yes	2
Functional status	
Independent	0
Partially or totally dependent	2
Recent weight loss	
No	0
Yes	1
Alkaline phosphatase (U/L)	
Low/normal (≤125)	0
High (>125)	1
BUN (mg/dL)	
Low/normal (≤40)	0
High (>40)	4

The risk score for each individual patient is determined by summing the value for each of the six variables at the time of preoperative evaluation. The total score may range from 0 to 13

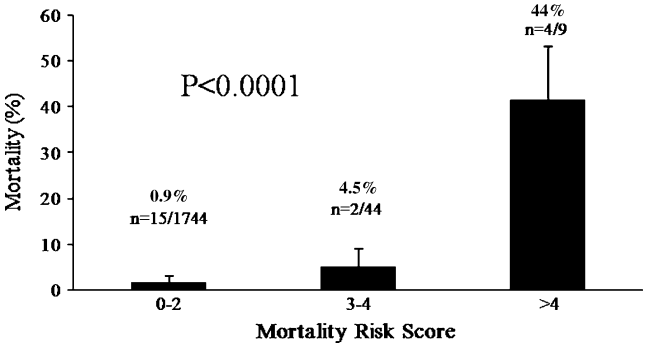

Fig. 2 Integer mortality risk score (derived from Table 6) correlates with 30-day mortality

In this cohort, we observed 30-day morbidity and mortality rates of 22.2% and 1.2%, respectively. This is similar to other recently published series. The most frequent complications included sepsis (8.7%), surgical site infection (5.9%), and pneumonia (4.8%). While ACS NSQIP does not specifically record the incidence of postoperative PF as a complication, clinically significant fistulae (grades B and C by ISGPF definition)[24] are likely to be recorded as organ space, deep incisional surgical site infection (SSI), sepsis, or septic shock based on the NSQIP definitions of these complications.[15,24] This is reflected by the fact that sepsis and surgical site infection are the most common complications that were observed in this study, whereas PF is the most common complication reported in essentially all other published studies evaluating outcome after DP.

In the current study, preoperative factors found to be independent predictors of morbidity included male gender, obesity (BMI > 30 kg/m^2), preexisting neurologic disease, steroid use, SIRS/sepsis, hypoalbuminemia (<3.4 g/dL), elevated creatinine (>1.4 mg/dL), and thrombocytosis (>400,000/mm^3). These findings are congruous with those previously reported by other investigators. Male gender, obesity, hypoalbuminemia, and elevated creatinine have been shown to be associated with morbidity after DP on univariate analysis.[6] Of these factors, only obesity has been previously demonstrated to be an independent predictor of morbidity after DP.[5] Hypoalbuminemia has been shown to predict the specific complication of PF, but has not been previously shown to predict overall morbidity.[14] No studies to date have demonstrated association between neurologic disease, steroid use, SIRS/sepsis, or thrombocytosis with morbidity after DP, which demonstrates the utility of ACS NSQIP for the assessment of previously undefined risk factors.

We initially considered exclusion of patients with preoperative SIRS/sepsis from our study because our aim was to design a model pertinent to elective DP. We noted, however, that a total of 31 patients in our cohort underwent elective DP and met the criterion of having SIRS (n=26) or

sepsis (n=5). ACS NSQIP defines preoperative SIRS as the presence of two or more of the following within the same time frame: temperature >38°C or <36°C; heart rate >90 bpm; respiratory rate >20 breaths/min or $PaCO_2$ <32 mmHg (<4.3 kPa); WBC >12,000 cells/mm^3, <4,000 cells/mm^3, or >10% immature (band) forms, or anion gap acidosis (>12). Sepsis was reported if the patient had clinical signs and symptoms of SIRS listed above plus an identified causative source of infection.[15] Given that the definitions were based on the simultaneous presence of two or more specific vital or laboratory parameters, it is feasible to think that in clinical practice, the presence of SIRS/sepsis might go unrecognized in a patient who does not "look ill" overall. We therefore felt that it was important to report our finding that preoperative SIRS/sepsis as defined in NSQIP is highly associated with perioperative morbidity (OR = 3.09, CI = 1.65–5.82, p = 0.003).

In the present study, preoperative factors found to be independent predictors of mortality included esophageal varices, preexisting neurologic disease, dependent functional status, elevated alkaline phosphatase (>125 U/L), and elevated BUN (>40 mg/dL). This is the first study to report these variables to be independent predictors of 30-day mortality after DP. Elevated BUN, poor functional status, and elevated alkaline phosphatase have been shown to predict 30-day mortality after major general surgery operations in a previous study based on VA-NSQIP data.[25]

We used the results of our multivariate logistic regression analyses to construct simple, integer-based preoperative risk scores. The predictive accuracy of our mortality score was greater than that of the morbidity score (validation C indices of 0.79 and 0.64, respectively). The finding of superior predictive validity of mortality models over morbidity models has been demonstrated previously in a VA-NSQIP study modeling the same preoperative variables assessed here.[26] Both scoring systems were superior to the NSQIP probability of mortality and probability of morbidity scores (C indices 0.62 and 0.61 in validation set, respectively).

Predictive modeling before surgery is being used with increasing frequency because it offers risk adjustment for comparison of outcomes among different institutions, which is important for quality assurance.[27] Predictive modeling using variables that can be determined in the preoperative setting offers additional benefits of more complete patient understanding of risk at the time of informed consent and the potential for risk reduction by optimization of modifiable risk factors.

Six of the nine variables in our morbidity risk score, including BMI, smoking, SIRS/sepsis, serum albumin, creatinine, and platelet count, are potentially modifiable. These data imply that interventions such as smoking cessation, weight loss for obese patients, and improvement in nutritional status for patients with hypoalbuminemia are interventions that could potentially reduce perioperative risk. Similarly, adequate preoperative hydration for patients with elevated creatinine without chronic kidney disease and a search for and treatment of inflammatory or infectious processes in patients who qualify as having SIRS/sepsis and those with thrombocytosis may reduce risk.

With the exception of BUN, the variables in our morbidity risk score are largely non-modifiable. Recent weight loss in patients with poor nutritional status could be addressed by interventions such as nasojejunal enteral feeding or dietary supplementation in the preoperative setting. Preexisting neurologic disease was found to be an independent predictor of both morbidity and mortality in this study. While this risk factor is non-modifiable, it is important to be cognizant of the implications of this variable when performing preoperative risk assessment.

The main limitations of our study include lack of data regarding the operative and hospital variables. With the current ACS NSQIP coding, it is not possible to differentiate open versus laparoscopic DP. It has been shown that perioperative morbidity is decreased after laparoscopic DP[28]; however, it is not known if risk factors for complications differ if the procedure is performed openly or laparoscopically. An additional limitation is lack of data regarding the volume of DP procedures performed at each participating center. It is not currently possible to say that this model is or is not applicable to low- (or high-) volume centers. Given the large number of participating centers and variability in operative volume among them, however, this model is likely more broadly applicable than one derived from a single-institution database. ACS NSQIP could be improved for the purpose of studying DP by including more variables specific to this procedure, such as pancreatic duct diameter, gland texture, length of resected specimen, type of stump closure, laparoscopic versus open procedure, concomitant resection of the spleen or other organs, extent of lymphadenectomy, use of drains, use of prophylactic octreotide therapy, incidence of PF, and incidence of post-pancreatectomy hemorrhage.

Conclusion

DP, a procedure that is increasingly performed for incidentally diagnosed pancreatic lesions, is associated with high perioperative morbidity. Simple risk scores based on preoperatively defined variables can predict both morbidity and mortality after DP. This scoring system is for preoperative patient counseling, for optimization of patient status prior to surgery, and for risk adjustment for the evaluation of quality outcome measures between institutions.

Disclaimer The American College of Surgeons National Surgical Quality Improvement Program and the hospitals participating in it represent the source of the data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or for the conclusions derived by the authors.

Conflicts of interest The authors declare no conflicts of interest.

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Discussant

Dr. David B. Adams (Charleston, SC): For pancreatic surgeons, experience trumps evidence. And the practicing surgeon would prefer to jaw about pancreatic fistula prevention than to discuss a NSQIP analysis. So there are gains and loss dimensions to NSQIP reviews, and we need

to remind ourselves, as you have reminded us, of the NSQIP weaknesses.

NSQIP 30-day mortality rates underestimate mortality rates for complicated GI procedures such as pancreatectomy. NSQIP does not capture readmission data. NSQIP is based on a limited sample that diminishes the opportunity to identify infrequent but serious complications, such as class C pancreatic fistula. And that's what we all are going to carp about in this analysis. What about the pancreatic fistula or pancreatic duct occlusion failure, the rate-limiting complication of distal pancreatectomy? How can you assess risks for distal pancreatectomy and not know the pancreatic fistula rate? And that's just a rhetorical question.

So here is my real, one and only question. If you were to advise the College on how to improve NSQIP to make it a better tool to assess risk and improve outcomes in distal pancreatectomy, what data would you add and what data would you subtract from the current model?

Dr. Kelly, I salute you and your mentors on your premium work and your poised presentation today.

Closing Discussant

Dr. Kaitlyn Jane Kelly: You bring up an excellent point about the lack of some of the pancreas-specific or pancreatectomy-specific postoperative data that we are currently not able to capture with NSQIP, such as, most importantly, pancreatic fistula.

We do think that in this analysis, clinically significant fistulas, defined as grade B or C, are most likely picked up in patients with organ space infection or sepsis, which are outcomes collected by NSQIP.

To improve the database, I would recommend adding more variables for postoperative factors such as the incidence of pancreatic fistula, as well as postpancreatectomy hemorrhage and delayed gastric emptying, particularly for pancreaticoduodenectomy procedures.

I think it would also be useful to reduce some of the other variables currently collected in NSQIP, and to do this selectively. Some of the laboratory valuables like albumin, platelet count, and BUN have repeatedly been shown to be predictors of complications after various general surgery procedures. Those variables should clearly be kept. But it would certainly be helpful in terms of cost and enabling more hospitals to participate in NSQIP, if we could reduce some of the variables currently in the dataset.

Discussant

Dr. Henry Pitt (Indianapolis, IN): Let me help you answer Dr. Adams' question. In fact, the College is doing just what he and you have suggested, meaning that the number of variables that don't really play into all these logistic regressions is being reduced. This last year, the variables that we have been talking about, which are pancreas surgery-specific, have been built into ACS-NSQIP and will be rolled out in January 2011. Therefore, the key will be for all of us to switch from the current "classic" ACS-NSQIP to the new "high-risk" module, which will include pancreatectomy and hepatectomy. In working with the statisticians at the College, and with Karl Bilimoria, we also analyzed risk factors for pancreatic surgery. However, we were advised to not examine just Whipple or just distal but also the spectrum of pancreatic surgery. Having procedures that had even higher and lower mortality, and increasing the numbers, actually adds to the validity of these risk models. In fact, we probably don't even have enough numbers with pancreatectomy, and need to lump hepatectomy and complex biliary to create an HPB Risk Calculator. When we complete this task, we will all have even a better mousetrap than any of us have developed. The ACS-NSQIP HPB Risk Calculator will be on their Web site and will provide the overall morbidity, the serious morbidity, and the mortality. Eventually, the risk of fistula will be available on these patients, and also we will have hospital-specific and surgeon-specific data.

Discussant

Dr. Lygia Stewart (San Francisco, CA): I take it this was an elective distal pancreatectomy database; is that correct? Can you explain to me the preoperative sepsis piece? Because it would seem to me that no pancreatic surgeon would take somebody for an elective pancreatectomy who had preoperative sepsis. Now, that would make sense if it was necrotizing pancreatitis. So can you explain that? And that was pretty important to your morbidity calculations, so it didn't make a lot of sense to me.

Closing Discussant

Dr. Kaitlyn Jane Kelly: That is a good point. And we initially considered excluding patients that fell into that group of being defined as having preoperative sepsis. But when we looked back, there were a total of 31 patients in the sample who qualified as having preoperative SIRS or sepsis. These variables were defined very specifically-SIRS as having two or more of the following: a temperature above >38° or <36°, a respiratory rate >20, heart rate >90, PCO_2 of <32. Those factors plus a known source of infection is defined as sepsis.

We thought it was interesting that such a large number of patients did fit this definition and still underwent elective DP. Given these definitions that are based on the very specific vital signs or laboratory parameters, that it's feasible in clinical practice, a patient could fit the definition but really not look ill overall, but this could be going unrecognized.

So we thought it was important to point out that we should pay attention to these things. Patients that do fit this definition are obviously at increased risk.

Discussant

Dr. John Chabot (New York, NY): Help some of us who are a little less sophisticated in these analyses with the *C* index concept. You told us that at 0.5, the predictability of this is random; and at 1.0, it's perfect. What does 0.64 mean? How useful is this to predict outcome for a specific patient with a *C* index of 0.64?

Closing Discussant

Dr. Kaitlyn Jane Kelly: It is, as you pointed out, a range. A *C* index of 0.64 is quite good and is comparable to many other predictive nomograms and models that have been used and published recently.

Just to mention, the NSQIP predictive scoring system for general non-cardiac surgery, called the probability of morbidity score, had a *C* index of 0.62 when we tested it in our validation sample.

Discussant

Dr. Shimul A. Shah (Worcester, MA): If I may make two editorial comments about NSQIP. We have to be careful about creating risk scores with every database that exists for certain complex procedures because we are limited by the variables that are in each database. So for instance, in NSQIP, we don't have spleen-preserving versus distal pancreatectomy with splenectomy, which, as we all know, would increase the morbidity or the complication rate, or the size of a cyst in the distal pancreas, or whether it's in the body or in the tail.

Secondly, NSQIP is 200 centers which voluntarily decide to join the database. It would be nice if we can—one other caveat for NSQIP that I would ask is that we could get 1,000 hospitals to join it. And in that way, we would have a more well-rounded distribution of hospitals that are involved in the risk assessment course that we make up.

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ORIGINAL ARTICLE

Management and Outcome of Intrathoracic Bleeding due to Vascular Injury During Transhiatal Esophagectomy

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Abstract
Study Objective The objective of this study was to ascertain the incidence and outcome of intrathoracic vascular injury during transhiatal resection of the esophagus.
Background Resection of the esophagus is indicated for a variety of benign and malignant diseases and can be performed via the transhiatal or transthoracic route. As the esophagus is in close vicinity to the aorta, pulmonary vessels and the azygous vein, these blood vessels can be injured during its resection.
Methods We extracted data on the incidence, management, and outcome of intrathoracic vascular injuries that occurred during transhiatal esophagectomy between 1983 and 2010 from a prospectively maintained esophageal diseases database.
Results During this period, 710 transhiatal esophagectomies were done for malignant (n=617) and benign causes (n=93). Intrathoracic vascular injury occurred in ten patients (1.4%). The indication for esophagectomy was malignancy (nine patients) and corrosive stricture (one patient). All nine patients with malignancy had squamous cell carcinoma, and the tumor was located in the midthoracic esophagus in seven and lower thoracic esophagus in two patients. Eight of nine patients with cancer had received preoperative radiotherapy. The site of injury was the aorta/its esophageal branch (six patients), azygous vein (three patients), and inferior pulmonary vein (one patient). The estimated median intraoperative blood loss was 4,450 ml (range, 2,000–6,000 ml), and the median duration of the surgery was 5 h (range, 4–7 h). On a multivariable analysis, location of tumor (in the midthoracic esophagus) was a significant risk factor for the occurrence of vascular injury. Seven patients required a thoracotomy to control the bleeding while in two patients, it could be identified and controlled transhiatally. Two patients died intraoperatively due to massive bleeding and another two died in the postoperative period. Of the patients who survived (n=6), three patients had an uneventful recovery, one patient developed a cervical anastomotic leak, and two patients developed chest infection.
Conclusion Vascular injury during transhiatal esophagectomy is a rare but life-threatening complication. There may be a higher risk in tumors located in the mid esophagus. Management involves prompt identification and control via a dilated hiatus or a thoracotomy.

Keywords Esophagectomy · Hemorrhage · Radiotherapy · Esophageal neoplasms

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Introduction

Resection of the esophagus is indicated for a variety of malignant and benign diseases. This can be done via the transhiatal or transthoracic approach. The intrathoracic esophagus lies in close vicinity to major vessels such as the aorta, azygous vein, and pulmonary vessels and is supplied mainly by small branches from the aorta. Resection of the esophagus via the transhiatal route is partly blind and entails blunt dissection with a potential for injury to these blood vessels. This risk may be higher in

patients with bulky esophageal tumors in close relation with the major vessels, in patients who have received preoperative chemotherapy/radiotherapy, and in patients with corrosive stricture of the esophagus in which there are periesophageal adhesions along the entire length of the esophagus. The bleeding that occurs following such injury can be massive and devastating. Management of such injuries requires prompt identification and control of the source of bleeding which may be done through the dilated esophageal hiatus. In most patients, however, a thoracotomy is required to control the blood loss.

We do about 90 esophageal surgical procedures every year for the management of esophageal diseases. We reviewed our prospectively maintained database of esophageal diseases to assess the management and outcome of such vascular injuries during transhiatal esophagectomy (THE).

Methods

We evaluated the incidence, management, and outcome of vascular injuries that occurred during THE. Vascular injury was defined as an injury to a major intrathoracic vessel in the vicinity of the esophagus that occurred during transhiatal esophageal mobilization resulting in hemodynamic instability and required control via maneuvers other than tamponade (either transhiatally or transthoracically).The data of all transhiatal esophageal resections done between 1983 and 2010 was extracted from a prospectively maintained esophageal diseases database. Patients who underwent a transthoracic procedure were not included in the analysis as the focus of the study was to ascertain the incidence and outcome of vascular injury during a partly blind mediastinal dissection that is done during THE. The various indications for the procedure included carcinoma of the lower and the middle third of the esophagus, corrosive strictures, megaesophagus due to achalasia cardia, and traumatic/iatrogenic perforations. Patients with esophageal cancer who, on imaging, had loss of planes with the aorta, tracheobronchial tree, and pulmonary vessels and where the tumor was supracarinal in location did not have a transhiatal esophageal resection and were not included in this study.

Results

Between 1983 and 2010, 710 patients underwent THE for malignant (n=617) or benign causes (n=93), including corrosive stricture of the esophagus (n=62) and other miscellaneous causes (n=31; achalasia cardia, esophageal perforation, peptic stricture, and leiomyomatosis). There was an intrathoracic vascular injury in ten patients (1.4%) during the transhiatal resection (Table 1). There were eight

Table 1 Clinical profile of patients with intrathoracic vascular injury

Patient	Age	Sex	Diagnosis	Level	Histology	Preoperative EBRT	Vessel injured	Blood loss (ml)	Control	Mortality	Complications
1	70	M	Carcinoma	Middle third	SCC	No	Azygous vein	3,000	Transthoracic	Yes	–
2	41	F	Carcinoma	Middle third	SCC	Yes	Aorta	5,000	Transthoracic	Yes	–
3	48	M	Carcinoma	Middle third	SCC	Yes	Esophageal artery	4,500	Transthoracic	No	Chest infection
4	35	M	Carcinoma	Middle third	SCC	Yes	Aorta	5,000	Transthoracic	Yes	–
5	53	M	Carcinoma	Middle third	SCC	Yes	Azygous vein	4,500	Transthoracic	No	Neck leak
6	38	M	Carcinoma	Middle third	SCC	Yes	Inferior pulmonary vein	6,000	Transthoracic	Yes	–
7	63	M	Carcinoma	Middle third	SCC	Yes	Azygous vein	3,500	Transthoracic	No	None
8	65	M	Carcinoma	Lower third	SCC	Yes	Esophageal artery	4,400	Transhiatal	No	Chest infection
9	45	M	Carcinoma	Lower third	SCC	Yes	Aorta	2,000	Transhiatal	No	None
10	32	F	Corrosive	–	–	–	Aorta	2,500	Transthoracic	No	None

M male, *F* female, *SCC* squamous cell carcinoma, *EBRT* external beam radiotherapy

males and two females. The median age of the patients was 46.5 years (range, 32–70 years). The indication for esophagectomy was malignancy (in nine patients) and corrosive stricture of the esophagus (in one patient). All nine patients with malignancy had squamous cell carcinoma. The tumors were located in the midthoracic esophagus in seven and lower thoracic esophagus in two patients. Eight of the nine patients with cancer had received preoperative radiotherapy (25 Gy/five fractions). The median duration between the radiotherapy and surgery was 26.5 days (range, 20–46 days).

Risk Factors

A univariate analysis was done to ascertain the risk factors for occurrence of vascular injury during THE (Table 2). For the purpose of this analysis, the study period was divided into two parts. In the first part of the study (between 1983 and 2000), 386 and in the second part (between 2000 and 2010), 324 THEs were performed. There was no significant difference in the incidence of vascular injuries during the two periods (p=0.36). Patients who underwent THE for tumors located in the midthoracic esophagus and those who received preoperative radiotherapy had a higher incidence of vascular injury (p=0.02 and 0.06, respectively). The indication of THE (carcinoma, corrosive stricture, or miscellaneous causes; p=0.9) and the pT stage (AJCC TNM) of the tumor (p=0.9) were, however, not associated with an increase in risk.

On multivariable analysis, only location of the tumor was a significant risk factor (p=0.03).

In all the patients, excessive blood loss was noticed from the esophageal hiatus during the attempted resection. The site of injury was the aorta (in four patients), an enlarged esophageal branch from the descending thoracic aorta (in two patients), azygous vein (in three patients), and inferior pulmonary vein (in one patient). The median estimated intraoperative blood loss was 4,450 ml (range, 2,000–6,000 ml), and the median duration of surgery was 5 h (range, 4–7 h). In the two patients who had tumors in the lower third of the esophagus, the bleeding site (from the aorta in one patient and an esophageal artery in the other) could be identified by positioning the patient in a Trendelenburg position, placing large abdominal retractors to retract the widened hiatus and retracting the esophagus anteriorly. The bleeding was controlled by prolene sutures. In the remaining patients, a thoracotomy was needed (right thoracotomy in six, left thoracotomy in one, and bilateral thoracotomy in one patient). The site of bleeding could be identified in all the cases. Vascular clamps were applied and the hemostasis was attempted by suturing. Two patients died intraoperatively due to massive bleeding and another two died in the postoperative period due to complications of prolonged hypotension and massive transfusion. In the patients who survived (n=6), three patients had an uneventful recovery, one patient developed a cervical anastomotic leak which was

Table 2 Risk factors for vascular injury

Parameter	No vascular injury	Vascular injury	Total	p value
Year				
1983–2000	379	7	386	0.36
2000–2010	321	3	324	
Diagnosis				
Carcinoma	608	9	617	0.9
Corrosive strictures	61	1	62	
Miscellaneous	31	0	31	
Location of carcinoma				
Middle third	210 (34.5)	7 (77.8)	217	0.02
Lower third	398 (65.5)	2 (22.2)	400	
Preoperative radiotherapy				
No	279 (45.9)	1 (11.1)	280	0.06
Yes	329 (54.1)	8 (88.9)	337	
TNM pT stage				
pTis	8	0	8	0.9
pT0	18	0	18	
pT1	37	0	37	
pT2	115	0	115	
pT3	400	7	407	
pT4	30	2	32	

pT0 includes patients who had complete pathological response following neoadjuvant radiotherapy

managed conservatively, and two patients had chest infection.

Discussion

Injury to the major intrathoracic vessels during transhiatal resection of the esophagus is a rare but potentially life-threatening complication.[1,2] As the esophagus is in close vicinity to the aorta, pulmonary vessels and the azygous vein, these blood vessels can be injured during its resection. The mild to moderate bleeding observed during transhiatal esophagectomy is because the esophageal arteries divide into minute branches within the periesophageal mediastinal tissue before entering the esophageal wall. The physiological response of these small vessels to tearing is posttraumatic contraction with secondary thrombosis, resulting in hemostasis.[3] Injuries to major vessels most commonly involve the aorta, its esophageal branches, or the azygous vein. In a review by Orringer et al.[2] of 2,029 patients who underwent a transhiatal esophagectomy, four patients died of uncontrolled hemorrhage, and in another seven, excessive bleeding (>4,000 ml) occurred due to an injury to the azygous vein (four patients) and a large prevertebral collateral vein (three patients). In our series, bleeding occurred from a torn azygous vein in three patients, the aorta in four patients, an enlarged esophageal branch from the aorta in two patients, and the inferior pulmonary vein in one patient.

Careful selection of patients for esophageal resection through the transhiatal route is necessary to prevent an injury to a major vessel. A transhiatal resection of bulky tumors located in the midthoracic esophagus near the tracheal bifurcation can injure the azygous vein and the aortic arch. Similarly, resection of bulky tumors in the lower part of the midthoracic esophagus (T7-T8 vertebrae) may result in injury to the inferior pulmonary vein. Transhiatal mobilization of an esophageal tumor stuck posteriorly can cause an aortic injury. Between 1983 and 2009, we did 710 transhiatal esophagectomies for malignant (n=617) and benign (n=93) causes. Esophageal tumors with loss of fat planes with the aorta or pulmonary vasculature and those in the supracarinal location were not resected transhiatally. Intraoperatively, if the tumor was found to be adherent, the transhiatal resection was abandoned and a thoracotomy was done to complete the resection. In most patients, the transhiatal resection was done under vision through a dilated hiatus at least till the level of the inferior pulmonary vein. The supracarinal dissection was blind.

In patients with corrosive strictures who underwent transhiatal resection (n=62), the dissection was done meticulously with a low threshold for conversion to the transthoracic route. In these patients, unlike cancer, the periesophageal adhesions are present along the entire length of the esophagus and can result in injury. Of these 62 patients, vascular injury occurred in one patient.

Transhiatal esophagectomy in patients who have received neoadjuvant chemotherapy/radiotherapy is challenging and may be associated with increased operative mortality.[4] This may be due to radiation-induced fibrosis (which develops especially if there is a time lag between its administration and surgery) which predisposes to injury to the adjacent structures. Of the nine patients with malignancy who developed vascular injury, eight had received preoperative radiotherapy of 25 Gy as part of an ongoing randomized trial. The median duration between administration of radiotherapy and surgical resection was 26.5 days.

Vascular injury and bleeding can, to a large extent, be prevented. Although a transhiatal resection may be attempted in high risk patients, the threshold for conversion should be low. Any undue difficulty should be an indication for conversion to a transthoracic exploration. An important technique while dissecting in the vicinity of delicate vascular structures like the azygous vein, inferior pulmonary vein, and the aorta is to push the periesophageal tissues towards them rather than the esophagus.

Injury to a major intrathoracic vessel is manifested by brisk bleeding from the hiatus associated with a drop in blood pressure. When encountered, the patient should be positioned in a Trendelenburg position, retractors should be placed at the esophageal hiatus and under good illumination; the blood should be suctioned out in an attempt to visualize the source of bleeding (in case of a bleeding source below the pulmonary vein like the aorta/branch). Blind application of vascular clamps through the hiatus should be avoided as this may worsen the bleeding. If identified, the source should be controlled with a non-absorbable suture. If the source is not identified, the bleeding occurs during dissection of the mid/upper esophagus or the bleeding is massive, the mediastinum is packed to achieve temporary tamponade. Further management depends on the anticipated location of bleeding. When uncontrolled bleeding is encountered during dissection of lower esophageal lesions, a left thoracotomy and in case of mid or upper thoracic lesions, a right thoracotomy should be done. Bleeding from the aorta is often due to a torn esophageal artery rather than from a direct injury to the aorta. Since this vessel usually gets retracted, it is not possible to ligate it. Digital occlusion of the bleeding point and suture transfixation is adequate. When the injury is large, the tear needs to be repaired after application of a vascular clamp.

The outcome depends on timely control of bleeding. The bleeding is usually brisk and results in a substantial blood loss by the time adequate control is achieved. A significant mortality following such injuries has been reported [2] as was our experience (mortality rate, 40%).

Conclusions

Vascular injury during transhiatal esophagectomy is a rare but life-threatening complication. There may be a higher risk in tumors located in the mid esophagus. Management involves prompt identification and control via a dilated hiatus or a thoracotomy.

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Conflicts of interest None

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ORIGINAL ARTICLE

A Nationwide Analysis of Changes in Severity and Outcomes of Inflammatory Bowel Disease Hospitalizations

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Abstract
Introduction The past decade has seen a change in inflammatory bowel disease (IBD; Crohn's disease (CD) and ulcerative colitis (UC)) treatment, with increasing use of immunomodulators and biologics. The impact of this on IBD hospitalization outcomes is unknown.
Methods We identified hospitalizations with a diagnosis of IBD using data from the Nationwide Inpatient Sample, a national US discharge database. We compared the proportion of hospitalizations resulting in surgery in the entire cohort and within each disease severity stratum for the years 1998, 2004, and 2007.
Results There were an estimated 89,673 hospitalizations for CD in 1998 increasing to 150,593 hospitalizations in 2007. UC hospitalizations increased from 56,911 in 1998 to 86,611 in 2007. This increase was primarily among low or intermediate severity hospitalizations not requiring surgery. For CD, the proportion of bowel surgeries during hospitalization decreased from 17.3% in 1998 to 12.4% in 2007 ($p<0.001$) while for UC, the proportion of colectomy decreased from 9.5% in 1998 to 6.2% in 2007 ($p<0.001$). For both diagnoses, this reduction was significant in those with a low severity of disease but not with in those with the highest severity stratum.
Conclusions There continues to be an increase in the number of hospitalizations in patients with IBD. The numbers of non-elective bowel surgeries among those with the highest severity of disease continues to increase suggesting need for further research into improving outcomes in this cohort at high risk for adverse outcome.

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Introduction

Inflammatory bowel diseases (IBD) are chronic, life-long immunologic disorders that frequently require hospitalization or surgery. Such hospitalizations account for a significant portion of the estimated US $6 billion in healthcare costs annually for IBD in the USA.[1] The past decade has seen major changes in the therapeutic armamentarium available for the management of IBD. Infliximab, a chimeric monoclonal antibody against tumor necrosis factor alpha (TNF-α), was

first approved for the treatment of Crohn's disease (CD) in 1998;[2–4] subsequently three other biologic agents—adalimumab (anti-TNF),[5–7] certolizumab (anti-TNF),[8] and natalizumab (alpha-4 integrin inhibitor)[9] became available for induction and maintenance of remission in CD. Infliximab is the only biologic agent approved for the treatment of ulcerative colitis (UC) after demonstrating success in the ACT I and ACT II trials.[10] In addition, the past decade has also seen an increase is the use of traditional immunosuppressive agents (azathioprine, methotrexate, and 6-mercaptopurine) in the treatment of both UC and CD.[11,12]

Cosnes et al. showed that despite a significant increase in the utilization of immunosuppressive agents, there was no reduction in the rate of surgery for CD between 1978 and 2002;[12] other studies similarly failed to find a difference in the rates of bowel resection for both CD and UC.[13–15] Prior research using national databases has shown a marked increase in the number of hospitalizations related to IBD.[13,15] However, a majority of these studies encompassed time periods prior to the widespread adoption of newer biologic agents. A second limitation of prior research has been the lack of stratification by disease severity. The healthcare costs in IBD, even among those requiring hospitalization, is not uniformly distributed but skewed to a small subset of patients with the greatest severity of disease who are at the highest risk for an adverse outcome and have the greatest healthcare costs.[16] There has been limited prior examination of temporal trends in the number of hospitalizations for IBD stratified by need for surgery and disease severity.

The aims of our present study are (1) to examine trends in the number of hospitalizations for CD and UC in the USA across three study years—1998, 2004, and 2007; (2) to describe these temporal changes in characteristics of hospitalized CD and UC patients stratifying by severity of hospitalization; and (3) to examine changes in the number and proportion of hospitalizations resulting in bowel surgeries within each severity stratum.

Methods

Data Source and Study Population

The source of data for our study was the Nationwide Inpatient Sample (NIS) for the years 1998, 2004, and 2007. The NIS is the largest all-payer inpatient hospitalization database in the USA and is maintained by the Healthcare Cost and Utilization Project of the Agency for Healthcare Quality and Research.[17,18] Using a stratified sample design, it consists of all discharges from a 20% sample of non-federal short-stay hospitals from 22–40 states and approximately 1,000 hospitals. Each hospitalization is coded with one primary diagnosis determined on discharge, up to 14 secondary diagnoses and 15 procedures associated with the hospitalization using the International Classification of Diseases, 9th edition, clinical modification (ICD-9-CM) codes. The NIS has been shown to correlate well with other hospitalization discharge databases in the USA[18] and has been used widely in IBD research.[11,15,19] Our study population consisted of patients with a primary or secondary discharge diagnosis of CD (ICD-9-CM 555.x) or UC (ICD-9-CM 556.x). The specific years were selected to examine pre-biologic (1998 for CD and 1998 and 2004 for UC) and post-biologic time periods (2004 and 2007 for CD and 2007 for UC).

Variables and Outcomes

Age, gender, race, and insurance status were obtained from the NIS. General co-morbidity was assessed using the Elixhauser co-morbidity index, a validated and widely used measure.[20] We assessed the occurrence of disease-specific complications using previously described diagnosis codes.[19] These include anemia, malnutrition, requirement for transfusion or total parenteral nutrition (TPN), *Clostridium difficile* infection, and hypovolemia. For CD patients, disease behavior was classified into internal penetrating/fistulizing disease, obstructing disease, and non-penetrating, non-stricturing disease based on the occurrence of diagnosis codes for the above complications during the hospitalization.[19]

We recently described disease-specific severity scores for CD[11] and UC[21] using administrative data (Appendices 1 and 2). These are simple quantitative scores that can be used to stratify severity of the hospitalization based on the presence of certain complications such as anemia, malnutrition, requirement for transfusion, or TPN. The scores range from 0–8 for UC and 0–13 for CD with higher scores representing greater severity of hospitalization, and thus a higher likelihood of bowel resection (for CD) or colectomy (for UC). We demonstrated that these scores performed well in predicting the outcome of interest in derivation and validation cohorts from the NIS and could be used to stratify hospitalizations into low, intermediate, and high-severity strata. While these severity scores, also termed 'risk scores' are approximate and limited to administrative research, they offer the advantage of stratifying by disease-specific co-morbidity rather than general co-morbidity as offered by the Charlson or Elixhauser indices which perform poorly when it comes to predicting likelihood of bowel surgery or colectomy.[11,21] Thus they allow us to examine changes in rate of surgery based on the likelihood of requiring surgery during that hospitalization, a unique method of analysis in our study.

Our outcomes of interest were (1) number of hospitalizations for CD or UC, overall and stratified by disease severity, (2) overall number and proportion of hospitalizations resulting in non-elective bowel surgery (for CD) or colectomy (for UC), stratified by disease severity, and (3)

length of hospital stay for patients who did not undergo surgery. Bowel surgery (for CD) and colectomy (for UC) were defined using previously employed procedure ICD-9-CM codes.[19,22] Surgeries were classified as elective if the admission was coded as being elective, the source of admission was not the emergency room, and surgery occurred on day 0 or 1 of hospitalization. All other surgeries were classified as non-elective.

Statistical Analysis

Data were analyzed using Stata 9.2 (StataCorp, College Station, TX) using the appropriate survey methods accounting for the stratified sampling design of the NIS. All calculations were carried out using the weighted estimates approximating nationwide population estimates. Continuous variables were summarized using means and standard deviations, while categorical variables were expressed as proportions. Chi-square and *t* tests were used to perform between group comparisons, while the ANOVA test was used for multi-group comparisons across the three study years. Univariate and multivariate logistic regressions were performed to analyze the independent effect of year of hospitalization on each of the primary outcomes. Variables common to both the Elixhauser index and our CD or UC risk scores (i.e. anemia) were counted only with our risk score and excluded from the Elixhauser score for multivariate analysis. Length of stay was analyzed using linear regression after log transformation owing to its skewed distribution. Planned subgroup analysis was performed for the proportion of surgery among each severity stratum for CD and UC. To test whether the effect of year of hospitalization differed by severity stratum or elective surgery status, an interaction term consisting of both these variables of interest was then introduced into the multivariate model. A p value<0.05 was indicative of independent statistical significance in the multivariate model. In the model with the interaction term, a $p<0.05$ for the interaction terms indicated that the effect of year of hospitalization on outcome differed significantly by severity stratum. A sensitivity analysis was performed among only those patients with a primary listed diagnosis of UC or CD, i.e., those who are most likely to be admitted for their IBD flare.

The study was approved by the Institutional Review Board of the Medical College of Wisconsin.

Results

Crohn's Disease

There were an estimated 89,673, 132,071, and 150,593 discharges with a primary or secondary diagnosis of CD during the years 1998, 2004, and 2007, respectively (Table 1). There was an increase in the general co-morbidity of patients with 13% of patients in 1998 having an Elixhauser score of 3 or more compared to 29% in 2007 ($p<0.001$). There was a decrease in both the proportion of internal penetrating/fistulizing disease (7.6% vs. 5.9%; $p<0.001$) and obstructing disease (17.7% vs. 16.0%; $p<0.001$) between 1998 and 2007. The overall proportion of hospitalizations resulting in bowel surgery decreased by one fifth between 1998 (17.3%) and 2007 (12.4%, adjusted odds ratio (OR) 0.81, 95% confidence interval (CI) 0.76–0.86). This decrease was of a larger magnitude for non-elective (OR, 0.72 and 95% CI, 0.67–0.78) compared with elective bowel surgery (OR, 0.94; 95% CI, 0.87–1.01; $p=0.01$ for interaction term) (Table 2).

Crohn's Disease: Bowel Resection by Disease Severity

Figure 1 is a graphical representation of the absolute number of hospitalizations for Crohn's disease stratified by disease severity. The absolute number of hospitalizations resulting in non-elective bowel surgery has remained fairly constant between 1998 and 2007 (8,241 in 1998 and 9,265 in 2007, +12.4%). The low severity cohort actually witnessed a decrease in the absolute numbers of non-elective bowel surgery (−10%) compared with rise in the absolute numbers among those with the highest severity of disease (+33%). Other hospitalizations which did not result in non-elective surgery increased dramatically during the same period (81,521 in 1998 and 141,328 in 2007, +73.4%). Stratifying by disease severity, the rate of rise in the number of such hospitalizations not requiring non-elective surgery was slightly greater for those with the lowest severity of disease (+72%) than those with a high severity of disease (+65%).

Analyzing proportion of hospitalizations resulting in surgery, the greatest reduction in non-elective bowel surgery was seen in those with the lowest severity of hospitalization with a nearly 50% reduction (OR, 0.56; 95% CI, 0.47–0.66) in 2007 compared to 1998 for patients in this stratum. Patients with an intermediate (OR 0.74; 95% CI, 0.66–0.83) and high severity (OR, 0.88; 95% CI, 0.75–1.02) hospitalizations experienced reductions of lesser magnitude or of no statistical significance between 1998 and 2007. In patients who did not undergo surgery, there was length of hospital stay was shorter in 2004 and 2007 compared to 1998. Similar to the differences in surgery, the magnitude of this benefit was also inversely proportional to the disease severity category.

Ulcerative Colitis

There were an estimated 56,911, 75,895, and 86,611 hospitalizations with a primary or secondary discharge

Table 1 Comparison of demographic and clinical characteristics of hospitalized patients with Crohn's disease

Variable	1998 (n=89,673)	2004 (n=132,071)	2007 (n=150,593)
Demographics			
Mean age (SD)	50.1 (18.2)	48.9 (18.2)	50.4 (18.3)
Female (%)	60.4%	60.2%	60.0%
Mean Elixhauser (SD)	1.14 (1.19)	1.44 (1.35)	1.81 (1.56)
Elixhauser category			
0	37.4%	29.9%	23.0%
1	30.4%	28.5%	26.2%
2	18.8%	21.3%	21.9%
≥3	13.4%	20.3%	28.9%
Individual complications (%)			
Fistula	7.6	6.8	5.9
Stricture	17.7	19.0	16.0
Hypovolemia	22.6	23.5	27.1
Anemia	18.7	17.8	20.4
Malnutrition	4.5	4.0	4.4
Clostridium difficile	0.7	1.2	1.5
Transfusion	4.5	7.2	8.2
TPN	3.9	3.6	3.3
Transfer from another hospital	2.5	2.9	2.3
Admission to a teaching hospital	46.3	46.8	46.3
Rate of surgery (%)			
Any bowel surgery	17.3	14.7	12.4
Elective bowel surgery	9.6	7.9	7.2
Non-elective bowel surgery	7.7	6.8	5.2
Severity strata (%)			
Low	55.1	55.6	55.3
Intermediate	36.9	36.4	37.3
High	8.1	8.0	7.4
Non-elective bowel surgery by severity stratum (%)			
Low	3.4	2.1	1.8
Intermediate	11.4	10	7.2
High	38.4	41.0	33.4
Length of stay in non-surgical patients by risk stratum (%)			
Low (SD)	4.4 (4.2)	4.1 (4.7)	4.0 (3.9)
Intermediate (SD)	5.8 (6.4)	5.5 (5.5)	5.2 (5.4)
High (SD)	9.0 (9.9)	9.1 (10.5)	8.5 (9.9)

SD standard deviation

diagnosis of UC in 1998, 2004, and 2007, respectively. There was an increase in the mean Elixhauser general comorbidity score between 1998 (mean score 1.40) and 2007 (mean score, 2.01; $p<0.01$) (Table 3). The overall proportion of hospitalizations resulting in colectomy decreased both during 2004 (8.3%) and during 2007 (6.2%) compared to 1998 (9.5%; $p<0.001$ for both comparisons). This decrease was of greater magnitude for non-elective (OR, 0.58; 95% CI, 0.51–0.67) vs. elective colectomies (OR, 0.75; 95% CI, 0.66–0.85; $p<0.05$ for the interaction terms) (Table 4).

Ulcerative Colitis: Colectomy by Disease Severity

Figure 2 presents the trends in the absolute number of hospitalizations for UC stratified by disease severity. Similar to the findings in CD, there is a striking increase in the number of low (43,201 hospitalizations in 1998 and 64,525 hospitalizations in 2007, +47%) and intermediate severity (9,760 hospitalizations in 1998 and 18,353 hospitalizations in 2007, +88%) hospitalizations not resulting in non-elective colectomy. The proportional change in high severity hospitalizations was 69%. While the overall numbers

Table 2 Multivariate analysis elective and non-elective bowel surgeries among hospitalized patients with Crohn's disease

Year	Non-elective bowel surgery Adjusted[a] odds ratio (OR; 95% CI)	Elective bowel surgery Adjusted[a] odds ratio (OR; 95% CI)	Length of stay Adjusted[a] regression co-efficient (95% CI)
All Crohn's disease			
1998	1.0	1.0	Reference
2004	0.91 (0.84–0.98)	0.89 (0.83–0.96)	−8% (−7% to −10%)
2007	0.72 (0.67–0.78)	0.94 (0.87–1.01)	−15% (−13% to −16%)
By severity stratum			
Low severity			
1998	1.0	1.0	Reference
2004	0.61 (0.52–0.72)	0.80 (0.71–0.90)	−10% (−8% to −12%)
2007	0.56 (0.47–0.66)	0.78 (0.69–0.88)	−14% (−13% to −16%)
Intermediate severity			
1998	1.0	1.0	Reference
2004	0.96 (0.86–1.07)	0.99 (0.90–1.10)	−7% (−4% to −9%)
2007	0.74 (0.66–0.83)	0.98 (0.88–1.09)	−14% (−12% to −17%)
High severity			
1998	1.0	1.0	Reference
2004	1.18 (1.02–1.37)	0.86 (0.73–1.00)	3% (−5% to 2%)
2007	0.88 (0.75–1.02)	1.14 (0.98–1.34)	−14% (−5% to −22%)

[a] Adjusted for age, gender, Elixhauser co-morbidity, and CD-specific severity score

of hospitalizations requiring non-elective colectomy remained stable (2,612 in 1998 and 2,434 in 2007, −6.8%), the lowest severity stratum witnessed a decrease in the number of non-elective colectomy (−34%) while the highest severity stratum witnessed a similar increase in the numbers of non-elective colectomy (+34%).

In the analysis by proportion of hospitalizations resulting in non-elective colectomy, similar to the pattern seen in CD, the reduction in surgery was inversely proportional to the severity stratum (Table 4; $p<0.05$ for the interaction terms). For patients with lowest severity of hospitalization, there was a greater than 50% reduction in proportion of non-elective colectomies in 2007 compared to 1998 (OR, 0.48; 95% CI, 0.40–0.58), but this difference was not significant in those with the highest severity of hospitalization (OR, 0.88; 95% CI, 0.61–1.29) correlating with our analysis of absolute numbers. Patients in the highest severity stratum also did not experience any decrease in length of hospitalization for non-surgical patients, but there was a significant reduction in those of low and intermediate severity.

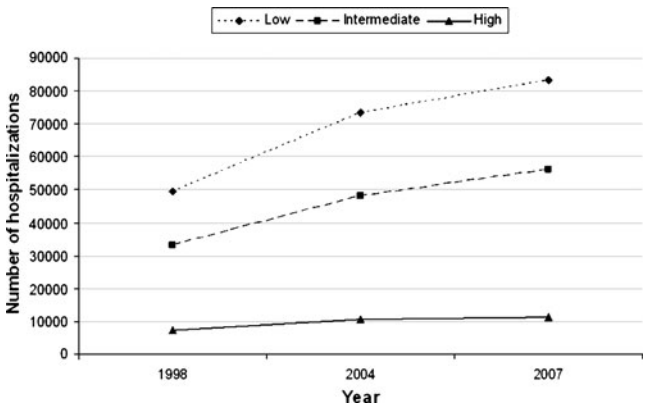

Fig. 1 Trends in absolute number of hospitalizations in patients with a diagnosis of Crohn's disease stratified by severity of hospitalization

Sensitivity Analysis

The overall proportion of hospitalizations with a primary discharge diagnosis of CD (among those with any listed diagnosis of CD) decreased from 41% in 1998 to 34% in 2007 ($p<0.01$). Among those patients with only a primary diagnosis of CD, the lowest severity category saw a decrease in the occurrence of non-elective bowel surgery from 8.1% in 1998 to 3.8% in 2007 (OR, 0.45; 95% CI, 0.37–0.54). This reduction was considerably less prominent among the cohort with the most severe disease (OR, 0.75; 95% CI, 0.60–0.93). Similarly among those with a primary diagnosis of UC, the greatest reduction in colectomy was seen among those with the lowest severity of hospitalization (OR, 0.52; 95% CI, 0.39–0.69) while those in the highest severity category actually had a greater odds of colectomy in 2007 compared to 1998 (OR, 1.70; 95% CI, 1.05–2.74). Excluding hospitalization with a length of stay less than 2 days did not significantly change our results. Analysis excluding patients with a diagnosis of colorectal cancer did not significantly alter our findings (data not shown).

Table 3 Comparison of demographic and clinical characteristics of hospitalized patients with ulcerative colitis

Variable	1998 (n=56,911)	2004 (n=75,895)	2007 (n=86,611)
Demographics			
Mean age (SD)	55.9 (19.5)	54.8 (20.0)	55.0 (19.5)
Female (%)	52.5%	54.8%	54.2%
Mean Elixhauser (SD)	1.40 (1.26)	1.68 (1.45)	2.01 (1.61)
Elixhauser category			
0	28.7	24.1	18.2
1	30.8	27.6	25.2
2	21.5	22.4	23.0
≥3	19.0	26.0	33.6
Individual complications (%)			
Hypovolemia	24.3	25.9	31.0
Anemia	24.5	24.4	26.8
Malnutrition	4.4	3.8	4.9
Clostridium difficile	2.4	4.1	5.4
Transfusion	6.8	11.0	12.2
TPN	3.5	3.0	3.2
Transfer from another hospital	3.0	3.4	2.8
Admission to a teaching hospital	47.2	48.2	48.9
Rate of surgery (%)			
Any colon resection	9.4	8.3	6.2
Elective colon resection	5.0	5.0	3.4
Non-elective colon resection	4.4	3.3	2.8
Severity strata (%)			
Low	78.5	77.0	74.5
Intermediate	18.6	20.2	22.4
High	3.0	2.8	3.2
Non-elective colon resection by severity stratum (%)			
Low	3.3	2.0	1.5
Intermediate	7.8	6.4	5.4
High	18.3	17.4	15.1
Length of stay in non-surgical patients by risk stratum (%)			
Low (SD)	5.2 (5.6)	4.8 (5.0)	4.6 (4.6)
Intermediate (SD)	7.9 (8.1)	7.3 (6.8)	6.9 (7.2)
High (SD)	12.8 (11.3)	14.5 (13.9)	12.5 (10.2)

Discussion

There has been a recent increase in the number of hospitalizations for both CD and UC.[13–15] Using a nationwide representative sample, we identified several interesting patterns in the changing epidemiology of hospitalized patients with IBD. We found that (1) there continues to be a significant increase in the number of hospitalizations in patients with IBD; (2) the bulk of this increase is predominantly among low and intermediate severity hospitalizations not requiring non-elective surgery during the hospitalizations though the high severity hospitalizations have also seen a comparable proportional increase. (3) Contrasting with this, the overall number of hospitalizations resulting in non-elective bowel surgery has remained fairly stable among those with mild disease severity but continues to rise among those with high severity of disease.

Two recent studies examined trends in hospitalization rates for IBD in the USA. Bewtra et al., using the National Hospital Discharge Survey, found a significant increase in the rate of CD (9.3/100,000 in 1990 to 17.1/100,000 in 2003; p=0.0002) but not UC hospitalizations between 1990 and 2003.[13] However, their analysis was restricted to patients with a primary discharge diagnosis of IBD which may sub-optimally capture all IBD-related hospitalizations. Nguyen et al. used the NIS to compare the rates of hospitalization between 1998 and 2004 and found a 4.3%

Table 4 Multivariate analysis elective and non-elective bowel resections among hospitalized patients with ulcerative colitis

Year	Non-elective colon resection Adjusted[a] odds ratio (OR) (95% CI)	Elective colon resection Adjusted[a] odds ratio (OR) (95% CI)	Length of stay Adjusted[a] regression co-efficient (95% CI)
All ulcerative colitis			
1998	1.0	1.0	Reference
2004	0.72 (0.63–0.82)	1.05 (0.94–1.18)	−7% (−5 to −9%)
2007	0.58 (0.51–0.67)	0.75 (0.66–0.85)	−15% (−13 to −17%)
By severity stratum			
Low severity			
1998	1.0	1.0	Reference
2004	0.63 (0.52–0.75)	1.06 (0.93–1.21)	−8% (−5% to −10%)
2007	0.48 (0.40–0.58)	0.76 (0.65–0.87)	−15% (−13% to −17%)
Intermediate severity			
1998	1.0	1.0	Reference
2004	0.80 (0.64–0.99)	0.94 (0.74–1.19)	−8% (−4% to −13%)
2007	0.66 (0.53–0.83)	0.63 (0.49–0.81)	−15% (−11% to −20%)
High severity			
1998	1.0	1.0	Reference
2004	1.02 (0.70–1.50)	1.91 (0.96–3.80)	10% (−2% to 23%)
2007	0.88 (0.61–1.29)	1.87 (0.95–3.67)	−3% (−15% to 9%)

[a] Adjusted for age, gender, Elixhauser co-morbidity, and CD-specific severity score

annual increase in hospitalizations for CD and a 3.0% annual increase for UC.[15] In contrast to these studies, Bernstein et al. found a decline in the rate of hospitalization for CD (but not UC) between 1994 and 2001 in the province of Manitoba, Canada.[22] In the present study, we extend the findings of the prior studies and find that there continues to be an increase in the absolute number of hospitalizations nationwide in the USA for both CD and UC till 2007. However, a novel contribution of our study is examination of changes in the characteristics of the patients requiring hospitalization. The small but significant increase in the mean Elixhauser co-morbidity burden suggests that non-IBD co-morbidity is likely to play an increasingly important role in the management of these patients.[23]

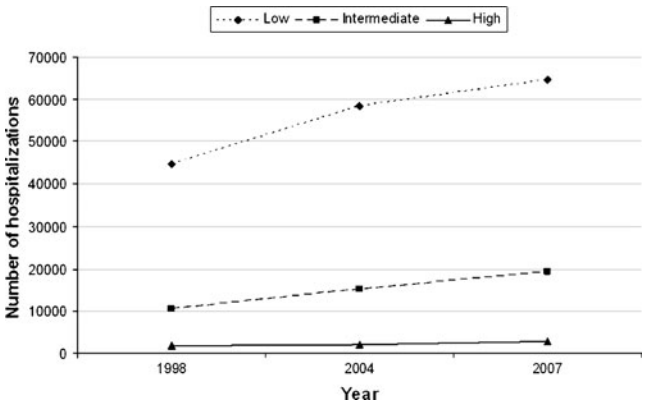

Fig. 2 Trends in absolute number of hospitalizations in patients with a diagnosis of ulcerative colitis stratified by severity of hospitalization

An important limitation of some of the prior studies has been the inability to stratify or adjust for the severity of hospitalizations. While there may have been an overall increase in number of hospitalizations, an important measure of effectiveness of current treatments is to examine if there has been a temporal change in disease severity. An interesting finding in our present study is that the increase in the total number of hospitalizations between 1998 and 2007 is primarily due to increases in those of low or intermediate disease severity. While there has also been a significant increase in the number of high severity hospitalizations, these remain a small fraction of the overall hospitalizations in patients with IBD. This increase is unlikely to be solely due to changes in non-IBD-related hospitalizations in patients with a diagnosis of IBD since we found similar patterns when analyzing patients with a primary discharge diagnosis of CD or UC alone (i.e. hospitalizations most likely related to IBD disease activity). Hospitalizations requiring non-elective surgery have remained relatively constant during the same time period except for the high severity cohort (for both UC and CD) which has continued to witness a rise in the absolute number of non-elective bowel surgery. There are a few possible, non-exclusive, interpretations of these results. Firstly, it could represent changes in admission thresholds over the past decade leading to a greater number of hospitalizations of mild and moderate severity. The lack of any specified criteria for 'appropriateness of a hospitalization' precludes our being able to analyze if this was indeed the case.

A second interpretation is that changes in clinical practice including the availability of advanced therapies have been able to limit the number of hospitalizations resulting in non-elective surgery. Similar to our findings, several previous studies found no change in the overall resection rates for hospitalized IBD patients.[13–15,22] In a study by Cosnes et al. of 565 patients with CD seen at the authors' hospital within 3 months after diagnosis, the 5-year cumulative probability of receiving immunosuppressants increased from 0 to 0.56, while the cumulative risk of intestinal resection remained unchanged.[12] In contrast to the above studies, Jess et al. found a significant decrease in the rate of surgery for CD from 1962 to 2005 in Copenhagen, Denmark with no change in the rates of surgery for UC.[24] It is interesting and important that after stratifying by severity of hospitalization, the reduction in both the absolute number as well as the proportion of non-elective surgeries for CD or UC was seen mainly in those with low severity of hospitalization, but not in those with the highest severity, a group that actually continues to witness an increase. While the biologic agents[6,25,26] and immunomodulators have been shown to decrease the need for resections in patients with Crohn's disease,[27,28] the long-term potential of these agents to alter natural history of severe disease has still not been adequately established. Despite availability of potent therapy, the Oxford acute severe colitis cohort revealed a high cumulative rate of colectomy.[29] Similarly, the results from other cohorts of acute severe colitis have yielded inadequate response to biologic therapy in this cohort of patients with severe disease with a substantial rate of colectomy.[30–32] Our study supports the results from these studies by demonstrating that changes in practice do not appear to have significantly impacted the outcomes of those with the highest severity of disease. This is also important because the rates of surgery and considerable healthcare costs associated with CD and UC are not uniformly distributed, but are skewed towards a subset of patients with the most severe disease who account for the highest costs.

Our findings have several implications. The results suggest that there continues to be a significant increase in the number of hospitalizations for both CD and UC. This increase seems to be predominantly among low and intermediate severity hospitalizations that do not require non-elective bowel surgery during the hospitalization. Likely related in part due to this trend and also due to potential impact of changes in clinical practice, there has been a significant reduction in the proportion of hospitalizations requiring surgery for low or intermediate severity hospitalizations but not among those with the greatest severity of disease. Since the NIS does not contain medication information, we are unable to directly attribute this reduction to immunosuppressive or biologic therapy, but studies have demonstrated increasingly widespread use of these agents in IBD.[11,12] It is also important to recognize that other clinical practice changes including provision of supportive care and timing and quality surgical consultation also likely influence rates of surgery in addition to medical therapies. Supported by both the increase in absolute numbers as well as the lack of significant reduction in the proportion of hospitalizations requiring non-elective surgery, we can conclude that the group of patients with the highest severity of disease still continues to be a high risk for adverse outcomes. There is need for continued research into defining effective and durable therapies in this cohort.

There are a few limitations to our study. While administrative databases are increasingly being used for clinical IBD research, such studies are potentially susceptible to errors of coding. However with the increasing use of electronic health records in the United States, it is likely that such administrative databases will continue to form an important source of data for IBD research. We also did not have detailed clinical or laboratory data to stratify severity of UC or CD hospitalizations; however, we used our previously described severity score using administrative data which performed well in predicting the need for bowel resection or colectomy.[11] While it is difficult from an administrative dataset to determine the exact reason for the hospitalization, that our findings were consistent in the subgroup of patients with a primary discharge diagnosis of UC or CD supports our findings. There may have been changes in billing practices with respect to inclusion of diagnoses within the hospitalization. However, one would expect that a trend towards more detailed coding in the later time periods would actually skew towards higher severity of hospitalizations with the inclusion of more diagnoses among the discharge codes.

In conclusion, there has been an increase in the number of hospitalizations for UC and CD between 1998 and 2007 while the absolute number of non-elective bowel surgery among such hospitalizations has remained fairly constant. The primary increase in the number of hospitalizations is attributable to those of mild or moderate disease severity. The proportion of hospitalizations resulting in surgery in the cohort of hospitalized patients with the most severe disease has actually increased for both UC and CD. Further research into altering course of disease in these patients at the highest risk of adverse outcomes is warranted.

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Financial conflicts of interest None.

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Appendix 1

Table 5 Risk score to predict severe hospitalized course among patients with Crohn's disease[11]

Characteristic	Points
Disease behavior[a]	
Inflammatory	0
Obstructing	2
Fistulizing	4
Hematologic (maximum score 2)	
None	0
Anemia	1
Requirement for blood transfusion	1
Nutritional status (maximum score 3)	
No malnutrition/TPN	0
Malnutrition	2
Total parenteral nutrition	1
Volume depletion	1
Transfer from outside hospital	1
Admission to teaching hospital	1
Clostridium difficile infection	1
Total	0–13

Risk stratification for severity of hospitalization: mild (0–1), moderate (2–4), and severe (5–13)

[a] Only one disease behavior is assigned per hospitalization

Appendix 2

Table 6 Risk score to predict colectomy among hospitalized patients with ulcerative colitis[21]

Characteristic	Points
Anemia	1
Requirement for blood transfusion	1
Malnutrition	2
Total parenteral nutrition	2
Transfer from outside hospital	1
Admission to teaching hospital	1
Total	0–8

Risk stratification for severity of hospitalization: low (0–1), intermediate (2–3), and high (≥4)

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ORIGINAL ARTICLE

Predictors of Outcome Following Surgery in Colonic Perforation: An Institution's Experience Over 6 Years

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Abstract
Background Colonic perforation is associated with abysmal outcome. The aims of our study were to review the surgical outcome of patients with perforated colon and to identify factors predicting peri-operative complications.
Methods A retrospective review of all patients who underwent surgery for colonic perforation from January 2003 to August 2008 was performed. Patients with iatrogenic or traumatic perforation were excluded. The severity of abdominal sepsis was graded using the Mannheim peritonitis index (MPI).
Results A total of 129 patients, with median age of 65 years (22–97 years), formed the study group. While 29.5% had severe peritoneal contamination, 56.6% had an American Society of Anesthesiologists (ASA) score ≥3. Sigmoid colon (47.3%) and caecum (24.8%) were the most common sites of perforation. Diverticulitis and malignancy were the diagnoses in 51.9% and 34.9%, respectively. Hartmann's procedure and right hemicolectomy were performed in 43.4% and 34.1% of the patients, respectively. Stoma was created in 59.7%. The in-hospital mortality rate in our series was 15.5%. After multivariate analysis, the independent variables associated with worse peri-operative complications were ASA score ≥3, MPI >26 and creation of stoma. Malignant perforation was associated with higher ASA score and lower haematocrit level compared to diverticular perforation. Stoma was created more frequently in patients with MPI >26 and left-sided perforation, and was associated with worse complications.
Conclusions Surgery for colonic perforation is associated with high morbidity and mortality rates. Short-term outcome is determined by ASA score and severity of peritonitis. A lower haematocrit level must alert the possibility of malignancy.

Keywords Perforation · Colon · Treatment outcome · Surgery

Introduction

Large-bowel perforation is a surgical emergency fraught with numerous complications.[1–4] Despite advances in surgical techniques and peri-operative care, their outcome remained abysmal.[1–4] Advanced age, worse degree of peritonitis and malignant perforation were some of the associated factors.[1–4]

With majority of current literature based on the Western population, a true reflection of the numerous issues surrounding large-bowel perforation in Asians is lacking. Firstly, Asians have a higher incidence of right-sided diverticulosis comparatively, and the sites and incidences of colorectal malignancy have also been reported to differ significantly between these two populations.[5–8]

Differentiation between malignant from diverticular perforation is also crucial as it determines the extent of surgery, but data are limited in the current literature.[9] Furthermore, the ideal surgical procedure in tackling colonic perforation is still controversial with a wide spectrum of recommendations.[10–15]

All these issues prompted us to undertake this study with the primary aim to review the outcome of patients who underwent surgery for colonic perforation. Our secondary aims were to evaluate the various factors predicting peri-operative complications, differences between diverticular and malignant perforations and also to compare right and left-sided perforations.

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Methods

Study Population

Tan Tock Seng Hospital is a 1,400-bed hospital, the second largest in Singapore, and provides secondary and tertiary medical care for about 1.5 million people. A retrospective review of all patients who underwent surgery for colonic perforation from January 2003 to August 2008 was performed. Patients were identified from the hospital's diagnostic index and operating records.

Right-sided pathologies were regarded if it was sited from the caecum until the transverse colon while left-sided pathologies commenced from the splenic flexure. Patients with colonic perforation from abdominal trauma or iatrogenic causes were excluded. Prior to the surgery, fluid resuscitation, parenteral antibiotics, optimisation of their medical conditions and nasogastric decompression would be administered to every patient. All gastrointestinal anastomoses were either hand-sewn or stapled while stoma created could be either a defunctioning or an end stoma.

The data collected included age, gender, American Society of Anesthesiologists (ASA) score, co-morbid conditions, presenting signs and symptoms, and clinical parameters. Laboratory values, including full blood count and renal panel, were also recorded. In addition, duration from symptoms to surgery, duration from admission to surgery, operative findings and interventions, length of surgery, peri-operative complications, mortality and length of hospital stay were also documented.

The severity of abdominal sepsis for all patients was graded using the Mannheim peritonitis index (MPI) (Table 1) with a score of >26 being defined as severe.[16] All colorectal cancers were staged according to the guidelines of the American Joint Committee of Cancer (AJCC).[17] The grades of complications (GOC) were in concordance to the classification proposed by Clavien and group (Table 2).[18–20]

Statistical analysis was performed using both univariate and multivariate analyses. The variables were analysed to the various outcomes using the Fisher's exact test, and their Odds ratio and 95% confidence interval were also reported. For the multivariate analysis, the logistic regression model was applied. All analyses were performed using the SPSS 17.0 statistical package (Chicago, Illinois); all p values reported are two-sided, and p values of <0.05 were considered statistically significant

Table 1 MPI[16]

Risk factor score	Score
Age >50 years old	5
Female sex	5
Organ failure[a]	7
Malignancy	4
Pre-operative duration of peritonitis >24 h	4
Origin of sepsis not colonic	4
Diffuse generalized peritonitis	6
Exudate	
Clear	0
Cloudy, purulent	6
Faecal	12

[a] Kidney failure, creatinine level >177 μmol/L or urea level >167 mmol/L or oliguria <20 ml/h; pulmonary insufficiency, PO_2<50 mmHg or PCO_2 of >50 mmHg; intestinal obstruction/paralysis >24 h or complete mechanical ileus, shock hypodynamic or hyperdynamic

Results

During the study period, 129 patients, median age of 65 years (range, 22–97 years), underwent surgery for colonic perforation. More than half (56.6%) of the patients had an ASA score of ≥3 (n=73). Hypertension, hyperlipidaemia and diabetes mellitus were the most common premorbid conditions in 57 (44.2%), 27 (20.9%) and 25 (19.4%) patients, respectively. Pre-operative computed tomography (CT) scan was performed in 77 (59.7%) patients. Table 3 illustrates the characteristics of the study group.

Operative Findings

The median MPI score was 20 (range 0–43) with 38 (29.5%) patients having severe peritonitis (MPI >26). Left-sided perforation occurred more frequently (n=77, 59.7%), with sigmoid colon involved in 61 (47.3%) patients. Diverticulitis and malignancy were the most common aetiologies in 67 (51.9%) and 45 (34.9%) patients, respectively. Table 4 highlights the surgical observations and procedures performed.

Hartmann's procedure was performed most frequently in 56 (43.4%) patients, followed by right hemicolectomy (n= 44, 34.1%) and anterior resection (n=13, 10.1%). In total, 77 (59.7%) patients had stoma created. As shown in Table 5, the in-hospital mortality rate in our series was 15.5% (n=20), with only 31 (24.0%) patients discharged well without any complications. The median length of stay was 10 days (2–141 days).

Analysis of the Complications

Worse complications (GOC III to V) occurred more frequently in patients of advanced age, higher ASA score (3–4), MPI >26, pre-operative renal impairment and in patients who had stoma created (Table 6). After multivariate

Table 2 Classification of surgical complications[18–20]

Grade of complications (GOC)
Grade I: Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions
Grade II: Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included
Grade III: Requiring surgical, endoscopic or radiological intervention
Grade IV: Life-threatening complication(s) requiring ICU management (including organ dysfunction)
Grade V: Death of a patient

analysis, the independent factors were high ASA score, MPI >26 and stoma creation. Factors such as malignancy and site of perforation were not related.

Analysis for the Comparison Between Diverticular and Malignant Perforations

Patients with malignant perforation had a higher ASA score and lower haematocrit level compared to those with perforated diverticulitis (Table 7). The other factors such as MPI, age, site of perforation and grading of complications were not significant.

Table 3 Characteristics of the study group

	Number (%)
Median age, range (yrs)	65 (22–97)
≤60	52 (40.3)
>60	77 (59.7)
Gender	
Male	68 (52.7)
Female	61 (47.3)
ASA score	
1	12 (9.3)
2	44 (34.1)
3	58 (45.0)
4	15 (11.6)
Premorbid condition	
Hypertension	57 (44.2)
Diabetes mellitus	25 (19.4)
Hyperlipidaemia	27 (20.9)
Ischaemic heart disease	14 (10.9)
History of cerebrovascular accident	8 (6.2)
Number of premorbid condition	
0–1	91 (70.5)
>1	38 (29.5)
Pre-operative CT scan	
Performed	77 (59.7)
Not performed	52 (40.3)

Analysis for the Comparison Between Right- and Left-Sided Perforations

Surgery in left-sided perforations usually took longer and often resulted in the creation of stoma (Table 8). Other factors such as age, ASA score, MPI and haematological results were not related.

Comparison of Stoma vs. No Stoma

The independent variables associated with stoma creation included MPI >26, left-sided perforation and malignant perforation (Table 9). Patients with stoma also fared worse than those without. ASA score was not an independent factor after multivariate analysis.

Discussion

To our knowledge, our series is one of the largest focusing on the numerous issues surrounding colonic perforation in an Asian population. Similar to the Western population, diverticulosis and colorectal cancers accounted for majority (86.8%) of the pathologies;[2–4] however, the differences in the distribution of diverticulosis and colorectal malignancy in Asians from their Western counterparts resulted in the paucity of related information in the literature.[5–8] Colorectal malignancies in Asians have been shown to occur more frequently at a younger age and were less advanced comparatively. This phenomenon has been attributed to genetic risk factors, cancer biology or other uncharacterized carcinogens.[5,6]

In addition, the incidence of right colonic diverticulosis is much higher in Asians, and its complications present in younger adults more frequently.[7,8] This has resulted in a significant proportion of patients undergoing unnecessary surgery on the misdiagnosis of acute appendicitis.[9] To complicate matters, left-sided diverticuli in the elderly Asian population still result in similar complications observed in the Western population.[21–23] This is also seen

Table 4 Surgical observations and procedures of the study group

	Number (%)
Mannheim peritonitis index (MPI)	20 (0–43)
≤26	91 (70.5)
>26	38 (29.5)
Site of perforation	
Right-sided	52 (40.3)
Caecum	32 (24.8)
Ascending Colon	10 (7.8)
Hepatic flexure	2 (1.6)
Transverse colon	8 (6.2)
Left-sided	77 (59.7)
Splenic Flexure	1 (0.8)
Descending Colon	4 (3.1)
Sigmoid Colon	61 (47.3)
Rectosigmoid	5 (3.9)
Upper rectum	6 (4.7)
Cause of perforation	
Diverticulitis	67 (51.9)
Hinchey II	29
Hinchey III	27
Hinchey IV	11
Malignancy	45 (34.9)
Stage I	0 (0.0)
Stage II	9 (20.0)
Stage III	20 (44.4)
Stage IV	16 (35.6)
Ischaemic colitis	6 (4.7)
Severe appendicitis causing caecal perforation	4 (3.1)
Stercoral ulcer	4 (3.1)
Tuberculosis	1 (0.8)
Volvulus	1 (0.8)
Idiopathic	1 (0.8)
Surgery performed	
Hartmann's procedure	56 (43.4)
Right hemicolectomy with/without stoma	44 (34.1)
Anterior resection with/without stoma	13 (10.1)
Subtotal or total colectomy	7 (5.4)
Defunctioning stoma	4 (3.1)
Sigmoid colectomy	3 (2.3)
Left hemicolectomy	1 (0.8)
Primary closure of perforation	1 (0.8)
Creation of stoma	
Yes	77 (59.7)
No	52 (40.3)
Duration of surgery	
≤120 min	45 (34.9)
>120 min	84 (65.1)

Table 5 Peri-operative outcome of the study group

	Number (%)
Grade of complications	
No complications	31 (24.0)
Grade I	16 (12.4)
Grade II	21 (16.3)
Grade III	9 (7.0)
Grade IV	32 (24.8)
Death or grade V	20 (15.5)
Median length of stay (days)	10 (2–141)

in our series with the majority (64%) of the perforated diverticulitis sited in the left colon.

Differentiation between malignant and diverticular perforation still confounds surgeons worldwide. This is especially so since their radiological findings could be indistinct;[24–27] however, this difference is crucial as it determines the extent of surgical resection. Through our series, it would be prudent to be suspicious of any underlying malignancy in patients with colonic perforation also having low haematocrit levels. Interestingly, despite reported worse outcome in malignant perforation,[28,29] this was not seen in our series. Though this association had been attributed to the higher likelihood of diffuse peritonitis in malignant perforation compared to a contained abscess in diverticulitis,[28,29] the majority of our patients with diverticular perforations actually had Hinchey III or IV diseases, and there was no notable difference in the severity of peritonitis from their MPI scores.

Our series also affirmed the high morbidity and mortality rates associated with colonic perforation.[1–4] Our mortality rate of 15.5% is similar to those quoted in other series while another 31.8% of our patients also had significant complications (GOC III–IV). Some of the independent factors in our series that are accountable for these abysmal results included worse peritonitis (MPI >26) and higher ASA score.

Suffice to say, it is the severity of peritonitis and not the surgical procedure or the underlying diagnoses that is responsible for the outcome. MPI has been adopted in our institution in recent years and has been shown to correspond to the patients' outcome.[9,30–32]

Compared to right-sided perforation, over 80% of our patients with left-sided perforation had stoma created with Hartmann's procedure accounting for 90% of them. Even though there was no difference seen in the degree of peritonitis or ASA score, the likely explanation for this difference is due to the higher quoted incidence of an anastomotic dehiscence in a colocolic or colorectal anastomosis compared to an ileo-colic anastomosis, especially in an unprepared colon.[33,34]

Table 6 Analysis of variables associated with worse peri-operative outcome

Characteristics	GOC 0–II (n=68; %)	GOC III–V (n=61; %)	OR (95% CI)	P value
>60 years old	33 (48.5)	44 (72.1)	**2.75 (1.32–5.72)**	**0.007**
Female gender	33 (48.5)	28 (45.9)	0.90 (0.45–1.80)	>0.05
ASA score 3–4	20 (29.4)	53 (86.9)	**15.90 (6.41–39.43)**	**<0.001**[a]
≥2 premorbid conditions	15 (22.1)	23 (37.7)	2.14 (0.99–4.63)	0.056
MPI >26	2 (2.9)	36 (59.0)	**47.52 (10.64–212.21)**	**<0.001**[a]
WBC >10.0	44 (64.7)	39 (63.9)	0.97 (0.47–1.99)	>0.05
HCT (<33.0) (%)	17 (25.0)	25 (41.0)	2.08 (0.99–4.41)	>0.05
Abnormal serum sodium level	13 (19.1)	23 (37.7)	**2.56 (1.16–5.68)**	**0.030**
Abnormal serum potassium level	17 (25.0)	22 (36.1)	1.69 (0.79–3.61)	>0.05
Serum Urea >9.3 (mmol/L)	5 (7.4)	26 (42.6)	**9.36 (3.30–26.55)**	**<0.001**
Serum creatinine >110 (μmol/L)	10 (14.7)	29 (47.5)	**5.26 (2.27–12.16)**	**<0.001**
Left-sided perforation	36 (52.9)	41 (67.2)	1.82 (0.89–3.73)	>0.05
Creation of stoma	25 (36.7)	52 (85.2)	**9.94 (4.20–23.54)**	**<0.001**[a]
Duration of operation >2 h	48 (70.6)	36 (59.0)	0.60 (0.29–1.25)	>0.05
Malignant perforation	24 (35.3)	21 (34.4)	0.96 (0.47–1.99)	>0.05

[a] Statistically significant on multivariate analysis

Bold figures are statistically significant

Apart from the site of perforation, stoma was also created more frequently in patients with underlying malignancy, worse peritonitis and higher ASA score. This is not surprising as stoma has always been advocated in patients with anticipated worse outcome.[11,35,36] The higher rate of complications seen in patients who had stoma created merely reflected the worse cohort of patients that necessitated its formation.

As seen in our series, Hartmann's procedure is the most frequently performed surgery as it has been shown to be a safe surgical option in our patients, who are mostly of advanced age with poor ASA score. Furthermore, the shorter operative time compared to an anterior resection also reduces the risks of a lengthier surgery and negates the complications of a primary anastomosis; however, the morbidity from a stoma is not negligible and numerous patients often ended up with a

Table 7 Comparison of patients with diverticulitis against malignancy

Characteristics	Diverticulitis (n=67; %)	Malignancy (n=45; %)	OR (95% CI)	P value
>60 years old	39 (58.2)	28 (62.2)	1.18 (0.55–2.56)	>0.05
Female gender	30 (44.8)	23 (51.1)	1.29 (0.61–2.75)	>0.05
ASA score 3–4	32 (47.8)	30 (66.7)	**2.19 (1.00–4.80)**	**0.055**
≥2 premorbid conditions	21 (31.3)	13 (28.9)	0.89 (0.39–2.03)	>0.05
MPI >26	15 (22.4)	14 (31.1)	1.57 (0.67–3.68)	>0.05
WBC >10.0	45 (67.2)	25 (55.6)	0.61 (0.28–1.33)	>0.05
HCT (<33.0) (%)	8 (11.9)	25 (55.6)	**9.22 (3.59–23.69)**	**<0.001**
Abnormal serum sodium level	15 (22.4)	16 (35.6)	1.91 (0.83–4.42)	>0.05
Abnormal serum potassium level	18 (26.9)	14 (31.1)	1.23 (0.54–2.82)	>0.05
Serum Urea >9.3 (mmol/L)	18 (26.9)	10 (22.2)	0.78 (0.32–1.89)	>0.05
Serum Creatinine >110 (μmol/L)	20 (29.9)	14 (31.1)	1.06 (0.47–2.41)	>0.05
Left-sided perforation	43 (64.2)	25 (55.6)	0.70 (0.32–1.51)	>0.05
Duration of surgery >120 min	45 (67.2)	29 (64.4)	0.89 (0.40–1.96)	>0.05
GOC III to V	28 (41.8)	21 (46.7)	1.22 (0.57–2.61)	>0.05

Bold figures are statistically significant

Table 8 Analysis of variables associated with site of perforation

Characteristics	Right-sided perforation (n=52; %)	Left-sided perforation (n=77; %)	OR (95% CI)	P value
>60 years old	26 (50.0)	51 (66.2%)	1.96 (0.96–4.03)	>0.05
Female gender	28 (53.8)	33 (42.9)	0.64 (0.32–1.31)	>0.05
ASA score 3–4	26 (50.0)	47 (61.0)	1.57 (0.77–3.19)	>0.05
≥2 premorbid conditions	12 (23.1)	26 (33.8)	1.70 (0.76–3.78)	>0.05
MPI >26	12 (23.1)	26 (33.8)	1.70 (0.76–3.78)	>0.05
WBC >10.0	35 (67.3)	48 (62.3)	0.80 (0.38–1.69)	>0.05
HCT (<33.0) (%)	17 (32.7)	25 (32.5)	0.99 (0.47–2.10)	>0.05
Abnormal serum sodium level	14 (26.9)	22 (28.6)	1.09 (0.49–2.39)	>0.05
Abnormal serum potassium level	15 (28.8)	24 (31.2)	1.12 (0.52–2.41)	>0.05
Serum urea >9.3 (mmol/L)	9 (17.3)	22 (28.6)	1.91 (0.80–4.57)	>0.05
Serum creatinine >110 (μmol/L)	9 (17.3)	30 (39.0)	**3.05 (1.30–7.15)**	**0.011**
Creation of stoma	15 (28.8)	62 (80.5)	**10.20 (4.48–23.23)**	**<0.001**[a]
Duration of operation >2 h	28 (53.8)	56 (72.7)	**2.29 (1.09–4.80)**	**0.038**[a]

[a] Statistically significant on multivariate analysis

Bold figures are statistically significant

permanent stoma due to the challenges incurred during reversal of Hartmann's procedures.[15,37–39]

Ultimately, the ideal surgical procedure to perform should be left to the discretion of the primary surgeon at the time of operation. As seen in our series and others in the literature, some of the factors that must be considered would include the site of perforation, state of the bowel, underlying pathology, degree of contamination and haemodynamic stability and physiological status of the patient.

As with most studies, there were several limitations in the present one. This series of patients was enrolled from a single institution, and despite our study being one of the largest in the literature, its retrospective nature and the relatively small number of patients may mask several other important factors that could be accountable for the outcomes measured. In addition, there were no prior standardised guidelines or protocol in the management of patients with colonic perforation, and any decisions were based on the discretion of the primary surgeon.

Although these limitations are significant, the authors felt that this study remains important in highlighting the numerous issues pertinent in colonic perforation that are

Table 9 Characteristics associated with stoma creation

Characteristics	No stoma (n=52; %)	Stoma created (n=77; %)	OR (95% CI)	P value
>60 years old	28 (53.8)	49 (63.6)	1.50 (0.73–3.07)	>0.05
Female gender	29 (55.8)	32 (41.6)	0.56 (0.28–1.15)	>0.05
ASA score 3–4	17 (32.7)	56 (72.7)	**5.49 (2.55–11.81)**	**<0.001**
≥2 premorbid conditions	14 (26.9)	24 (31.2)	1.23 (0.56–2.68)	>0.05
MPI >26	2 (3.9)	36 (46.8)	**21.95 (4.98–96.68)**	**<0.001**[a]
WBC >10.0	37 (71.2)	46 (59.7)	0.60 (0.28–1.28)	>0.05
HCT (<33.0) (%)	8 (15.4)	34 (44.2)	**4.35 (1.81–10.46)**	**0.001**
Abnormal serum sodium level	7 (13.5)	29 (37.7)	**3.88 (1.55–9.75)**	**0.003**
Abnormal serum potassium level	14 (26.9)	25 (32.5)	1.31 (0.60–2.84)	>0.05
Serum urea >9.3 (mmol/L)	4 (7.7)	27 (35.1)	**6.48 (2.11–19.91)**	**<0.001**
Serum creatinine >110 (μmol/L)	5 (9.6)	34 (44.2)	**7.43 (2.67–20.73)**	**<0.001**
GOC III to V	9 (17.3)	52 (67.5)	**9.94 (4.20–23.54)**	**<0.001**[a]
Left-sided perforation	15 (28.8)	62 (80.5)	**10.20 (4.48–23.23)**	**<0.001**[a]
Malignant perforation vs. diverticulitis	14/49 (28.6)	31/63 (49.2)	**2.42 (1.10–5.35)**	**0.033**[a]
Duration of operation >2 h	33 (63.5)	51 (66.2)	1.13 (0.54–2.36)	>0.05

[a] Statistically significant on multivariate analysis

Bold figures are statistically significant

rarely seen in the Western population or reported in the literature. Our study also identified various factors that could perhaps aid all surgeons in the management of patients with colonic perforation.

Conclusions

Surgery for colonic perforation is associated with high morbidity and mortality rates. Short-term outcome is determined by ASA score and severity of peritonitis but not aetiology or site of the perforation. A lower haematocrit level must alert the possibility of malignant perforation.

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ORIGINAL ARTICLE

Treatment of Colorectal Cancer with Unresectable Synchronous Liver-Only Metastases with Combined Therapeutic Modalities

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Abstract
Background Resection + radiofrequency ablation (RFA) + hepatic artery infusion (HAI) + systemic chemotherapy for patients with unresectable synchronous liver-only metastases from colorectal cancer was rarely used previously.
Methods We compared the outcomes of 42 patients underwent resection + RFA + HAI + systemic chemotherapy (RRHS) with that of 43 patients underwent resection + RFA + systemic chemotherapy (RRS).
Results The overall survival, the survival free of hepatic recurrence and the median survival in the RRHS group were all significantly higher than those in RRS group at 4 years. While the rates of adverse effects were similar in the two groups.
Conclusion For patients with unresectable synchronous liver-only metastases from colorectal cancer, RRHS not only decreases but also postpones hepatic recurrence and therefore improves overall survival at 4 years, as compared with RRS.

Keywords Colorectal cancer · Liver metastases · Radiofrequency ablation · Hepatic artery infusion · Systemic chemotherapy

Introduction

Colorectal cancer is the third commonest malignancy in the world and liver is the commonest (or most preferable) metastases site.[1] Surgical resection remains the main treatment that can ensure cure and long-term survival in some patients.[2–5] However, only 10~20% of the patients are candidates for resection because of the number and distribution of metastases and liver function.[6] Several studies have shown that hepatic resection combined with radiofrequency ablation (RFA) is safe and efficient for unresectable diseases.[4,7] Furthermore, several randomized studies have shown hepatic artery infusion (HAI) plus systemic chemotherapy have better results when compared with systemic chemotherapy alone.[8–10] Therefore, resection + RFA + HAI + systemic chemotherapy may give a new hope for the patients of colorectal cancer with unresectable liver metastases. However, other trials have shown HAI is most commonly linked with hepatic toxicity.[9] Correspondently, it is necessary to find new substances with less toxicity and higher efficacy. Studies in animals and patients all confirmed HAI with oxaliplatin has less hepatic toxicity and higher efficacy.[11–14] However, HAI with oxaliplatin was only used as palliative treatment for unresectable liver metastases or neoadjuvant therapy before operation, hardly any studies about adjuvant therapy after operation. The present study is important because it not only used resection + RFA for the unresectable synchronous metastases which was rarely used previously, but also compared HAI with oxaliplatin + systemic chemotherapy with systemic chemotherapy alone after operation. Perhaps most important, patients between groups had similar tumor biologic profiles which avoided

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comparison between "apples" and "oranges". We sought to confirm the validity of combined therapeutic modality of resection + RFA + HAI + systemic chemotherapy.

Patients and Methods

Patient Selection

Between July 1, 2001 and April 30, 2008, 152 colorectal cancer patients with synchronous liver metastases underwent simultaneous bowel and liver resection plus RFA at The Tianjin Cancer Hospital. Hepatic metastases of all these patients could not be completely resected because the number or distribution of metastases or the liver function. In these patients, some accepted resection + RFA + HAI + systemic chemotherapy (RRHS) and some accepted resection + RFA + systemic chemotherapy (RRS) under the experience of surgeons and the requests of patients. To make reasonable compatibility, only patients who met the following criteria were considered for further analysis. Such criteria included the following: (1) primary tumor totally resected; (2) synchronous hepatic metastases without evidence of extrahepatic metastases or hepatocirrhosis; (3) number of metastases ≥4 and ≤10; (4) hepatic involvement <75%; (5) the presence of metastatic lesions distributed diffusely in both lobes of the liver that would require more than a right or left trisegmentectomy; (6) age ≥18 years and ≤75 years; (7) no prior chemotherapy or radiation treatment; (8) general conditions and liver function sufficient for hemihepatectomy; (9) complete follow-up data; (10) resection and RFA and/or HAI were performed at the time of resection of primary tumor. In total, 85 patients met the criteria and were considered for further analysis.

Methods

Surgical Technique

At the time of laparotomy, the confirmation that the primary tumor could be totally resected and no evidence of extrahepatic metastases or hepatocirrhosis were made first. In addition, then intraoperative hepatic ultrasonography was performed routinely to identify the number, location and relationship with surrounding vascular and biliary structures of the metastatic lesions. The extent of resection was determined by the patient's condition, liver function and the distribution of the metastatic lesions. Wedge, segmentectomy or hemihepatectomy was planned for the eligible patients (the number of lesions left after resection ≤4, maximum diameter ≤3cm and the left lesions not adjacent to major biliary structures). After assessment, RFA was performed first. The model 70 probe (RITA Medical Systems, Inc), and the StarBurst XL 5-cm needle with a 150-W electrode (RITA Medical Systems, Inc) were used. Under intraoperative ultrasonographic guidance, the electrode was optimally positioned to achieve complete destruction of the tumor and at least a 1-cm zone of normal liver parenchyma when possible. After RFA completed, liver resection was performed as planned; and then, for the RRHS group, placement of the implantable infusion pump was performed. Catheter was positioned in the ligated gastroduodenal artery with the catheter tip located at the junction of the gastroduodenal and hepatic artery. Furthermore, we performed cholecystectomy routinely to prevent potential chemical cholecystitis during chemotherapy. The HAI pump was placed subcutaneously and sutured to the fascia of the abdominal wall. At last, the primary tumor was totally resected in both groups.

HAI and Systemic Chemotherapy

For the RRHS group, the regimen mainly consisted of HAI administration of oxaliplatin 100 mg/m^2 over 2 h on day 1, combined with IV FU and leucovorin according to the classic LV5FU2 de Gramont regimen; and for the RRS group, the regimen was FOLFOX4, which consisted of biweekly oxaliplatin 85 mg/m^2 followed sequentially by leucovorin 200 mg/m^2, bolus FU 400 mg/m^2, and then continuous-infusion FU 600 mg/m^2 over 22 h on day 1. These same doses of FU and leucovorin were repeated on day 2 without oxaliplatin.

Chemotherapy was initiated 4 weeks after operation. Twelve courses of chemotherapy were given to both groups as mentioned above. In both groups, the following adjustments were made according to the severity of toxicity at day 15 using the National Cancer Institute common toxicity criteria. Chemotherapy was delayed until recovery if neutrophils less than 1.5×10^9/L or platelets less than 100×10^9/L or for significant persisting non-hematological toxicity. The FU dose was reduced by 25% in the event of grades 3 or 4 diarrhea, stomatitis occurred or neutrophils less than 1.0×10^9/L or platelets less than 75×10^9/L. Oxaliplatin dose was to be reduced by 25% in the event of grades 3 or 4 vomiting or neutrophils less than 1.0×10^9/L or platelets less than 75×10^9/L or temporary (7~14 days) painful paresthesia or functional impairment or more mild abdominal pain. In cases of persistent (14 days or longer) painful paresthesia or functional impairment, oxaliplatin was omitted from the regimen until recovery. In the event of further toxicity after dose decreases or non-recovery of satisfactory hematologic parameters, treatment was discontinued.

When recurrence emerged, the second-line systemic chemotherapy was administered without HAI or just followed up according to the experience of surgeons and

the request of patients. In second-line therapy, oxaliplatin was replaced by irinotecan mostly.

Treatment Evaluation

Tumor recurrence was assessed every 2 months by abdominal CT scan. Pulmonary metastasis was assessed every 2 months by chest X-ray.

Data Collection

The following data were collected for each patient: disease status, laboratory data, operative details, date of last follow-up, administration and timing of chemotherapy, postoperative complications, toxic effects of chemotherapy, date of disease progression and death, as well as tumor number, size and location.

Data Analysis

We used SPSS statistical software, version 13.0 (SPSS Inc, Chicago, Illinois), for data analysis. Categorical variables were compared using χ^2 test and continuous variables by Wilcoxon's rank-sum test. Survival comparisons were performed by the Kaplan–Meier method and the log-rank test. Cox-proportional hazards model for multivariate analysis. Results are reported as median with range unless otherwise stated. Survival data were measured from the time of simultaneous resection of bowel and liver. Significance was defined as $P<0.05$.

Results

Characteristics of the Patients

Table 1 gives the characteristics of the 85 patients in the study. Forty-three patients received RRS and 36 of them received the operation between 2001 and 2005, seven between 2006 and 2008. Forty-two patients received RRHS and all of them received the operation between 2005 and 2008. The median follow-up was 32.4 months (range, 6.5 to 62). There were no significant differences between the two groups with respect to the characteristics (Table 1), including the age and sex of patients, primary tumor, CEA, hepatic metastases, type of resection, size and number of tumors treated by RFA.

Characteristics of Treatment

Table 2 shows the characteristics of treatment in two groups. There were no significant differences between groups with respect to the characteristics of treatment. In cases of recurrence, second resection or RFA was performed when possible. In the RRHS group, there were nine repeated liver resections and seven repeated RFA and two lung resections. In the RRS (N=7+36) group, there were 12 repeated liver resections and six repeated RFA and one lung resection.

Overall Survival

During follow-up, 29 patients were dead of disease in the RRHS group and 35 patients in the RRS (N=7+36) group. An univariate analysis of overall mortality at 4 years (Table 3) showed an unadjusted risk ratio for death of 0.55 (95% confidence interval, 0.33 to 0.93; P=0.025) in the RRHS group as compared with the RRS (N=7+36) group. Kaplan–Meier survival curves (Fig. 1) demonstrated an estimated median survival of 38.5 months in the RRHS group and 28.6 months in the RRS (N=7+36) group. In univariate log-rank analysis, there were differences in the 2-, 3-, 4-year overall survival (81.0% versus 62.8%, P=0.043; 56.4% versus 38.3%, P=0.049; 37.0% versus 17.9%, P=0.023) between the RRHS group and the RRS (N=7+36) group, except for 1-year overall survival (97.6% versus 95.3%, P=0.654). In the RRS (N=7+36) group, 5-year overall survival was 14.9%, while in the RRHS group, it had not been reached because no patients in this group were followed up 5 years. Furthermore, significant difference was only seen in 4-year overall survival between the RRS (N=36) group and RRHS group (18.6% versus 37.0%, P=0.035) (Fig. 2).

The 1, 2, 3, 4-year overall survival were 85.7%, 57.1%, 42.9%, 14.3% in the RRS (N=7) group and 97.2%, 63.9%, 37.2%, 18.6% in the RRS (N=36) group (Fig. 2).

To evaluate the effect of treatment while controlling for other variables, we used the best subgroup-selection method to choose a multivariate regression model. After adjustment for variables selected in the final model-the number of metastases (≤6 versus >6) and the number of RFA (≤2 versus >2), the risk ratio for death in the RRHS group as compared with the RRS (N=7+36) group was 0.44 (95% confidence interval, 0.26 to 0.76; P=0.003).

Survival Free of Hepatic Progression

During follow-up after surgery, 31 of 42 patients in the RRHS group and 38 of 43 patients in the RRS (N=7+36) group had hepatic recurrences. The 1-, 2-, 3-, 4-year actuarial rates of survival free of hepatic progression were 78.6%, 42.9%, 27.8%, 27.8% in the RRHS group and 48.8%, 25.6%, 12.2%, 9.2% in the RRS (N=7+36) group. Kaplan–Meier estimates of survival free of hepatic progression (Fig. 3) showed a clear divergence between the rates in the two groups throughout the study period (P=

Table 1 Characteristics of the patients

CHARACTERISTIC	RRS (*N*=7+36)	RRHS (*N*=42)
Age (median (IOR), year)	63 (55.00~72.00)	63.5 (52.75~70.25)
Male sex (No. (%))	25 (58.14%)	27 (64.29%)
Preoperative CEA level (median (IQR), ng/mL)	15.2 (4.36~224.40)	21.3 (3.90~332.80)
Primary tumor T stage (No. (%))		
T1 or T2	2 (4.65)	1 (2.38)
T3 or T4	41 (95.35)	41 (97.62)
Positive lymph nodes (No. (%))	31 (72.09)	34 (80.95)
Hepatic metastases		
Liver involvement (median (IQR),%)	35 (25.60~45.00)	32 (25.25~40.00)
Size of largest lesion (median (IQR), cm)	4.5 (3.88~5.75)	4.05 (3.50~5.95)
No. of liver metastases (No. (%))		
4–6	20 (46.51)	23 (54.76)
7–10	23 (53.49)	19 (45.24)
Type of resection (No (%))		
Wedge resection	6 (13.95)	9 (21.43)
Segmentectomy	11 (25.58)	11 (26.19)
Hemihepatectomy	7 (16.28)	7 (16.67)
Segmentectomy + wedge resection	17 (39.53)	11 (26.19)
Hemihepatectomy + wedge resection	2 (4.65)	4 (9.52)
RFA		
Size of largest lesion (median, cm)	2.1 (1.65~2.65)	2.0 (1.50~2.58)
No. of liver metastases (No. (%))		
1–2	28 (65.12%)	24 (57.14)
3–4	15 (34.88)	18 (42.86)

Table 2 Characteristics of treatment

	RRHS	RRS (*N*=7+36)
Total courses	337	343
Median number of courses	10 (range, 2 to 12)	11 (range, 1 to 12)
Total dose of oxaliplatin (%)	76.5%	77.6%
Total dose of FU	75.6%	76.3%
The reasons for the dose reduction of oxaliplatin		
Abdominal pain	3 courses	–
Hematologic toxicity	39 courses	36 courses
Neurotoxicity	7 courses	16 courses
Mucositis\diarrhea\vomiting	2 courses	9 courses
The reasons for the dose reduction of FU		
Hematologic toxicity	39 courses	46 courses
Mucositis\diarrhea\vomiting	10 courses	20 courses
The reasons for treatment discontinued		
Obstruction of the catheter	11 patients	–
Toxicity	4 patients	7 patients
Disease progression	11 patients	15 patients
Patients received 6 or more courses	85.7%	86.1%
Patients received more than 50% of the planned dose of oxaliplatin	81.0%	81.4%
Patients received more than 50% of the planned dose of FU	78.6%	76.7%

Table 3 Univariate and multivariate analysis of the risk ratios for overall survival, disease-free survival and survival free of hepatic progression during 4 years after surgery

Variable	Univariate analysis		Multivariate analysis	
	Risk ratio (95% CI)	*P* value	Risk ratio (95% CI)	*P* value
Death				
Treatment (RRHS vs.RRS (*N*=7+36))	0.55 (0.33~0.93)	0.025	0.44 (0.26~0.76)	0.003
No. of RFA (>2 vs. ≤2)	1.83 (1.10~3.06)	0.020	1.88 (1.11~3.18)	0.018
No. of metastases (>6 vs. ≤6)	2.03 (1.20~3.42)	0.008	2.11 (1.24~3.59)	0.006
Hepatic progression				
Treatment (RRHS vs.RRS (*N*=7+36))	0.58 (0.36~0.94)	0.027	0.50 (0.31~0.82)	0.006
No. of RFA (>2 vs. ≤2)	1.62 (1.00~2.62)	0.048	1.64(1.01~2.68)	0.047
No. of metastases (>6 vs. ≤6)	1.69 (1.04~2.74)	0.033	1.72 (1.05~2.81)	0.031
Overall progression				
No. of metastases (>6 vs. ≤6)	2.10 (1.31~3.39)	0.002	–	–

0.024 by the log-rank test). The median survival free of hepatic progression was 18 months in the RRHS group and 10 months in the RRS (*N*=7+36) group. Furthermore, Kaplan–Meier estimates of survival free of hepatic progression (Fig. 3) also showed a clear divergence between the rates in the RRS (*N*=36) group and RRHS group throughout the study period (*P*=0.045 by the log-rank test). In the univariate analysis, RRS and the number of metastases (>6) and number of RFA (>2) were significantly associated with the risk of hepatic progression (Table 3). In a multivariate analysis, RRHS had a strong protective effect, with a relative risk of hepatic progression of 0.50 in the RRHS group as compared with the RRS (*N*=7+36) group (95% confidence interval, 0.310 to 0.82; *P*=0.006), after adjustment for the interval between the number of metastases (≤6 versus >6) and the number of RFA (≤2 versus >2).

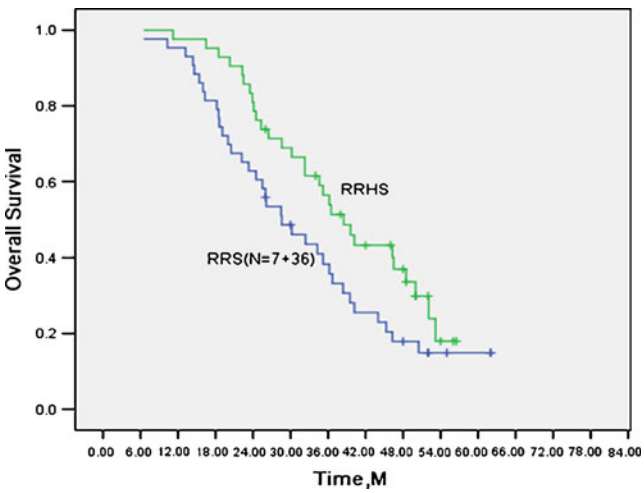

Fig. 1 Kaplan–Meier estimates of overall survival of RRHS group and the RRS (*N*=7+36) group. Differences between groups were not significant (*P*=0.055 by the log-rank test)

The 1-, 2-, 3-, 4-, 5-year actuarial rates of survival free of hepatic progression were 47.2%, 30.6%, 15.2%, 11.4%, 11.4% in the RRS (*N*=36) group and 57.1%, 14.3%, 14.3%, 0%, 0% in the RRS (*N*=7) group (Fig. 4).

Overall Progression-Free Survival

During follow-up after surgery, 36 patients in the RRHS group and 38 in the RRS (*N*=7+36) group had disease progression. During this period, new liver metastases and/or local recurrence were identified in 31 patients in the RRHS group and 37 patients in the RRS (*N*=7+36) group; lung metastases in 14 patients and 12 patients; extrahepatic abdominal metastases in ten patients and 11 patients, other

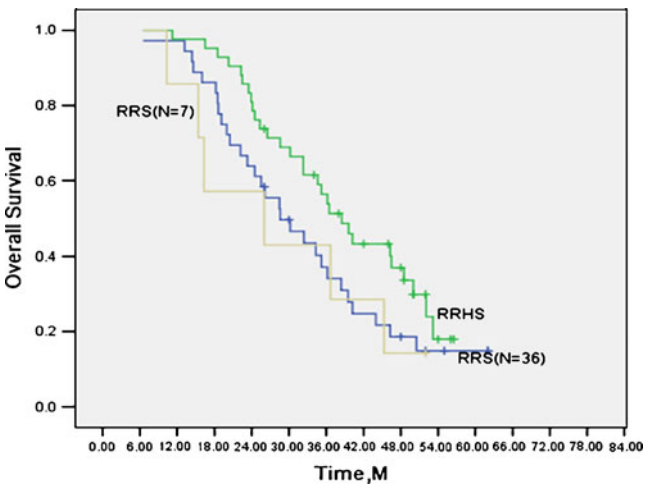

Fig. 2 Kaplan–Meier estimates overall survival in the RRHS Group and the RRS (*N*=7) group and RRS (*N*=36) group. Differences between groups were not significant (*P*=0.079) between RRHS group and RRS (*N*=36) group; *P*=0.143 between RRHS group and RRS (*N*=7) group; *P*=0.787 between the RRS (*N*=36) group by the log-rank test

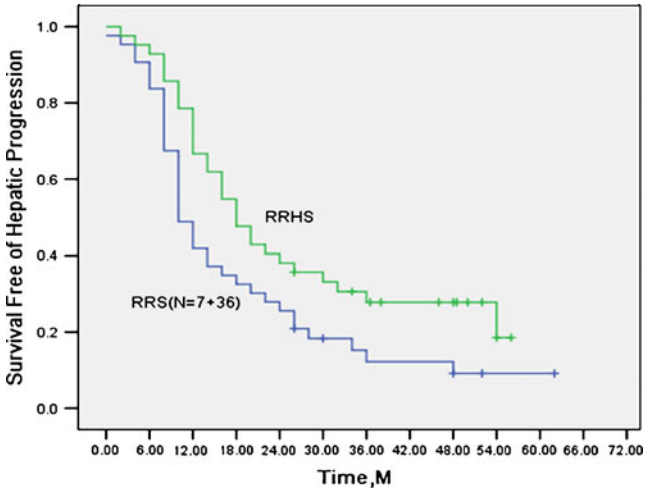

Fig. 3 Kaplan–Meier estimates of survival free of hepatic progression in the RRHS group and the RRS (N=7+36) group. Differences between groups were significant (P=0.024 by the log-rank test)

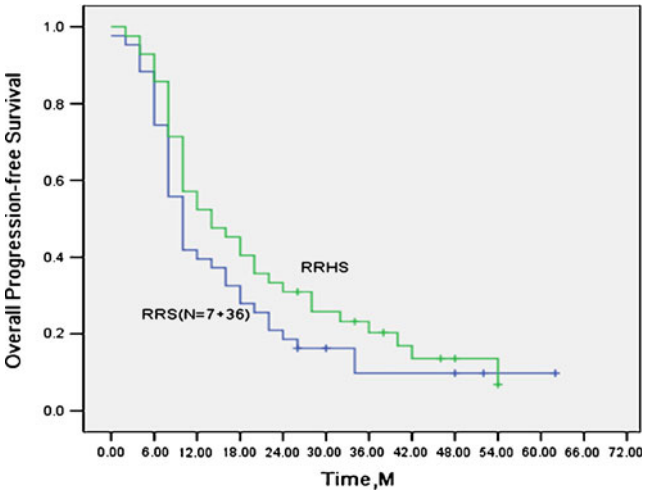

Fig. 5 Kaplan–Meier estimates of overall progression-free survival in the RRHS group and the RRS (N=7+36) group. Differences between groups not significant (P=0.186 by the log-rank test)

site metastases in seven patients and seven patients, respectively. Kaplan–Meier survival curves (Fig. 5) demonstrated an estimated median progression-free survival of 12 months in the RRHS group and 8 months in the RRS (N=7+36) group. The 1-, 2-, 3-, 4-year actuarial rates of overall progression-free survival were 57.1%, 31.0%, 20.3%, 13.5% in the RRHS group and 39.5%, 18.6%, 9.8%, 9.8% in the RRS (N=7+36) group, respectively. Actuarial rates of progression-free survival at 5 years were 9.8% in the RRS (N=7+36) group, while it had not been reached in the RRHS group. Kaplan–Meier estimates of overall progression-free survival showed no differences between RRHS group and RRS (N=7+36) group (P=0.186 by the log-rank test) as well as RRHS group and RRS (N=36) group (P=0.269 by the log-rank test). In the univariate analysis, only the number of metastases (>6) was significantly associated with the risk of overall progression (Table 3).

The 1-, 2-, 3-, 4-, 5-year actuarial rates of overall progression-free survival were 42.9%, 14.3%, 0%, 0%, 0% in the RRS (N=7) group and 41.7%, 22.2%, 12.5%, 12.5%, 12.5% in the RRS (N=36) group (Fig. 6).

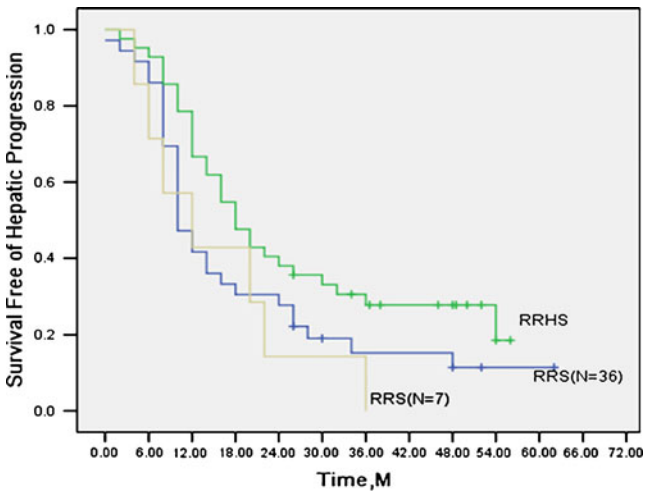

Fig. 4 Kaplan–Meier estimates of survival free of hepatic progression in the RRHS group and the RRS (N=7) group and RRS (N=36) group. Differences between RRHS group and RRS (N=36) group were significant (P=0.045 by the log-rank test). Differences between RRHS group RRS (N=7) group were not significant (P=0.093 by the log-rank test). Differences between the RRS (N=7) group and RRS (N=36) group were not significant (P=0.505 by the log-rank test)

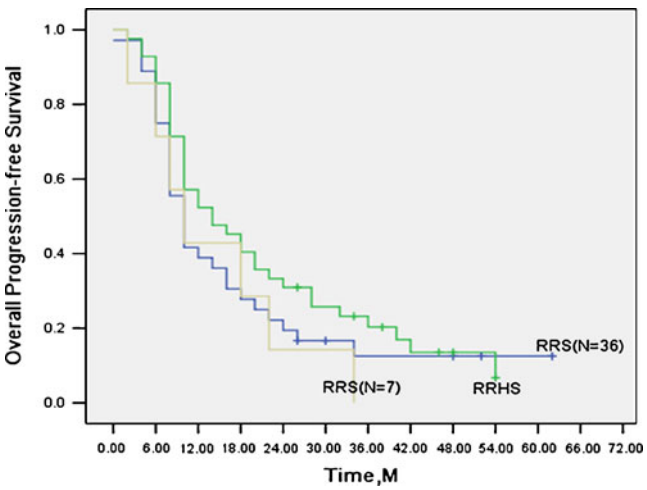

Fig. 6 Kaplan–Meier estimates of overall progression-free survival in the RRHS group and the RRS (N=7) group RRS (N=36) group. Differences between groups were not significant (P=0.269 between RRHS group and the RRS (N=36) group; P=0.213 between RRHS group and RRS (N=7) group; P=0.847 between the RRS (N=7) group and RRS (N=36) group by the log-rank test)

Postoperative Complications and Toxic Effects of Chemotherapy

There were no deaths in the postoperative period in our study. Postoperative complications occurred in 11 patients (26.2%) in the RRHS group and 12 patients (26.9%) in the RRS (N=7+36) group, respectively. Postoperative complications included postoperative hemorrhage, infection, pleural effusion and other complications. All the complications were cured through medical treatment.

The toxic effects of chemotherapy were similar among groups except that more patients had diarrhea, nausea, vomiting and neurotoxicity in the RRS group but without significant differences. The main toxicities observed were listed in Table 4.

Complications of Hepatic Arterial Infusion

Obstruction of the catheter occurred in 11 patients during the first 14 months of the study, rendering the infusion device unusable. In six patients, the catheter and pump were taken out at the time of repeated liver resection.

Discussion

Resection combined with FRA gives a new hope for the patients of colorectal cancer with unresectable synchronous liver metastases. Two studies about resection+FRA for unresectable hepatic metastases from colorectal cancer reported that actuarial 3-year survival was 44.9%[15] and 47%,[16] respectively. Their survival rates seem to be lower than that of RRHS group which was 56.4%. Maybe HAI of oxaliplatin plus systemic chemotherapy accounted for the difference.

Several randomized studies had shown better results for HAI plus systemic chemotherapy when compared with systemic chemotherapy alone.[8–10] The Cancer and Leukemia Group B 9481 randomized trial compared floxuridine by HAI with systemic 5-FU and LV in 135 patients. The median overall survival time (24.4 versus 20.0 months), time to hepatic progression (9.8 versus 7.3 months) were all significantly better with HAI, and quality of life assessment showed better physical function in the HAI group at 3 and 6 months.[10] Another randomized trial conducted by the Memorial Sloan–Kettering Cancer Center compared resection+systemic chemotherapy+HAI of floxuridine with resection+systemic chemotherapy in 156 patients. The respective actuarial rate of overall survival at 2, 10 years was 86%, 41.1% in resection+HAI+systemic chemotherapy group and 72%, 27.2% in resection+systemic chemotherapy group. The respective median survival was 68.4 and 58.5 months, the rates of survival free of hepatic recurrence were 90% and 60% at 2 years (P<0.001), and the rates of progression-free survival were 57% and 42% at 2 years (P=0.07). Resection+HAI+systemic chemotherapy markedly improved the outcome at 2 years.[8,9] In our study, the outcomes in both groups were inferior to those of the Memorial Sloan–Kettering Cancer Center study, but it was encouraging: the respective actuarial rate of overall survival at 4 years was 37.0% in the RRHS group and 17.9% in the RRS group (P=0.023), the median survival was 38.5 and 28.6 months, the rates of survival free of hepatic recurrence were 27.8% and 9.2% (P=0.019), and the rates of progression-free survival were 13.5% and 9.8% (P=0.157). As disease extent seems to be the main determinant of survival, the difference between the two studies was just the patient's disease extent: in the Memorial Sloan–Kettering Cancer Center study, all hepatic metastases were completely resected; however, all hepatic metastases were unresectable in our study. In addition, metastases outside the liver were similar between groups in our study which maybe the reason for no difference in the overall progression-free survival.

The extrahepatic metastases were similar between the two groups and the commonest site was lung, 33.3% in the RRHS group and 27.9% in the RRS group. That is to say the relatively low systemic availability of oxaliplatin administered by the intra-arterial route did not increase the risk of extrahepatic metastases. However, the gap between two groups in hepatic progression-free survival reduced gradually in the first 3 years (78.6% versus 48.8%; 42.9%

Table 4 Chemotherapy toxicity: grades 3 to 4 toxicity

Toxicity	RRHS group		RRS (N=7+36) group	
	No. of patients	%	No. of patients	%
Nausea and vomiting	2	4.76	6	13.95
Diarrhea	3	7.14	7	16.28
Neurotoxicity	5	11.90	9	20.93
Neutropenia	17	40.48	20	46.51
Thrombopenia	4	9.52	4	9.30
Mucositis	1	2.38	1	2.33

versus 25.6%; 27.8% versus 12.2%). It suggested that most liver recurrences could not be avoided by RRHS, while were just postponed.

Hepatic or biliary toxicity has been reported with high occurrence rate, ranging from 9.3% to ~65% when HAI with floxuridine was employed.[9,17,18] Nancy Kemeny et al. reported only 26% patients received more than 50% of the planned HAI dose of floxuridine because of elevations in serum hepatic-enzyme levels.[9] However, the toxic effects of chemotherapy were similar in both groups and no hepatic or biliary toxicity was observed in our study and 81% patients received more than 50% of the planned dose. The reasons for it maybe that oxaliplatin has no inherent hepatic toxicity and was administered in the form of a short infusion (2 h). The occurrence of abdominal pain during or immediately after HAI seems characteristic of the intra-arterial administration of oxaliplatin and the frequency was 66.7% in our study. The same pains were also observed in the phase I study by Kern et al. (23%)[11] and Michel Ducreux et al. (70%).[14] The differences of abdominal pain frequency between studies maybe attributed to the different doses of oxaliplatin administered and race of people, but the pathophysiology has not been clear.

Dose reduction was similar in the two groups; however, definitive obstruction of the catheter occurred in 26.2% of patients in the RRHS group which leaded to treatment discontinued. If this weakness could be overcome, the dose reduction maybe less and the outcome maybe better.

In our hospital, HAI with oxaliplatin after resection+RFA for unresectable synchronous liver-only metastases from colorectal cancer was only launched in 2005. Since then, all such patients were treated with RRHS except those who refused this treatment just like the RRS (N=7) group. And RRS was the only treatment choice for these patients prior to 2005. We must emphasize that all the resections, RFA and HAI were done by the surgeons of the same group, who were skillfully experienced in hepatic resection and RFA. In addition, the techniques and regimens of resection, RFA and systemic chemotherapy were not changed before and after 2005. Therefore, we believe that the better prognosis in RRHS group is only attributable to HAI rather than other improved treatment modalities. Furthermore, the trends of the outcomes of the RRS (N=7) group were similar to those of the RRS (N=36) group rather than those of the RRHS group, which also confirmed the conclusion we drew above.

Conclusion

Our findings confirm that the use of RRHS improves the outcomes of patients with unresectable synchronous liver-only metastases from colorectal cancer. The use of HAI of oxaliplatin combined with systemic chemotherapy not only decreased but also postponed hepatic recurrence and therefore improved overall survival, as compared with the use of systemic therapy alone.

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ORIGINAL ARTICLE

Predictive Value of POSSUM and ACPGBI Scoring in Mortality and Morbidity of Colorectal Resection: A Case–Control Study

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Abstract
Background Preoperative risk prediction to assess mortality and morbidity may be helpful to surgical decision making. The aim of this study was to compare mortality and morbidity of colorectal resections performed in a tertiary referral center with mortality and morbidity as predicted with physiological and operative score for enumeration of mortality and morbidity (POSSUM), Portsmouth POSSUM (P-POSSUM), and colorectal POSSUM (CR-POSSUM). The second aim of this study was to analyze the accuracy of different POSSUM scores in surgery performed for malignancy, inflammatory bowel diseases, and diverticulitis. POSSUM scoring was also evaluated in colorectal resection in acute vs. elective setting. In procedures performed for malignancy, the Association of Coloproctology of Great Britain and Ireland (ACPGBI) score was assessed in the same way for comparison.
Methods POSSUM, P-POSSUM, and CR-POSSUM predictor equations for mortality were applied in a retrospective case–control study to 734 patients who had undergone colorectal resection. The total group was assessed first. Second, the predictive value of outcome after surgery was assessed for malignancy (n=386), inflammatory bowel diseases (n=113), diverticulitis (n=91), and other indications, e.g., trauma, endometriosis, volvulus, or ischemia (n=144). Third, all subgroups were assessed in relation to the setting in which surgery was performed: acute or elective. In patients with malignancy, the ACPGBI score was calculated as well. In all groups, receiver operating characteristic (ROC) curves were constructed.
Results POSSUM, P-POSSUM, and CR-POSSUM have a significant predictive value for outcome after colorectal surgery. Within the total population as well as in all four subgroups, there is no difference in the area under the curve between the

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POSSUM, P-POSSUM, and CR-POSSUM scores. In the subgroup analysis, smallest areas under the ROC curve are seen in operations performed for malignancy, which is significantly worse than for diverticulitis and in operations performed for other indications. For elective procedures, P-POSSUM and CR-POSSUM predict outcome significantly worse in patients operated for carcinoma than in patients with diverticulitis. In acute surgical interventions, CR-POSSUM predicts mortality better in diverticulitis than in patients operated for other indications. The ACPGBI score has a larger area under the curve than any of the POSSUM scores. Morbidity as predicted by POSSUM is most accurate in procedures for diverticulitis and worst when the indication is malignancy.

Conclusion The POSSUM scores predict outcome significantly better than can be expected by chance alone. Regarding the indication for surgery, each POSSUM score predicts outcome in patients operated for diverticulitis or other indications more accurately than for malignancy. The ACPGBI score is found to be superior to the various POSSUM scores in patients who have (elective) resection of colorectal malignancy.

Keywords Colorectal surgery · Abdominal surgery · Risk prediction · Surgical audit

Introduction

A large number of scoring systems to assess patient's risks of complications or death have been developed. The physiological and operative score for enumeration of mortality and morbidity (POSSUM) was reported to be the most appropriate of the scores currently available for general surgical practice.[1] It uses 12 physiological and 6 operative variables to give a calculated risk of morbidity and death. POSSUM was intended to be used in a comparative surgical audit. It was applied to a number of surgical procedures, including vascular (V-POSSUM),[2] oesophagogastric (O-POSSUM)[3] or colorectal (CR-POSSUM)[4] surgery. Since the introduction of POSSUM in 1991 by Copeland et al.,[5] several studies have shown the POSSUM score to overestimate the mortality risk.[6–8] The Portsmouth POSSUM was proposed to improve the predictive value of the initial model and has been primarily validated on patients undergoing vascular surgery.[8–10]

In 2003, the Association of Coloproctology of Great Britain and Ireland (ACPGBI) developed its own scoring system for surgical patients with colorectal cancer. The ACPGBI score is supposed to be easier to use than the three POSSUM models.[11,12]

The first aim of this study was to assess the role of POSSUM in surgical audit.

For this purpose, observed mortality and morbidity of colorectal resections performed in a tertiary referral centre were compared with mortality and morbidity as predicted with POSSUM, P-POSSUM, and CR-POSSUM scores and the ACPGBI score for patients operated on colorectal cancer.

The second aim of this study was to examine the accuracy of the various POSSUM scores for individual risk prediction in surgery performed for malignancy, inflammatory bowel diseases, and diverticulitis.

Methods

Inclusion

A retrospective case–control study was performed of all patients older than 15 years undergoing colorectal resection between January 2003 and January 2008 in the Radboud University Nijmegen Medical Centre. Surgical interventions were performed in an elective or acute setting. Acute operation was defined as surgical interventions after emergency admission. All other operations were classified as elective.

Data Extraction

The following data were extracted from the medical records: demographics, body mass index, coexistent morbidity, use of immunosuppressive medication, American Society of Anesthesiology (ASA) grade, indication and type of surgery, type of anastomosis, surgical re-intervention (laparotomy, not radiological drainage), hospital stay, POSSUM, Portsmouth POSSUM (P-POSSUM), colorectal POSSUM (CR-POSSUM), morbidity predicted by POSSUM, postoperative mortality, and morbidity. Morbidity was defined as an unexpected event within 30 days after surgery, which was harmful for the patient's health and required a change of therapeutic strategy. Complications were classified as defined by POSSUM (http://www.sfar.org/scores2/possum2.html). Mortality was defined as any death within 30 days after surgical intervention. ACPGBI scores were calculated in patients who had colorectal resection for histological proven cancer.

POSSUM and ACPGBI

The POSSUM score comprises a physiological and an operative component. The physiological score is based on 12 variables to be assessed in different grades. The operative severity score uses six variables. The definitive POSSUM score is calculated with the physiological as well as the operative severity score. (http://www.sfar.org/scores2/possum2.html, http://www.riskprediction.org.uk/)

According to the literature on POSSUM, a normal grade was used if a variable was not available. The ACPGBI score, developed for oncologic resections, uses multifactorial logistic regression analysis to adjust for multiple risk factors, their interactions, and the clustering of adverse outcome. It is the result of a nationwide attempt in the UK to provide accurate risk adjusted outcomes involving over 8.000 patients from 77 centers. The ACPGBI score assesses five operative variables: age, cancer resection, ASA grade, Dukes' stage, and operative urgency (http://www.riskprediction.org.uk/).

Outcome

The (P-, CR-) POSSUM-predicted mortality and morbidity was compared with the observed mortality and morbidity. Subgroup analysis was made for operations performed for carcinoma, inflammatory bowel disease, diverticulitis, and other indications, e.g., trauma, endometriosis, volvulus, or ischemia. Primary outcome was mortality. Secondary outcome measures were morbidity, (POSSUM-) complications, and hospital stay.

Statistical Analysis

Receiver operating characteristic (ROC) curves were constructed of each group analyzed in order to examine sensitivity and specificity of each POSSUM score. Areas under the curves were compared within and between subgroups. Analysis of ROC curves is a widely accepted method to investigate the properties of a diagnostic test. The area under the curve (AUC) measures the ability of the test to correctly classify those with and without a disease. Comparing the AUC in several subgroups and for different POSSUM scores therefore is the most appropriate manner to distinguish the diagnostic abilities between certain POSSUM scores in a specific subgroup or between subgroups for a specific POSSUM score.

Results

From January 2003 to January 2008, colorectal resection was performed in 734 patients: 385 women (52.5%) and 349 men (47.5%). The mean age was 58.4 years (±16.8; range, 16–96 years). In 386 (52.5%) patients, the indication for surgery was malignancy, in 113 (15.4%) inflammatory disease, and 91 (12.4%) diverticulitis. One hundred forty-four (19.6%) patients underwent colorectal surgery for other reasons: intestinal ischemia, volvulus, trauma, endometriosis, or carcinoma of urogenital or gynecologic origin. The most frequent surgical procedures were resection of the sigmoid (23.2%) and right hemicolectomy (19.8%; Table 1). Elective operations were performed in 555 patients (74.9%), and 179

Table 1 Demographics and performed procedures in the different subgroups

Type of surgery	Malignancy		Inflammatory bowel disease		Diverticulitis		Other		Total
	Elective	Acute	Elective	Acute	Elective	Acute	Elective	Acute	
n	335	51	93	20	50	41	77	67	734
Male	177	25	40	5	21	21	24	34	349
Female	158	26	53	15	29	20	53	33	385
Age (years)	65.4 (12.8)[a]	64.7 (15.6)	40.3 (14.3)	42.3 (16.0)	58.2 (12.0)	58.7 (15.9)	49.4 (15.1)	58.5 (17.9)	58.4 (16.8)
Body mass index (kg/m^2)	25.2 (4.3)	24.7 (3.7)	23.5 (4.3)	21.7 (3.5)	26.3 (4.4)	25.3 (4.0)	25.9 (4.9)	23.7 (2.8)	24.8 (4.2)
ASA	2.1 (0.7)	2.2 (0.7)	1.9 (0.5)	2.2 (0.8)	2.0 (0.8)	1.9 (0.8)	2.1 (0.8)	2.7 (1.0)	2.1 (0.7)
Right hemicolectomy	99	16	5	0	0	5	7	13	145
Left hemicolectomy	25	6	3	1	4	0	21	5	65
Transversum resection	11	3	2	1	2	0	5	9	33
Ileocoecal resection	19	5	55	15	4	5	7	11	121
Sigmoid resection	52	12	4	2	35	30	15	21	171
(Sub-)total colectomy	35	4	17	1	1	0	6	5	69
Rectosigmoid resection	94	5	7	0	4	1	16	3	130

[a] Numbers in parentheses are the standard deviations

Table 2 POSSUM scores, observed mortality and morbidity, re-intervention rate, and hospital stay in the different subgroups

Type of surgery	Malignancy		Inflammatory bowel diseases		Diverticulitis		Other		Total		
	Elective	Acute	Elective	Acute	Elective	Acute	Elective	Acute	Elective	Acute	Total
n	335	51	93	20	50	41	77	67	555	179	734
Predicted mortality (%)											
POSSUM	14.5	24.6	6.7	17.3	8.8	22.0	9.3	25.5	10.7	24.4	17.0
P-POSSUM	5.4	12.2	2.3	5.7	2.8	10.8	2.9	12.4	3.7	11.2	5.9
CR-POSSUM	3.9	8.7	1.3	3.0	2.1	8.4	1.6	7.9	2.5	7.7	4.0
Observed mortality (%)	27 (8.1)	7 (13.5)	1 (1.1)	1 (5.0)	3 (6.0)	6 (14.6)	4 (5.2)	16 (23.9)	35 (6.3)	30 (16.7)	65 (8.9)
Predicted morbidity (%)	50.7	64.1	29.6	45.2	35.9	58.8	35.7	64.7	40.1	61.0	46.0
Observed morbidity (%)	130 (38.8)	18 (35.3)	32 (34.4)	10 (50.0)	18 (36.0)	16 (39.0)	32 (41.6)	33 (49.3)	212 (38.2)	77 (43.0)	289 (39.4)
Wound hemorrhage	2								2		2
Deep hemorrhage	6	3	1		1		1	1	9	4	13
Chest infection	14	6	5	2	2	1	5	3	26	12	38
Wound infection	19	7	8	1	7	4	4	7	38	19	57
Urinary infection	17	6	3		1	1	3	3	24	10	34
Deep infection	15	2	6		4	4	8	8	33	14	47
Septicaemia	9	8	1	2	1	3	1	4	12	17	29
Pyrexia of unknown origin			1						1		1
Wound dehiscence	9	1	2	2		1		4	11	8	19
Deep venous thrombosis and pulmonary embolus	6		1				1		8		8
Cardiac failure	8	2		4	1	2		2	9	10	19
Impaired renal function	3	1		1		1		1	3	4	7
Hypotension	2			1		1			2	2	4
Respiratory failure	2	3	1	1	1	2	2	4	6	10	16
Anastomotic leakage	29	5	8	1	4	2	4	9	45	17	62
Total complications	141	44	37	15	22	22	29	46	229	127	356
Re-intervention	56	11	16	5	9	10	20	25	101	51	152
Hospital stay (median days) (range)	10 (2–127)	11 (2–150)	8 (1–55)	7 (1–64)	9 (3–57)	8 (3–61)	12 (1–59)	15 (5–132)	10 (1–127)	12 (1–150)	10 (1–150)

(25.1%) were operated in an acute setting. The number of patients who had one or more surgical re-interventions was 152 (20.7%; Table 2).

Morbidity was 289 in 734 (39.4%). The total number of complications amounted 356, so the mean number of complications per patient is 1.7. Among electively operated patients, 212 (38.2%) had one or more complications. Seventy-seven (43.0%) patients, operated on in an acute setting, had an unfavorable postoperative course. The most common complications were anastomotic leakage, surgical site infection, pulmonary, and urinary infections. Mean morbidity as predicted by POSSUM was 46.0% (Table 2).

Sixty-five patients (8.9%) died within 30 days after surgery (Tables 2 and 3). The predicted mortality by POSSUM was 17.0%, Portsmouth POSSUM 5.9%, and colorectal-POSSUM 4.0%. In the total population as well as the subgroups (except the group with patients operated for inflammatory bowel diseases), POSSUM, P-POSSUM, and CR-POSSUM had a significantly larger predictive value for outcome after (elective and acute) colorectal surgery than can be expected by chance alone ($P<0.001$). Within the total population (Fig. 1), as well as in all four subgroups (Fig. 2), there is no difference in the area under the curve between the POSSUM, P-POSSUM, and CR-

Table 3 Causes of mortality

Type of surgery	Malignancy		Inflammatory bowel diseases		Diverticulitis		Other		Total		
	Elective	Acute	Elective	Acute	Elective	Acute	Elective	Acute	Elective	Acute	Total
Observed mortality	27	7	1	1	3	6	4	16	35	30	65
Respiratory insufficiency	2	2				2	1	5	3	9	12
Cardiac failure	3		1						4		4
Abdominal sepsis											
Leakage	5	2		1	1			3	6	6	12
Disease		1			1	2	1	2	2	5	7
Ischemia	2					1		2	2	3	5
Change of treatment strategy[a]	7	2				1	1	3	8	6	14
Unknown	5						1		6		6
Cerebrovascular accident	1							1	1	1	2
Bleeding	1				1				2		2
Transfusion reaction	1								1		1

[a] Due to metastasis, progressive hematological malignancy, loss of perspective

POSSUM scores. In the subgroup analysis, smallest areas under the ROC curve are seen in operations performed for malignancy (0.65; 0.65; 0.65). This is significantly worse than in the diverticulitis group (0.86, P=0.01; 0.88, P< 0.001; and 0.89, P=0.02, respectively) and in operations performed for other indications (0.80, P=0.03; 0.80, P=0.03; and 0.79, P=0.03, respectively). For elective procedures, P-POSSUM and CR-POSSUM predictions are significantly worse in patients operated for carcinoma than in patients with diverticulitis (0.61 vs. 0.85, P=0.02, and 0.63 vs.0.89, P<0.001, respectively). For acute surgical interventions, CR-POSSUM predicts mortality better in diverticulitis than in patients operated for other indications (0.89 vs. 0.66, P= 0.02).

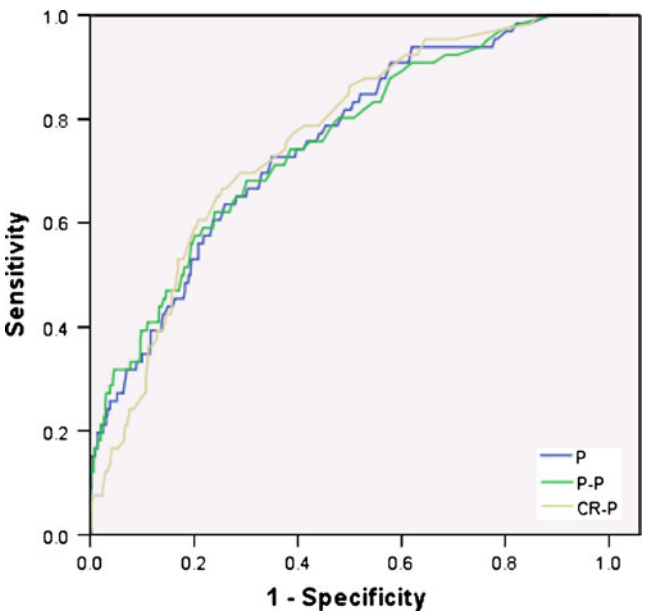

Fig. 1 ROC total group

Within the group operated on carcinoma, 190 patients had a known histology and the ACPGBI score was calculated (Table 4). The observed mortality in this group was 4.7% and morbidity 30.5%. The ACPGBI score predicted a mortality rate of 5.55% (±4.48). Twenty-seven of the 190 performed procedures were in an acute setting.

The ACPGBI score, designed for oncologic colorectal resections, has a larger area under the curve than any of the POSSUM scores (0.854, P<0.001; Fig. 3). The same applies to oncologic resections performed in the elective setting (P<0.001). ACPGBI was found not to be superior to POSSUM (P=0.83), P-POSSUM (P=0.56), and CR-POSSUM (P=0.84) in acute oncologic surgery. Fourteen out of 65 patients (21.5%) died after a change in treatment policy due to extensive oncological disease (n=11) or the lack of perspective on a acceptable outcome (n=3). Morbidity as predicted by POSSUM is most accurate in procedures for diverticulitis (0.757) and worst when the indication is malignancy (0.532).

Discussion

When POSSUM is applied for individual risk prediction in patients undergoing colorectal resections for malignancy, inflammatory bowel diseases, or diverticulitis, the most accurate mortality predictions with any of the POSSUM scores was in patients with diverticulitis. The ACPGBI score is found to be superior to POSSUM

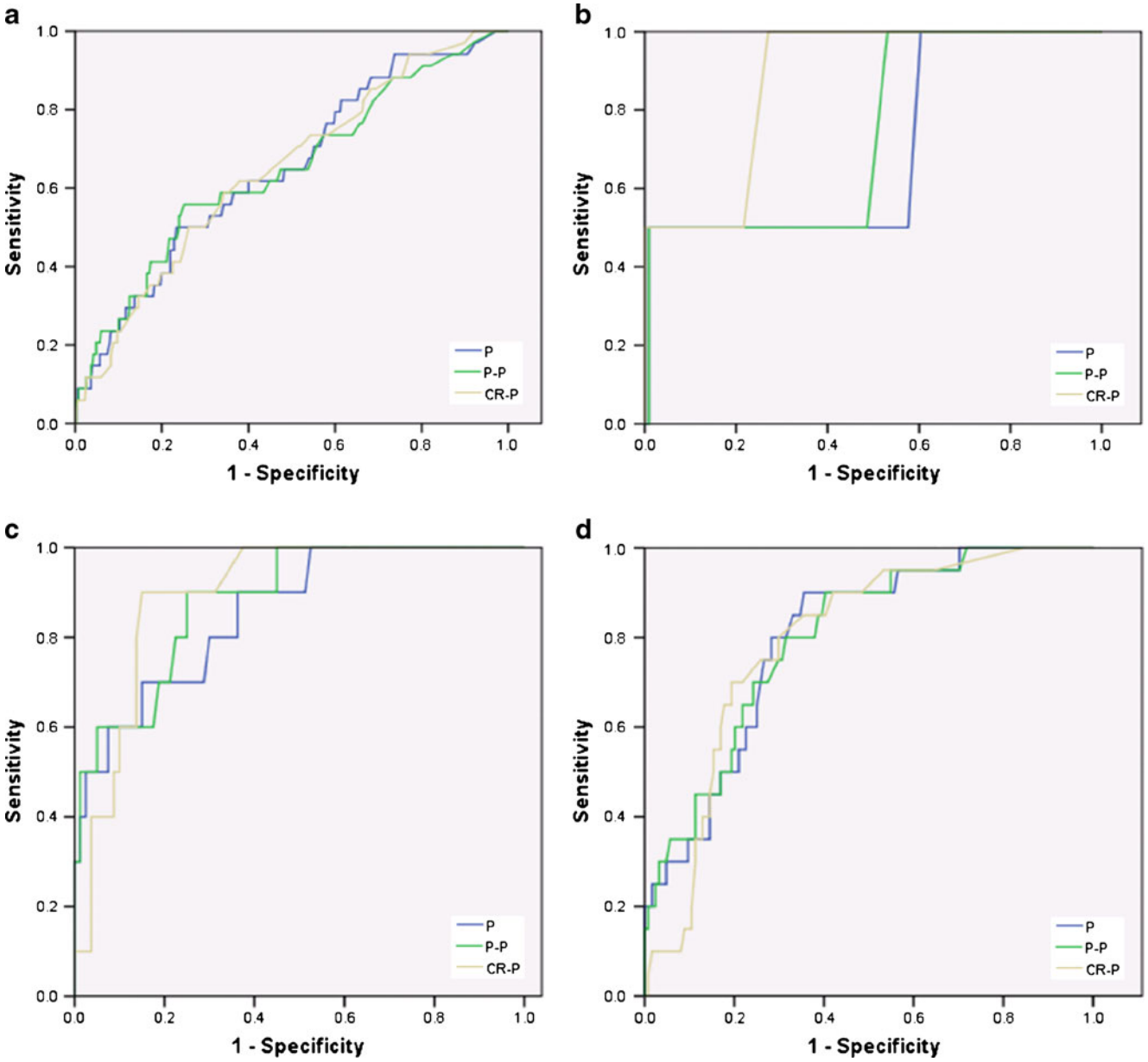

Fig. 2 Subgroup analysis: malignancy (**a**), inflammatory bowel disease (**b**), diverticulitis (**c**), and other (**d**)

Table 4 ACPGBI score in 190 patients with carcinoma

	Carcinoma
N	190
Male/female	108:82
Age (mean ± SD, range)	66±12.2 (33–89)
Elective/acute	163:27
ASA (mean ± SD)	2.11±0.73
Observed mortality (%)	9 (4.7)
Observed morbidity (%)	58 (30.5)
ACPGBI score (mean ± SD)	5.55±4.48

scoring in patients who had (elective) resections of colorectal cancers.

POSSUM and Surgical Audit

One of the main concerns in POSSUM scoring is its overestimation of mortality. The mortality rate predicted by POSSUM (17.0%) was double the observed mortality in our total study population (8.9%). The drawbacks of the original POSSUM score led to the development of Portsmouth POSSUM and colorectal POSSUM. In our study, both scores underestimated the mortality risk (5.9% and 4.0%, respectively). Several reasons can be pointed out.

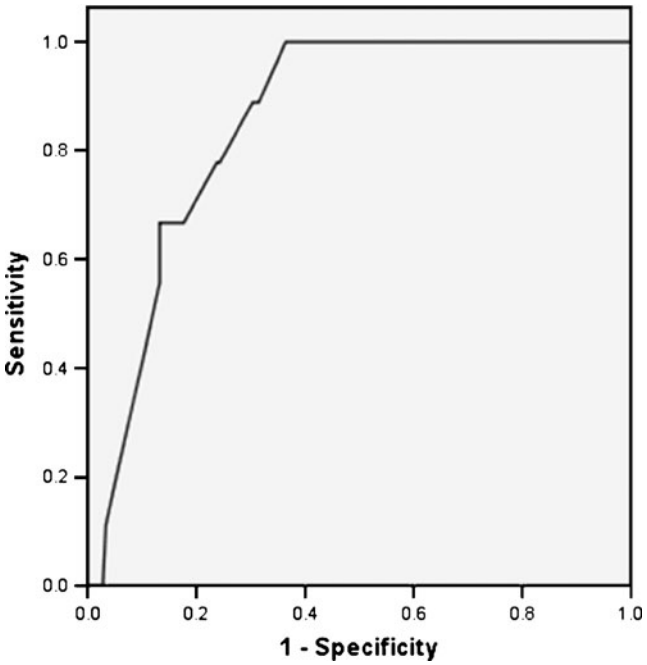

Fig. 3 Predictive value of ACPGBI score on outcome after colorectal resection for malignancy

First, the primary studies on POSSUM extend their analyses back to the early 1990s and are less likely to represent current practice.[13] Better understanding of diseases and improvements in diagnostic and therapeutic techniques have lowered mortality rates. Regarding surgical practice, developments such as laparoscopic intervention and enhanced recovery programs have caused a decrease in mortality.[14] Hence, mathematical prediction models may be outdated. Law et al.[15] reported overprediction of the POSSUM scores for laparoscopic colorectal resections. In converted controls, however, POSSUM scoring was reliable, which implies a discrepancy in predictive value due to operative technique. Second, POSSUM was originally developed with patients in the UK. However, outcomes may vary with other countries or high-volume specialized centers.[16,17] Third, surgery got more and more specialized over time. The original POSSUM score was designed for the general surgical patient. The accuracy of these models is under discussion due to the use of mixed patient populations. More recently, several studies specify risk prediction for different subgroups.[13]

In our opinion, the main argument against the use of POSSUM in surgical audit is found in the validation as a risk prediction model. Nearly all reports on POSSUM scoring validate the score on their own series, which leads to different conclusions of reports regarding over- or underpredicting of the scores. Patient selection, local facilities, and skills may be confounding factors. This is illustrated by a broad range of observed vs. expected

Table 5 Observed/expected ratios in the literature

Author	POSSUM		P-POSSUM		CR-POSSUM		ACPGBI	Mortality
	POSSUM	O/E	P-POSSUM	O/E	CR-POSSUM	O/E		
Malignancy								
Oomen[29]	10.6	0.16	3.8	0.45	3.8	0.45		1.7
Slim[7]	13.3	0.28	5.5	0.67				3.7
Ferjani[11]	12.7	0.80	4.4	2.32	9.6	1.06	8.1	10.2
Ren[38]	5.6	0.18	2.8	0.35	4.8	0.20		1.0
Horzic[39]			6.7	1.24	7.5	1.11		8.3
Ugolini[40]			7.9	0.79	9.14	0.68	19.4	6.3
Menon[9]			15.6	0.56				8.7
Tez[27]			9.0	0.77	7.8	0.88		6.9
Bromage[26]	1.9	3.37		1.59		1.25		6.5
Ibister[41]	6.7	0.21	3.5	0.40				1.4
Poon[42]			15.0	0.75				11.3
Tan[43]					11.2	0.14	5.4	1.6
Ugolini[44]			11.2	0.92	13.1	0.79		10.3
Can[45]	13.4	0.27	5.2	0.69				3.6
Diverticulitis								
Oomen[29]	6.3	0.52	2.2	1.50	2.3	1.43		3.3
Slim[7]	6.9	0.38	2.8	0.93				2.6
Oomen[46]	7.7	0.74						5.7
Constatinides[28]	21.9	0.49	10.5	1.03	10.0	1.08		10.8

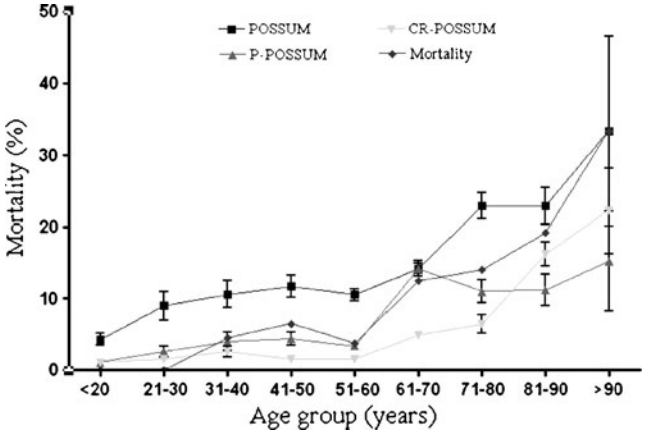

Fig. 4 Observed and predicted mortality related to age group

ratios in the literature (Table 5). In our opinion, risk prediction models need to be validated to a "gold standard" in order to allow comparative audit. Since reports on surgical outcome differ and definitions of adverse outcome may vary, this desired standard may be unrealistic. Russell[18] and Ferjani[11] have stated that a system with standard definitions is mandatory before clinical performance can be compared between health care systems and institutions. A proper and uniform definition of mortality is essential in risk prediction. Most studies on POSSUM describe mortality as primary outcome only. As Brooks et al.[6] pointed out, the majority of surgical procedures carry a low risk of death. However, along with decreasing mortality rates, the relevance of predicting morbidity is increasing. POSSUM also predicts the chance that a patient develops one or more complications with only moderate accuracy (area under the curve 0.53–0.76).

Cumulative sum techniques (CUSUM), described in 1954 by Page and its first introduction in surgical practice in 1994, might encounter the drawbacks mentioned above. This technique allows one to judge whether an observed variation in performance is acceptable (i.e., probably due to chance) or whether the variation is greater than what could be expected from random variation and thus may be a cause for concern. However, acceptable and unacceptable outcome rate as type I and II error rate has to be defined first. CUSUM is helpful in the evaluation of a clinical procedure before its implementation without the drawbacks of a randomized clinical trial. Plotting of the cumulative sum has been proven valuable for examining sequential measures, detecting changes over time, and is applied as a means of assessing surgical skills of trainees. Continued surveillance using the CUSUM allows the early detection of factors that lead to an increased failure rate. Quality control and objective and quantified recording of the findings meet the recommended criteria for medical audit.[19–23]

POSSUM and Individual Risk Prediction

By tailoring POSSUM to patient- and procedure-specific assessment, it becomes a tool that can help inform the individual patient on a certain procedure and the risk on adverse outcome. Several studies reported the value of POSSUM in surgery for colorectal cancer.[9,17,24–27] Tekkis et al.[4] developed the colorectal POSSUM and differentiated for elective or acute procedures and procedures performed for malignancy or no malignancy. Constantinides et al.[28] studied the value of POSSUM scoring in patients with complicated diverticulitis and concluded that CR-POSSUM was more accurate to predict outcome than (P-)POSSUM. Oomen et al.[29] retrospectively compared the different POSSUM scores in 241 patients undergoing elective resection of the sigmoid for carcinoma or diverticular disease. Although patients with diverticular disease had a higher score than patients with malignancy, mortality rate did not differ. It was concluded that none of the POSSUM scores was predictive of disease-specific mortality. However, we found significant differences in POSSUM scoring related to the indication of surgery. All POSSUM scores predicted outcome more accurately in patients with diverticular disease than in patients operated on colorectal cancer. Within the subgroup of patients with diverticular disease, we could not define a superior POSSUM score. POSSUM, P-POSSUM, and CR-POSSUM scores also predicted equally in patients with colorectal cancer. In our opinion, disease-specific patient and operative variables should be included to improve the scores. Furthermore, patients are getting older and preexistent morbidity is likely to increase. In our series, a larger variation of the various POSSUM scores is found in octogenarians (Fig. 4). This is in accordance with Slim et al.[6] who studied risk prediction by POSSUM and the AFC index (Association Française de Chirurgie). It is unclear whether the introduction of more extensive cardiac and pulmonary risk indexes might further improve the predictive accuracy of POSSUM scoring. It may further complicate POSSUM scoring. The AFC index is a simpler instrument without any mathematical formulas. It uses only four independent preoperative factors and is found to be as predictive as P-POSSUM.

Malignant Colorectal Disease

All mean POSSUM scores were higher in the carcinoma group than in diverticulitis, whilst observed mortality rates were comparable.

ACPGBI scoring was found to be superior in predicting mortality after resection of colorectal cancer both in elective

and acute interventions, which is consistent with the literature.[11,30] Thirty-seven out of 386 patients operated for colorectal malignancy (9.6%) had known metastasis. Mortality rate was 29.7% (11/37); all patients died as consequence of a change to tender loving care due to a lack of perspective on a reasonable outcome (Table 3). Mean POSSUM, P-POSSUM, and CR-POSSUM score in the deceased group were lower than in patients who survived (respectively 11.7 vs. 21.1, P=0.02; 3.9 vs. 7.8, P=0.05; and 2.5 vs. 3.6, P=0.07). Although based on a small population, these results demonstrate the insufficient predictive value of POSSUM scoring in patients with extensive oncological disease. Patients with colorectal cancer are likely to be immunosuppressed due to elderly age, nutritional status, and the colorectal cancer itself.[31,32] The Dukes' classification is too coarse to reflect today's pathologists' power to detect disease parameters in cancer.[29] Implementation of nutritional status in POSSUM might help improve the area under the curve in malignancy.[4,7,26] Both suggestions for improving POSSUM scoring need further research.

Question remains whether or not these patients have to be taken into account in validating risk prediction models. Well-informed patients with advanced cancers may trade off a short-term risk in exchange for cancer cure. In this population, the risks of resectional surgery may outweigh the benefits of a simpler and possibly safer palliative operation, but this requires reliable risk estimations.[12]

Inflammatory Bowel Diseases

No previous studies evaluated POSSUM scoring in patients with inflammatory bowel disease. Due to the view of the physiological variables included in POSSUM, the younger, relatively healthy patient with inflammatory bowel disease is likely to have a different score than the elderly with an extensive medical history operated for colorectal carcinoma. Patients with colitis often have an increased white blood cell count and low levels of hemoglobin or albumin, reflecting disease activity. Furthermore, these patients often use immunosuppressive medication and have a poor nutritional status, which is found to increase adverse outcome after surgery.[33] We found lowest POSSUM scores in this subgroup for mortality, which corresponded with the observed death rate. However, morbidity was underestimated by POSSUM. Younger age and the absence of cardiopulmonary comorbidity may explain the capability to overcome postoperative complications. POSSUM scoring for IBD may require a more prominent role of age, use of medication, nutritional status, level of hemoglobin, albumin, and white blood cell count.[26] Calibration of POSSUM for patients with inflammatory bowel disease may be hard since recent review showed improved outcome of surgery to be highly dependent on accurate timing of the surgery and better perioperative care.[34]

Diverticular Disease

The most reliable predictions as demonstrated by the highest areas under the curve were found for patients with diverticulitis. The observed mortality was considerably higher than in patients operated for inflammatory bowel diseases and almost similar to patients with carcinomas. Patients with diverticulitis had the highest body mass indexes and were operated urgently more often, both associated with an increased complication rate.[35–37] Left-sided resections were more frequently performed in patients with diverticular disease (81.3%) than in malignancy (50.3%) and inflammatory bowel diseases (15%). Left-sided resections are known to cause more complications.[33] Another explanation may be patient selection. High-risk patients with diverticular disease may be withheld from surgery, whereas a malignant indication for surgery will not allow a conservative treatment strategy. Accurate definition of high-risk patients is essential. Body mass index, operative urgency, and degree of peritoneal contamination may be important variables in order to calibrate POSSUM scoring for diverticulitis.

This study questions the role of POSSUM for the comparison of clinical performance between health care institutes. Poor definitions of surgical outcome and problematic validation of this risk prediction model are the main objections to use POSSUM for surgical audit.

In its present form, POSSUM scoring should not be used for medical decision making in individual patients either.

Future investigation needs to point out whether further calibration of POSSUM is feasible, or that alternative risk prediction models need to be developed. One solution may be for models to be more disease-specific.

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ORIGINAL ARTICLE

The Use of a Compression Device as an Alternative to Hand-Sewn and Stapled Colorectal Anastomoses: Is Three a Crowd?

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Abstract
Background The NiTi CAR™ 27 is a newer device that uses compression to create an anastomosis. An analysis of this device in the creation of colorectal anastomoses in humans has yet to be reported in the USA.
Methods A non-randomized, prospective pilot study of the NiTi CAR™ 27 device in patients undergoing a left-sided colectomy between March 2008 and August 2009 was performed.
Results Twenty-three patients (9 men and 14 women) underwent a left-sided colectomy and compression anastomosis with the CAR™ 27 device. Minor morbidities, 3 of 23 (13%) patients, included one small postoperative abscess requiring antibiotics alone and two postoperative anastomotic strictures requiring balloon dilation. Major morbidities, 1 of 23 (4%) patients, included a partial anastomotic dehiscence/leak requiring surgical dismantling of the anastomosis and diversion.
Conclusion The CAR™ 27 device shows promise as a safe and effective alternative for the creation of colorectal anastomoses. However, studies in a larger patient population are warranted to demonstrate equivalence of this device.

Keywords Anastomosis · Anastomotic leak · Compression · Colorectal · Stricture · Nitinol

Introduction

Currently, the two available methods used for the creation of colorectal anastomoses include hand suturing and stapling devices. Although both are well established, they are not without their faults. Neither provides an immediately "sealed" anastomosis and both are prone to uncommon but serious complications such as anastomotic bleeding, strictures, or leaks. After colorectal resection, the incidence of anastomotic leak ranges from 2.9% to 15.3%,[1] while the incidence of subsequent stenosis or stricture ranges from 1.2% to 4.2%.[2] These complications may require further surgical intervention and can lead to significant morbidity and mortality.

As a result, the concept of tissue compression during colorectal anastomoses has been revisited. This idea is not new and previous attempts have included the Murphy button, the biofragmentable anastomotic ring, and AKA-2 devices.[3–11] Drawbacks of these devices included retained foreign material within the tissue, narrowing of the lumen, necrosis at the anastomotic site, and problems with passage of the deployment device.[3] As a result, the use of these devices became extremely limited and was eventually replaced with the more reliable stapling devices.

Recently, the FDA-approved NiTi CAR™ 27 (endoluminal compression anastomosis ring) device has been introduced and may overcome many limitations of the previous compression devices. The device is intended for use in the colon and rectum for the creation of end-to-end, end-to-side, and side-to-side anastomoses in both open and laparoscopic surgeries. This novel device consists of two disposable rings that trap the ends of transected bowel,

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bringing them into opposition and is intended for the creation of intestinal compression anastomoses in colorectal surgery in both open and laparoscopic surgeries. These compression anastomosis rings, composed of a nitinol alloy, exhibit super elasticity and shape memory to provide uniform compression to the tissue resulting in a secured, immediately sealed anastomosis. This translates, in animal models, to anastomoses with higher bursting strength and less stricture formation.[12] Early research with the device in vitro, ex vivo, and in animal experiments suggests a safe and effective anastomosis when compared to that produced by staplers and sutures. Available clinical data suggest that the NiTi CAR™ 27 device may address some of the limitations of the current methods for creating colorectal anastomosis.[13] Our plan was to evaluate the safety, technical feasibility, and effectiveness of the NiTi CAR™ 27 device in the creation of left-sided colorectal or colo-colonic end-to-end compression anastomoses.

Methods

Design and Study Population

A non-randomized, prospective pilot study sponsored by NiTi™ Surgical Solutions, Ltd. (Netanya, Israel) was undertaken to evaluate the outcomes of the NiTi CAR™ 27 compression anastomosis device in patients undergoing a left-sided colectomy between March 2008 and August 2009. Patients with either benign or malignant disease requiring a non-emergent open or laparoscopic colorectal resection with a high colorectal anastomosis (≥10 cm from the anal verge) were eligible for trial inclusion. Patients with a known allergy to nickel were excluded from the study. Informed consent was obtained from all patients involved in the trial and approval for this trial was obtained from the Institutional Review Board at University of California-Irvine Medical Center.

Clinical Parameters and Study Outcomes

Clinical endpoints to be evaluated included intra- and postoperative complication rates, patient recovery, and anastomotic integrity. More specifically, the primary study outcome was the anastomotic leak rate. Anastomotic leakage was defined as clinical symptoms such as fever or sepsis in combination with abdominal/pelvic abscess, rectovaginal or colocutaneous fistula, or peritonitis within 30 days postoperatively, leading to a clinical and ⁄or radiological interventional procedure of the subject or operation that confirms the leakage.[14] Secondary study outcomes included time to return of bowel function as indicated by first postoperative passage of flatus or bowel movement, first postoperative toleration of liquids and solids, intraoperative device failure (i.e., cases of conversion to stapled or sutured anastomosis that are device related), presence of bleeding or stricture (either clinical evidence of a stricture or the inability to pass a sigmoidoscope through the anastomosis on postoperative follow-up), septic complications (i.e., wound infection, abscess formation, or peritonitis), and readmission, reoperation, or death within 30 days of the procedure. Length of time of the surgical procedure as well as ring expulsion time and awareness were also recorded for each patient.

Device Description and Function

The CAR-27™ device is similar to a regular circular stapler. It comprised two main parts, an applier and an implanted compression element. The compression element is composed of a plastic anvil ring and a metal ring, including shape memory nickel–titanium alloy (nitinol) leaf springs. When "fired," the device holds the two ends of tissue together with circumferentially placed barbed points, which penetrate through the tissue, holding it to the plastic ring. The nickel–titanium ring is released, creating equal compression both radially and longitudinally around the ring. The device has a circular blade which cuts the tissue within the ring, creating a patent anastomosis. The tissue heals around the circular edges that are held within the ring and the device along with the compressed tissue slough off over the following 8–10 days, at which point the ring is expelled from the body with a later bowel movement (Figs. 1 and 2). The result is a full circumferential, hemostatic sealed anastomosis without any retained foreign material (Fig. 3).

Fig. 1 NiTi CAR™ 27 compression anastomosis device. Components include the firing instrument, ring loader, anvil, nitinol metal compression ring

Fig. 2 Compression anastomosis ring (*CAR*) containing shape memory nickel–titanium alloy springs inside a ring with barbs allowing for equal compression around the ring. The device, along with the compressed tissue, sloughs off over the following 8–10 days, at which point the ring is expelled from the body with a later bowel movement

Study Procedures

Pre-surgery

Procedures performed such as routine hospital examinations, mechanical bowel preparation, and antibiotic prophylactic treatment were completed according to our standard management protocol. During preoperative surgical evaluation for each patient, the following information was recorded: demographic data, ASA status, diagnosis leading to surgery, relevant surgical and medical comorbidities, and current treatments and medications received in the last 6 months. Preoperative protocol for all enrolled patients included completion of a routine bowel preparation the day prior to surgery in combination with a clear liquid diet. Stool softeners were provided for all patients before and after the surgical procedure to avoid hard stools, which may exert an undesirable mechanical force on the anastomotic area while the ring is still in place. Additionally, a single dose of prophylactic, broad-spectrum intravenous antibiotics was administered <60 min prior to incision.

Intraoperative

Surgeon Use of Device

All procedures were performed by one of two board-certified colorectal surgeons at our institution. To ensure that the surgeons were competent with using the device prior to participation in the study, each was trained in the use of the device on a porcine model. The device functions almost identically to the current circular staplers in widespread use, facilitating the minimal "learning curve." All surgeons went through a review of the procedure using the CAR™ 27 prior to the study. The device was used according to the manufacturer's guidelines. Initially, the surgeon divided the colon proximal to the diseased colon to place a purse string and also divided the colon or rectum distal to the diseased intestine using a linear stapler (from within the abdomen). To create the anastomosis, several steps were performed:

Prior to loading the CAR, the alloy ring was cooled by immersing in a bowl of sterile, cold water for at least 5 min. The detached anvil head of the device was inserted into the proximal colon and secured with a purse-string suture. One of the surgeons then inserted the device body carefully through the anal canal. The compression ring housing (with sharp point) was advanced (preferably near the center of the staple line) and the trocar (spike) was exposed via a counter clockwise rotation of the device (almost identical to a standard circular stapling device). The two parts of the device and bowel were then attached—the detachable anvil head secured with purse string and the trocar side. After a

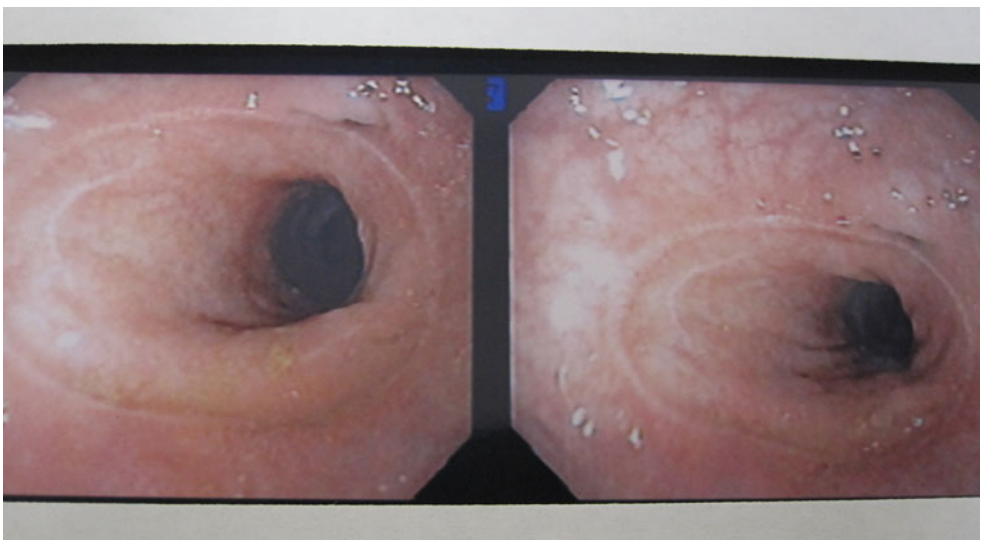

Fig. 3 Fully circumferential, hemostatic sealed anastomosis without any retained foreign material seen on flexible sigmoidoscopy at 3-month follow-up

clockwise closure of the two device parts, the firing mechanism was triggered, creating the anastomosis. The anastomosis height was measured and recorded in the patient's case report form (CRF). The device rings created the anastomosis, and a circular rim or donut of tissue from the proximal and distal margins was removed with the device. Approximating body temperature, the ring recovers its programmed shape, applying pressure on the tissue. After removal of the device, the integrity of the anastomosis was checked by direct palpation from the abdominal side. Insufflation of air via proctoscope was performed with the pelvis filled with saline to verify the absence of leak. The anastomotic donuts were also checked for integrity.

Intraoperative variables recorded included: date and duration of surgery, ASA status, estimated blood loss, and CAR lot number; type of operation (open, laparoscopic), laparoscopic conversion, and if drains were used (number and type); and ease of CAR deployment (1=very difficult to 5=very easy) and technical complications. Additional recorded information included the presence or absence of leak detected with air testing, concomitant procedures performed during surgery, use of a diverting ileostomy, and other procedural complications.

Postoperative Follow-Up

Follow-up evaluations were performed every day while patients were hospitalized. The following information was recorded for all patients while they were hospitalized (until discharge or postoperative day 20): passing flatus and bowel movements, tolerating liquids and solids, and temperature (max. for 24-h period), ring expulsion if it occurred during this time, and date of discharge.

There were two postoperative clinic visits: ≤1 month and a 3-month (±2 weeks) visit which included a proctoscopic exam of the anastomotic site during one of the visits (performed at the first visit per standard of care if symptoms suggested stricture and at the second visit for the same reasons or as routine protocol even in the absence of symptoms). Information concerning bowel movements, liquid and solid tolerability, temperature, and when ring passage occurred was collected.

Results

A total of 23 patients (9 men and 14 women) underwent a left-sided colectomy and subsequent compression anastomosis (12 laparoscopic and 11 open) with the CAR™ 27 device. Age at operation ranged from 34 to 78 (mean age, 60.0 years) and BMI ranged from 20.0 to 36.5 (mean BMI, 26.0). A majority of the patients were Caucasian (78%). The ASA classification for the population was: ASA II, 65% and ASA III, 35%. The most common patient comorbidities included hypertension (57% of patients), malignancy (26%), obesity (22%), diabetes mellitus (17%), and coronary artery disease (13%). Diagnoses leading to surgery included rectal prolapse (eight patients), chronic diverticulitis (sux patients), diverticular colonic fistula (five patients), and malignancy (four patients; Table 1). Of note is that one patient had a sigmoid colectomy for diverticulitis with a concomitant distal pancreatectomy performed by a pancreatic surgeon for a previously diagnosed neuroendocrine tumor.

The duration of surgery range for this patient population was 75–330 min (median, 149 min). Estimated blood loss ranged from 20 to 700 mL (median, 150 mL), and none of the 12 laparoscopic procedures required conversion to an open operation. For each of the 23 anastomoses, the average time for creation was 5.7 min (range, 3–17 min). The ease of CAR deployment, assessed by the operating surgeon, was also recorded (1 = very difficult to 5 = very easy). Overall, the operating surgeons thought that the CAR™ 27 device was easy to use (mean score, 4.5). The score was 1 (very difficult) in 4.3% of patients, 3 (difficult) in 4.3%, 4 (easy) in 26.1%, and 5 (very easy) in 65.2% of patients. The reason for a lower score (3 or less) in two patients was failure of the device to fire appropriately on first attempt. No case had to be converted to a stapled or hand-sutured anastomosis. The distance from the anal verge to the anastomosis ranged from 9 to 20 cm (mean distance, 14 cm).

The median time to return of bowel function as indicated by the passage of flatus was 4 (range, 2–31)days. The median length of hospital stay was 5 (range, 3–41)days, and the median postoperative follow-up was 91 (range, 14–214)days. Of note is that one patient failed to return for 1- and 3-month follow-up visits. Time to ring expulsion was difficult to measure since most patients were surprisingly unaware of this event. However, one patient stated that the ring passed without complication on the tenth postoperative day.

Overall, surgical complications were grouped into two categories: (1) minor morbidities, 3 of 23 (13%) patients, which included one small postoperative abscess requiring antibiotics alone and two postoperative anastomotic strictures (diagnosed by flexible sigmoidoscopy at 3-month visit) receiving balloon dilation and (2) major morbidities, 1 of 23 (4%) patients, which included a partial anastomotic dehiscence/leak requiring a return to the operating room for dismantling of the anastomosis and diversion. The patient had a prolonged hospital course but slowly improved and was discharged home on postoperative day (POD)41 tolerating a regular diet. Of note is that air testing for anastomotic integrity just after completion of the anastomosis did not demonstrate a leak in any patient.

At 1-month follow-up, all patients were tolerating a regular diet and all except one patient reported having

Table 1 NiTi patient characteristics

Race	ASA score	BMI	Major comorbidities
Caucasian	3	26	COPD
Caucasian	2	24.8	Hypothyroidism
Caucasian	3	36.5	HTN, DM, obesity
Hispanic	2	24	HTN
Caucasian	3	23.9	CAD, HTN
Caucasian	2	23	HTN, testicular cancer
Caucasian	3	34.5	DM, CAD, obesity, breast cancer
Asian	2	23.1	HTN, gout
Caucasian	2	30.2	HTN, obesity
Caucasian	2	20.3	Tobacco use
Caucasian	2	26.6	HTN
Caucasian	3	22.8	HTN, DM, asthma
Caucasian	2	25.8	HTN
Caucasian	2	20.7	–
Caucasian	2	20.4	Tobacco use
Hispanic	2	34	Obesity
Asian	2	26.2	HTN, DM
Caucasian	3	22.8	HTN, CAD
African-American	2	26.7	HTN, asthma
Caucasian	3	33.2	Obesity
Caucasian	2	26.3	HTN, atrial fibrillation
Caucasian	2	20	Hypothyroidism
Caucasian	3	21	Carotid artery stenosis

COPD chronic obstructive pulmonary disease, *HTN* hypertension, *DM* diabetes mellitus, *CAD* coronary artery disease, *ASA* American Society of Anesthesiologists

normal bowel movements. This patient had intermittent episodes of loose bowel movements prior to operation, most likely as a result of rectal prolapse. Postoperatively, the patient continued to have intermittent episodes of loose bowel movements with improved frequency that finally resolved by the 3-month follow-up visit. At 3-month follow-up, all patients were tolerating a regular diet and all reported having normal bowel movements, except two patients who reported mild abdominal pain and bowel movements with a string-like consistency. Flexible sigmoidoscopy of the anastomotic sites of both patients performed at this time revealed tight strictures. Both patients subsequently underwent endoscopic balloon dilation to resolve their strictures and both have made full recoveries. Flexible sigmoidoscopy of all remaining patients was unremarkable (Table 2).

Discussion

Use of the newer CAR™ 27 compression anastomotic device has the advantage of overcoming several obstacles previously encountered with earlier compression devices. Older devices resulted in the creation of lumen too narrow for the passage of intestinal contents, retention of foreign material within the tissue, necrosis at the anastomotic site, and problems with passage of the device. The CAR™ 27 device has an anatomical design not unlike that of current stapling devices used to create end-to-end anastomoses and therefore eliminates the previous problems of passage and withdrawal of the device from the anus. Compression of the two ends of bowel to be connected creates a controlled region of necrosis isolated within the compression ring only, allowing a more rapid healing outside the ring. Because the ring is expelled early in the healing process, retention of foreign material ceases to be an issue. In addition, the CAR™ 27 device has potential advantages over current methods of large bowel anastomosis, most notably the lag phase of anastomotic healing.[13] The tissue compression exerted through the CAR™ 27 device provides a strong seal circumferentially immediately at the time of surgery secondary to the exhibition of super elasticity and shape memory, and the ability to eliminate the permanent implantation characteristics inherent in stapled anastomosis by the nitinol-based compression ring. In addition, the longitudinally orientated metal prongs further fixate both bowel ends and prevent tissue slippage from axial movements. The overall goal of such a design is the creation of a safe and effective anastomosis with mitigation of complications commonly seen with current methods of large bowel anastomosis, namely leaks, strictures, and bleeding.

Table 2 NiTi patient outcomes

Diagnosis	Lap/open	Return of bowel function (days)	Immediate postoperative complications	Length of stay (days)	Follow-up complications	Flexible sigmoidoscopy (3 months' visit)
Rectal prolapse	Open	3	None	5	None	Normal
Rectal prolapse	Open	7	None	8	None	Normal
Rectal prolapse	Open	4	UTI	11	None	Normal
Coloenteric fistula	Lap	4	Abscess	12	None	Normal
Diverticulitis	Lap	3	Improper firing on first attempt	4	None	Normal
Sigmoid cancer	Lap	2	None	4	None	Normal
Colovaginal fistula	Open	6	Wound infection	6	Wound infection improved	Normal
Sigmoid cancer	Lap	7	None	8	None	Normal
Diverticulitis	Open	5	Pancreatic leak[a]	9	None	No Follow up
Diverticulitis	Lap	2	None	7	None	Stricture (Balloon dilation
Colovaginal fistula	Open	5	None	6	None	Stricture (Balloon dilation)
Rectal cancer	Lap	4	None	7	None	Normal
Rectal prolapse	Open	2	None	4	Diarrhea	Normal
Rectal prolapse	Open	3	Improper firing on first attempt	3	None	Normal
Rectal prolapse	Open	4	None	4	None	Normal
Diverticulitis	Lap	3	None	6	None	Normal
Sigmoid cancer	Lap	3	None	4	Readmit–dehydration	Normal
Colovesicular fistula	Lap	2	None	4	Wound abscess	Normal
Colonic fistula	Lap	2	None	4	None	
Rectal prolapse	Open	4	None	6	Intermittent–incontinence	Normal
Diverticulitis	Lap	2	None	3	None	Normal
Rectal prolapse	Open	2	None	3		Normal
Diverticulitis	Lap	31	Anastomotic disruption	41	Hartmann's pouch and colostomy	N\A

Lap laparoscopic

[a] This patient had a distal pancreatectomy for a neuroendocrine tumor at the same time as colon resection

Improvements in these outcomes have been observed in earlier studies with the CAR™ 27 device on human subjects. D'Hoore et al.[13] demonstrated early promising findings with the CAR™ 27 device. In ten patients who underwent left-sided colectomy, no anastomotic leakage occurred, median hospital stay was 4 days, and only three patients noticed passage of the ring. Ring passage was verified with a plain abdominal X-ray 3 weeks after operation. Similar findings were reported in 12 patients after use of the compression device resulting in no complications related to the anastomosis, with only two patients noticing ring passage.[15]

In comparison, our study involving 23 patients resulted in an anastomotic leak in one patient (4.3%) and stricture formation in two patients (8.6%). The patient with the anastomotic leak required complete dismantling of the anastomosis and creation of an end colostomy. Investigation into possible reasons for anastomotic failure initiated by the operating surgeon and the device manufacturer failed to elucidate any definitive cause. The early presentation of the leak (POD 4) and the intraoperative findings suggested that premature necrosis of the tissue may be a contributor. This patient's preexisting comorbidities (i.e., diverticulitis and moderate malnutrition) may also have been a contributing factor. In the two patients who developed strictures, one possible explanation was a retained ring for a longer duration than is typically experienced, inciting an ongoing inflammatory response causing scarring. Although, since neither patient noticed ring passage, this is only conjecture. Fortunately, balloon dilation easily resolved their symptoms.

Overall the operating surgeons felt that the device was easy to use; however, in two different patients, device failures occurred. In both instances, the circular blade within the device that cuts the tissue within the ring malfunctioned, preventing removal of the anvil from the anastomotic site.

This required manual withdrawal of the anvil and device, resection of this anastomotic site, and creation of a new anastomosis. The second attempt was successful for each patient and neither experienced further sequelae. Time to creation of anastomosis was relatively short, as was time to return of bowel function and length of hospital stay, further enhancing the attractiveness of this device. Only one patient noticed passage of the ring, indicating no postoperative concern by both patient and surgeon for retained foreign objects. Furthermore, flexible sigmoidoscopy performed at 3 months postoperatively confirmed a well-healed anastomosis and verified ring passage.

The present study consists of a small number of patients using a new compression anastomotic device to create colorectal anastomoses. Although there was only one definitive anastomotic leak translating to a 4.3% leak rate for high rectal anastomoses, such a small sample size makes it impossible to draw firm conclusions regarding the efficacy and safety of the CAR™ 27 device. This leak rate is within the range expected for this level of anastomosis (3–5%).[16–18] Additionally, the two strictures encountered, although easy to manage, raise questions regarding the frequency of this complication relative to current stapled anastmoses. Finally, although the two "misfirings" of the device are troubling, they may be related to the learning curve and therefore can be avoided with further training. Larger, randomized trials with a head-to-head comparison to stapled and/or hand-sewn anastomoses will be necessary to accurately assess this new technique.

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ORIGINAL ARTICLE

Radiofrequency Ablation Versus Surgical Resection for Hepatocellular Carcinoma in Childs A Cirrhotics—a Retrospective Study of 1,061 Cases

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Abstract
Introduction The long-term outcomes of radiofrequency ablation (RFA) vs. surgical resection in cirrhotic patients with hepatocellular carcinoma (HCC) remain controversial. One thousand sixty-one cirrhotic HCC patients were included into a retrospective study. Four hundred thirteen received RFA and 648 received surgical resection.
Results Overall (OS), recurrence-free (RFS), and tumor-free survival (TFS) were compared between the two groups and in subgroup analyses. The 5-year OS and corresponding RFS as well as DFS were significantly higher in the surgical resection group compared with the RFA group ($p<0.001$, $p<0.001$, $p<0.001$). In subgroup analyses of solitary HCC ≤3 cm, there was no significant difference in RFS between the two groups ($p=0.719$). Nonetheless, surgical resection was superior to RFA for OS and TFS in this subgroup as well as for OS, RFS, and TFS in subgroup analyses for solitary lesions 3 cm<HCC<5 cm and multifocal HCC. Serum AFP was the only significant predicting factor for all survival analyses.
Conclusions When treating Childs A cirrhotic patients with solitary HCC larger than 3 cm but less than 5 cm, or with two or three lesions each less than 5 cm, surgical resection provides a better survival than RFA. When treating Childs A cirrhotics with solitary HCC≤3 cm, RFA has a comparable RFS to surgical resection, but RFA is less invasive.

Keywords Radiofrequency ablation · Hepatectomy · Hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) is one of the most common liver neoplasms in the world, with an estimated global incidence of over 500,000 new cases per annum.[1] It is prevalent in Asia and Africa, and its prevalence is increasing in the USA and Europe.[2,3] Clear guidelines for the treatment of HCC have yet to be established. Surgical resection is the most widely used treatment worldwide.[4] Surgical resection can only be used in around 5% of patients in the western world and around 40% of Asian patients due to poor liver functional reserve caused by liver cirrhosis and intrahepatic dissemination.[5,6] Radiofrequency ablation (RFA) has emerged as a new effective and reliable therapy modality for small HCC with encouraging outcomes.[7–13] This study was designed to compare long-term outcomes of surgical resection versus RFA for the treatment of HCC patients with Childs A cirrhosis.

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Material and Methods

Diagnostic and Selection Criteria

The study was performed according to the guidelines of the Helsinki Declaration. A written informed consent was

obtained from each every patient before intervention. A retrospective review was performed at our center on all patients who presented between July 2000 and October 2005 with liver cirrhosis and who were diagnosed as having HCC. The diagnosis of liver cirrhosis was made by either biopsy or by clear clinical signs of cirrhosis such as: ascites, coagulopathy, or radiological features. The diagnosis of HCC was made according to the diagnostic criteria used by the European Association for the Study of the Liver,[14] which based on histopathological confirmation by ultrasound-guided fine-needle aspiration biopsy or noninvasive methods: (1) the concordant classical dynamic radiological features of HCC were represented in two radiologic techniques; (2) one radiologic technique showed typical features of HCC together with an elevated alpha fetoprotein (AFP) level over 400 ng/ml; (3) when a tumor ≤2 cm was found in the cirrhotic liver, magnetic resonance imaging (MRI), and hepatic digital subtraction angiography (DSA) confirmation were both needed before making a diagnosis. Radiologic imaging techniques included ultrasonography, spiral computer tomography (CT), MRI, and hepatic DSA.

Inclusion criteria were as follows: up to three nodules, each ≤5 cm, no extrahepatic metastasis or obvious vascular invasion, well-compensated liver function of Pugh-Child Class A, a platelet count $>50\times10^9$/L and a prothrombin time prolongation ≤5 s, no previous or simultaneous malignancies, HBV-infected surgery-treated patient should have a HBV-DNA-PCR quantitation of less than 10^5 copies/ml. Patients were excluded if they had undergone other treatments prior to radical resection or RFA.

Follow-up

Patients were followed-up at 3-month intervals after treatment. Abdominal ultrasonography and helical CT, measurement of serum AFP and liver function tests were performed during each visit. When intrahepatic recurrence was suspected, spiral CT, MRI, or contrast-enhanced ultrasonography was performed. When extrahepatic metastases were suspected, thoracic CT, and bone scintigraphy were performed. Once the recurrence was confirmed, the second-time treatment was proposed by a multidisciplinary team of specialists including surgeons, pathologists, and radiologists; however, the patient's opinion was conclusive. The therapies included liver transplantation, RFA, percutaneous ethanol injection, surgical resection, transcatheter hepatic arterial chemoembolization (TACE), and systematic chemotherapy.

Statistical Analysis

Differences between the RFA and surgical resection groups were analyzed using the unpaired t test for continuous variables and by the χ^2 test or continuity correction method for categorical variables. Survival curves, recurrence-free survival curves, and tumor-free survival curves were generated using the Kaplan–Meier method and compared by the log-rank test. The relative prognostic significance of the variables in predicting overall survival and overall recurrence were assessed by univariate and multivariate Cox proportional hazards regression models. All variables with a p value <0.05 by univariate comparison were subjected to multivariate analysis. Results of multivariate analysis were presented as relative risk with corresponding 95% confidence intervals (CI). All statistical tests were two-sided, and differences were considered when $p<0.05$. The statistical analyses were performed using SPSS 13.0 statistical software (SPSS Company, Chicago, IL, USA).

Radiofrequency Ablation

Procedure The RFA procedures were performed with a commercially available system (Radionics, Cool-Tip System, Burlington, MA, USA), single/clustered needle electrode(s) with a 2-cm or 3-cm exposed tip and ultrasound guidance (Vivid4, GE, USA; iU22, Philips, USA). The clustered electrodes were systematically applied in lesions larger than 3 cm. The percutaneous RFA procedure was employed when appropriate (n=361). Open approach was selected when the tumors were located near the subhepatic inferior vena cava or gastrointestinal tract (n=52). The assessment of response was made according to the modified European Association for the Study of the Liver criteria.[14] A spiral triphasic enhanced CT or MRI was performed 1 month after treatment. A complete ablation response was indicated by the absence of enhancing tissue at lesion site. Residual viable tumor was diagnosed if an enhanced area was noted within the treatment zone (n=42). In order to achieve complete ablation, the treatment course could be repeated with another CT/MRI evaluation 1 month later. If residual viable tissue of the tumor still existed, RFA was considered a failure and the patient was treated with TACE (n=12).

Surgical Resection

The hepatectomy procedure was defined according to the Brisbane terminology proposed by Strasberg et al.[15] Anatomic resection was defined as resection of the lesion together with the portal vein related to the lesion and the corresponding hepatic territory. Nonanatomic resection was defined as resection of a lesion without regard to segmental, sectional, or lobar anatomy. We performed anatomic partial hepatectomy when appropriate (n=279). In other cases, we performed nonanatomic resection with a resection margin

of 1 cm over the tumor by visual estimation intraoperatively (n=369).

Results

From July 2000 to October 2005, 2,637 consecutive patients with liver cirrhosis who were diagnosed as having HCC were treated in our center. Of these, 1,576 patients did not meet the aforementioned inclusion criteria. The remaining 1,061 patients consisted of 413 patients treated by RFA and 648 patients received surgical resection, respectively. The diagnosis of HCC and liver cirrhosis of the 648 patients in the surgical resection group were all confirmed by the excised specimens histopathologically. Of the 413 patients treated by RFA, the diagnosis of HCC and liver cirrhosis established noninvasively in 256 patients and was proven by biopsy in 157 patients.

Demographic characteristics as well as the number of patients in each subgroup for both patients in the RFA group and in the surgical resection group can be seen in Table 1. *Significant* differences between the two groups were seen in three parameters: age, gender, and AFP. The surgical resection group had older, more-female population, and with higher AFP level. In subgroup of solitary HCC ≤3 cm, there were 311 patients in the surgical resection group and 212 patients in the RFA group. Demographic characteristics were comparable except for the surgical resection group had older population. The tumor locations by intervention group can be seen in Table 2. The mean follow-up time was 33.7±17.4 months for surgical resection group and 36.1±12.4 months for RFA group (p=0.178), respectively. The censored patients were more in the surgical resection group (87/648) than in the RFA group (33/413, p=0.006).

The RFA Group

Two hundred twelve of 413 RFA-treated patients had single lesion ≤3 cm; the mean treatment session was 1.68±0.81/lesion. One hundred and one of 413 patients had solitary HCC >3 cm, but <5 cm, the mean treatment session was 3.07±0.23/lesion. 93/413 patients had two lesions, the treatment session were 2.13±0.34/lesion. Seven patients had three lesions, and the mean treatment session was 1.94±0.57/lesion. The complete ablation response rate after first treatment was 89.83% (371/413) and 97.09% (401/413) after the second-time treatment. Twelve patients resulted in treatment failure by RFA, and they all treated by TACE and other palliative therapies.

Table 1 Demographic characteristics of surgical resection group and RFA group

	Surgical resection group n=648	RFA group n=413	p value
Age (years)	46.13 ±16.89	54.67 ±12.18	0.015
Gender:			0.000
Male	489 (75.5%)	361 (87.4%)	
Female	159 (24.5%)	52 (12.6%)	
Viral hepatitis status:			0.210
Hepatitis B viral infected (HBV)	598 (92.3%)	391 (94.7%)	
Hepatitis C viral infected (HCV)	28 (4.3%)	15 (3.6%)	
Non-HCV/HBV	22 (3.4%)	7 (1.7%)	
Cause of liver cirrhosis			0.189
Hepatitis-B	598 (92.3%)	391 (94.7%)	
Hepatitis-C	28 (4.3%)	15 (3.6%)	
Alcoholic	7 (1.1%)	4 (1.0%)	
Drugs	13 (2.0%)	2 (0.5%)	
Autoimmune hepatitis	0 (0%)	1 (0.2%)	
Others	2 (0.3%)	0 (0%)	
Tumor category:			0.076
Solitary tumor ≤3 cm	311 (48.0%)	212 (51.3%)	
Solitary tumor >3 cm	196 (30.2%)	101 (24.5%)	
Multifocal	141 (21.8%)	100 (24.2%)	
Mean tumor size	3.56 ±1.47	4.01 ±1.21	0.132
AFP			0.000
≤400	290 (44.8%)	256 (62.0%)	
400<AFP≤1,200	327 (50.5%)	149 (36.1%)	
>1,200	31 (4.8%)	8 (1.9%)	

Non-HBV/HCV patients negative for both HBV and HCV antibody except HBV surface antibody

Table 2 Tumor locations of surgical resection group and RFA group

Group	Location (segment)							
	I	II	III	IV	V	VI	VII	VIII
Surgical resection (lesions n=808)	4	86	62	125	231	168	107	25
RFA (lesions n=518)	0	41	45	87	174	107	54	10

P=0.099 by Pearson χ^2 test

Register per lesion

Lesion between segments, registered as major location

The Surgical Resection Group

Two hundred seventy-six of 648 operated patients received anatomic partial hepatectomy, the remaining 372 received nonanatomic resection. Ninety-one of 276 patients were treated with monosegmentectomy; 152/276 patients received bisegmentectomy; 23/122 underwent hemihepatectomy; 9/276 were treated with tri-sectorectomy, and 1/122 received right lateral sectorectomy plus bisegmentectomy of segment II+III. Pringle maneuver was performed in 217/648 patients. Mean blood-loss during operation was 501.2± 214.3 ml (range, 200–2,750 ml), 111/648 patients required intraoperative blood transfusion.

Fifty-nine new lesions were found in 57 patients intraoperatively, 58 by IOUS during the operations, and one by specimen examination. The smallest "safe margin" from the lesion measured in nonviable specimens were from 0.5 to 3.5 cm, and insufficient resection were revealed in 23 patients. There were 126 specimens poorly differentiated, 295 moderately differentiated, and 227 well differentiated. Twenty-four specimens were found microsatellites while 12 found microvascular invasion. Fifty-nine patients (23 with insufficient resection, 24 with microsatellites, and 12 with microvascular invasion) each underwent one session of TACE.

Hospitalization Length, Mortality, Complications, and Adverse Events

The hospitalization length was significantly longer in the surgical resection group (17.83±3.25 day) than in RFA group (6.12±2.98 day; p<0.001).

There was one death related to acute pulmonary embolism on postoperative day 7 in the surgical resection group. No patient died within 30 days after treatment in the RFA group.

Frequency of complications was significantly higher in the surgical resection group than in the RFA group (71/648 vs. 19/413, p<0.001). Complications in the surgical resection group were as follows: acute pulmonary embolism (one case), hepatic failure (four), refractory ascites (24), encapsulated effusion needing percutaneous drainage (21), bile leakage (12), postoperative bleeding (six), and gastrointestinal bleeding (three). Complications in the RFA group were: gastric perforation (one case), procedure-related hemorrhage (11), malignant seeding (three) hepatic infarction (one), skin burn (three). A significantly higher number of patients required analgesics after treatment in the surgical resection group than in the RFA group (339/648 vs. 131/413, p<0.001).

Survival

One hundred seventy-seven patients in the RFA group died during the follow-up. Causes of death were cancer recurrence (148 cases), liver failure (12), upper gastrointestinal hemorrhage (11), and miscellaneous (six). One hundred forty-one patients in the surgical resection group died during the follow-up, causes of death were cancer recurrence (114cases), liver failure (23), and miscellaneous (four).

The 1-, 2-, 3-, 4-, and 5-year overall survival rates for the RFA group, and the surgical resection group were 86.19%, 75.06%, 63.20%, 56.54%, 53.34%, and 94.14%, 87.89%, 83.26%, 79.48%, 76.47%, respectively. The surgical resection group had significantly better overall survival than the RFA group (p<0.001 by log-rank test, Fig. 1).

The corresponding recurrence-free survival rates were 73.25%, 54.02%, 44.89%, 31.78%, and 26.51% for the RFA group and 80.19%, 67.01%, 57.13%, 49.09%, and 42.97% for the surgical resection group, respectively. The recurrence-free survival of the surgical resection group was significantly better than the RFA group (p<0.001by log-rank test, Fig. 2).

The corresponding tumor-free survival (defined by the absence of a detectable tumor at the endpoint) rates were 78.69%, 60.77%, 46.97%, 36.83%, and 31.71% for the RFA group and 87.80%, 75.31%, 63.88%, 53.09%, and 43.67% for the surgical resection group, respectively. The tumor-free survival of the surgical resection group was significantly better than the RFA group (p<0.001by log-rank test, Fig. 3).

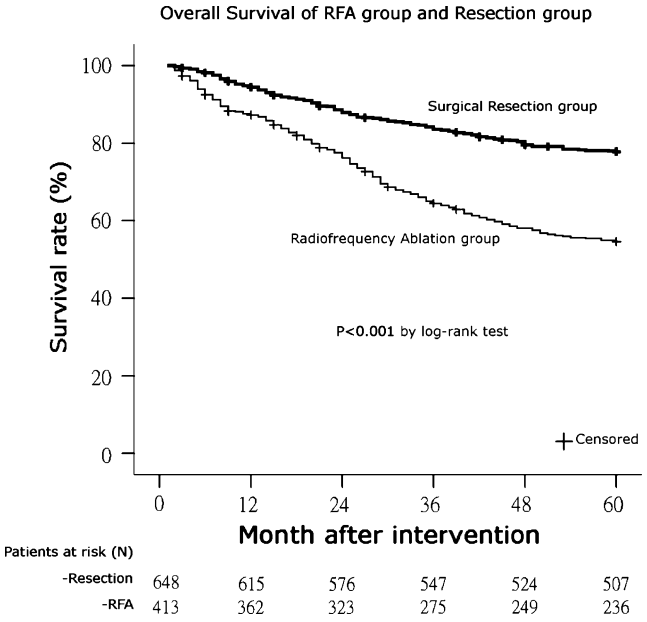

Fig. 1 Overall survival of RFA group and resection group

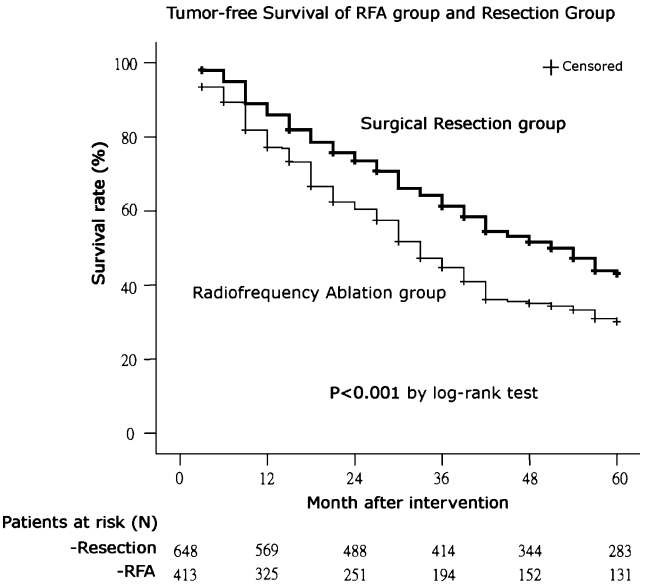

Fig. 3 Tumor-free survival of RFA group and resection group

Subgroup Analyses In subgroup analyses of overall survival performed in solitary HCC ≤3 cm, surgical resection was superior to RFA in overall survival ($p<0.001$by log-rank test, Fig. 4); however, there was no statistical difference in recurrence-free survival ($p=0.719$ by log-rank test, Fig. 5). The tumor-free survival result was concordant with overall survival between the two groups ($p<0.001$ by log-rank test, Fig. 6). In subgroup analyses for solitary lesions, 3 cm<HCC<5 cm and multifocal HCC surgical resection was superior to RFA for overall survival, recurrence-free survival, and tumor-free survival.

The main causes of liver cirrhosis in this study were HBV and HCV infection. There were 989/1061 patients infected by HBV and 43 infected by HCV (Table 1). The 1-, 3-, and 5-year overall survival rates for the HBV-infected patients were 91.27%, 75.45%, and 66.67% and 83.33%, 54.72%, and 26.20% for the HCV-infected patients, respectively. The corresponding recurrence-free survival rates were 75.61%, 62.47%, and 35.17% for the

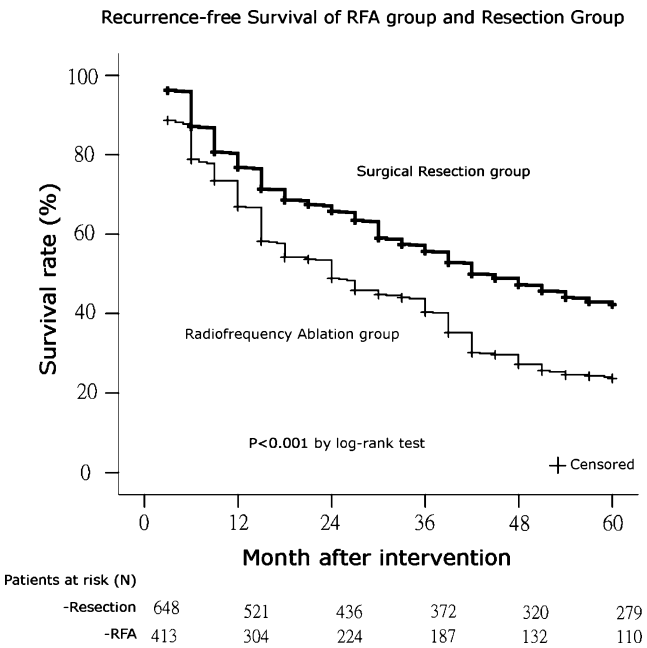

Fig. 2 Recurrence-free survival of RFA group and resection group

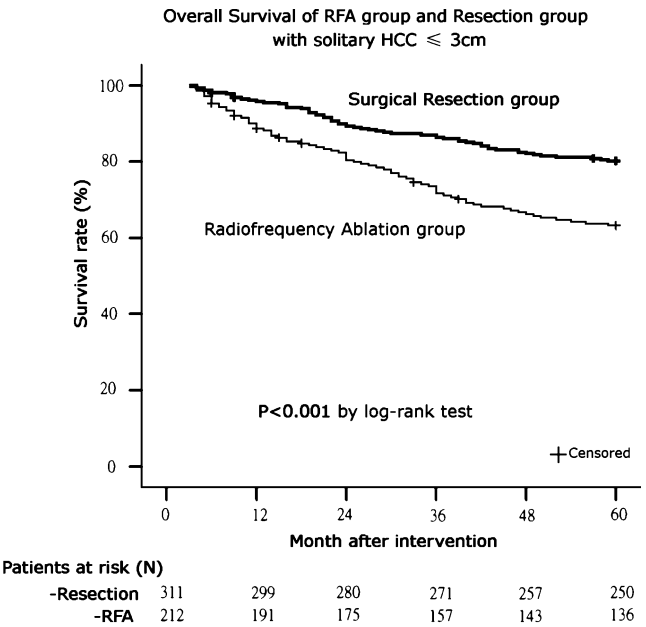

Fig. 4 Overall survival of RFA group and resection group with solitary HCC≤3 cm

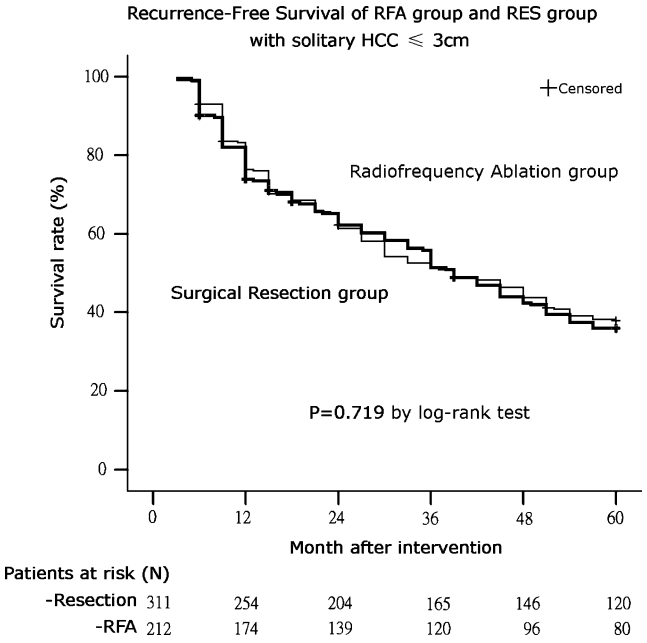

Fig. 5 Recurrence-free survival of RFA group and RES group with solitary HCC≤3 cm

HBV-infected patients and 76.19%, 47.61%, and 14.29% for the HCV-infected patients, respectively. The corresponding tumor-free survival rates were 80.14%, 71.25.47%, and 40.01% for the HBV-infected patients and 78.57%, 52.38%, and 19.05% for the HCV-infected patients, respectively. The HCV-infected patients had significantly poorer outcomes in overall, recurrence-free, and tumor-free survival analyses ($p<0.001$, $p<0.001$, $p<0.001$ by log-rank test).

The univariate and multivariate analyses of predictors of overall survival, recurrence-free survival, and tumor-free survival for all 1,061 patients were shown in Table 3. Significant predicting parameters for the overall survival were: intervention (surgical resection vs. RFA), recurrence intervention (non-radical vs. radical), serum AFP, tumor size, and tumor number. The corresponding relative risks were 3.471 (95% CI 1.217–5.574), 2.012 (95% CI 0.098–4.221), 9.041(95% CI 3.764–25.133), 1.893 (95% CI 1.231–5.865), and 2.981(95% CI 2.010–4.351), respectively. For recurrence-free survival, significant predicting parameters were the same as overall survival except recurrence intervention. The corresponding relative risks were 2.611 (95% CI 1.521–3.894), 9.033 (95% CI 4.510–24.315), 2.031 (95% CI 1.049–4.508), and 4.151(95% CI 2.186–10.481), respectively. However, for tumor-free survival, intervention (surgical resection vs. RFA), recurrence intervention (non-radical vs. radical), and serum AFP were the significant predicting parameters, and the relative risks were 2.079 (95% CI 1.144–3.586), 1.559 (95%CI 0.751–2.874), and 4.656 (95% CI 2.688–9.147), respectively.

In the subgroup of solitary HCC≤3 cm, univariate and multivariate analyses of predictors of overall survival, recurrence-free survival, and tumor-free survival were shown in Table 4. Intervention (surgical resection vs. RFA) was not related to overall survival, recurrence-free survival, and tumor-free survival. Nonetheless, recurrence intervention (non-radical vs. radical) was related to overall survival and tumor-free survival. Serum AFP was a significant predictor for all survival analyses.

Recurrence

Till the endpoint date of this study, recurrence was observed in 282 patients in the RFA group and 346 in the surgical resection group. Two hundred nine recurrent patients in the RFA group and 275 in the surgical resection group were amenable for radical treatment (i.e., excision, ablation, or transplantation). The other patients were either with extensive intrahepatic tumor dissemination or extrahepatic metastasis. They were treated by TACE or other palliative therapies. In the RFA group, 161/209 patients were treated by iterative RFA, 46 were given hepatic resection, and two received transplantation. In the surgical resection group, RFA was performed in 217/275 patients, and a repeat resection was applied in 58 patients. There was no significant difference in proportion of recurrence amenable to radical treatment between the two groups ($p=0.112$). The frequency of applying RFA was significantly higher than excision for

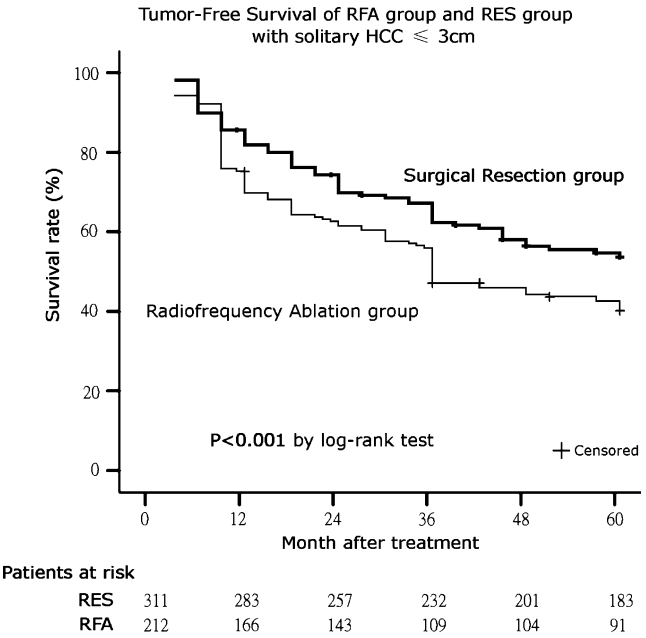

Fig. 6 Tumor-free survival of RFA group and RES group with solitary HCC≤3 cm

Table 3 Univariate and multivariate analysis of the predictors for survival of all patients

Variable	Univariate analysis (p value)	Multivariate analysis	
		Relative risk (95%CI)	p value
Survival			
Intervention (RFA vs RES)	0.000	3.471 (1.217–5.574)	0.000
Recurrence intervention (RFA vs RES)	0.038		
Recurrence intervention (non- vs radical)	0.001	2.012 (0.098–4.221)	0.001
Age (years) (>65 vs ≤65)	0.032		
Underlying liver disease			
HBV vs non-HBV	0.518		
HCV vs non-HCV	0.945		
Albumin (g/L) (≤35 vs >35)	0.521		
Total bilirubin (mmol/L) (>10 vs ≤)	0.493		
Serum AFP (ng/ml) (≥400 vs <400)	0.015	9.041 (3.764–25.133)	0.000
Prothrombin time (<15′ vs >15′)	0.917		
Tumor size (cm) (>3 vs ≤3)	0.001	1.893 (1.231–5.865)	0.001
Tumor number (multifocal vs single)	0.000	2.981 (2.010–4.351)	0.000
Recurrence-free survival			
Intervention (RFA vs RES)	0.000	2.611 (1.521–3.894)	0.000
Age (years) (>65 vs ≤65)	0.531		
Underlying liver disease			
HBV vs non-HBV	0.032		
HCV vs non-HCV	0.067		
Albumin (g/L) (≤35 vs >35)	0.241		
Total bilirubin (mmol/L) (>10 vs ≤10)	0.971		
Serum AFP (ng/ml) (≥400 vs <400)	0.012	9.033 (4.510–24.315)	0.000
Prothrombin time (<15′ vs >15′)	0.651		
Tumor size (cm) (>3 vs ≤3)	0.001	2.031 (1.049–4.508)	0.023
Tumor number (multifocal vs single)	0.001	4.151 (2.186–10.481)	0.000
Tumor-free survival			
Intervention (RFA vs RES)	0.017	2.079 (1.144–3.586)	0.001
Recurrence intervention (RFA vs RES)	0.041		
Recurrence intervention (non- vs radical)	0.031	1.599 (0.751–2.874)	0.012
Age (years) (>65 vs ≤65)	0.211		
Underlying liver disease			
HBV vs non-HBV	0.081		
HCV vs non-HCV	0.121		
Albumin (g/L) (≤35 vs >35)	0.322		
Total bilirubin (mmol/L) (>10 vs ≤10)	0.856		
Serum AFP (ng/ml) (≥400 vs <400)	0.018	4.656 (2.688–9.147)	0.010
Prothrombin time (<15′ vs >15′)	0.557		
Tumor size (cm) (>3 vs ≤3)	0.167		
Tumor number (multifocal vs single)	0.133		

Non-HBV/HCV patients negative for both HBV and HCV antibody except HBV surface antibody

the recurrent HCC patients amenable to radical treatment ($p<0.05$).

However, in the subgroup of solitary HCC≤3 cm, there were 112 patients in the RFA group, and 194 in the surgical resection group were amenable to radical treatment. There were significantly more recurrent HCC patients amenable to radical treatment in the surgical resection group ($p=0.030$).

Table 4 Univariate and multivariate analysis of the predictors for survival of patients with solitary HCC≤3 cm

Variable	Univariate analysis (*p* value)	Multivariate analysis	
		Relative risk (95%cl)	*p* value
Survival			
Intervention (RFA vs RES)	0.041		
Recurrence intervention (RFA vs RES)	0.047		
Recurrence intervention (non- vs radical)	0.004	1.510 (0.311–3.023)	0.001
Age (years) (>65 vs ≤65)	0.341		
Underlying liver disease			
HBV vs non-HBV	0.087		
HCV vs non-HCV	0.189		
Albumin (g/L) (≤35 vs >35)	0.351		
Total bilirubin (mmol/L) (>10 vs ≤10)	0.344		
Serum AFP (ng/ml) (≥400 vs <400)	0.000	11.552 (5.853–31.568)	0.000
Prothrombin time (<15′ vs >15′)	0.035		
Recurrence-free survival			
Intervention (RFA vs RES)	0.013		
Age (years) (>65 vs ≤65)	0.487		
Underlying liver disease			
HBV vs non-HBV	0.158		
HCV vs non-HCV	0.264		
Albumin (g/L) (≤35 vs >35)	0.544		
Total bilirubin (mmol/L) (>10 vs ≤10)	0.762		
Serum AFP (ng/ml) (≥400 vs <400)	0.031	5.122 (1.587–8.994)	0.001
Prothrombin time (<15′ vs >15′)	0.632		
Tumor-free survival			
Intervention (RFA vs RES)	0.035		
Recurrence intervention (RFA vs RES)	0.056		
Recurrence intervention (non- vs radical)	0.021	2.077 (0.988–4.556)	0.006
Age (years) (>65 vs ≤65)	0.117		
Underlying liver disease			
HBV vs non-HBV	0.122		
HCV vs non-HCV	0.207		
Albumin (g/L) (≤35 vs >35)	0.410		
Total bilirubin (mmol/L) (>10 vs ≤10)	0.799		
Serum AFP (ng/ml) (≥400 vs <400)	0.045	3.114 (0.877–8.7557)	0.003
Prothrombin time (<15′ vs >15′)	0.845		

Non-HBV/HCV patients negative for both HBV and HCV antibody except HBV surface antibody

Discussion

Several different treatment modalities exist for patients with HCC and cirrhosis. Liver transplantation has been shown to have superior results with regards to overall and recurrence-free survival; however, with organs in limited supply other modalities must be fully examined.[16] Radiofrequency ablation has gained support in recent years due to its postulated decrease in complication rates when compared with surgical resection. Previous studies have compared RFA with surgical resection with mixed results. Several observational studies have shown that surgical resection is superior to RFA in terms of overall and recurrence-free survival.[17] Other observational studies and one randomized prospective trial have suggested that with smaller HCC lesions (<4 cm) there are no significant differences in overall and recurrence-free survival between RFA and surgical resction.[12,18,19] To our knowledge the current study is the largest published to date comparing RFA and surgical resection. Our results had demonstrated superior survival benefit for the Childs A cirrhotic patients undergoing surgical resection as compared with radio-

frequency ablation. However, in subgroup analysis of lesions ≤3 cm, we found no significant difference in recurrence-free survival between RFA and surgical resection. This corresponds with the findings of the aforementioned studies.[12,18,19]

According to the results of this study, recurrence was the main reason of death which directly affected the survival analyses (148/177 in the RFA group and 114/141 in the surgical resection group). The difference of local tumor clearance between the two modalities might be the essential factor that affected recurrence. HCC mainly disseminates through portal veins and hepatic veins. The tumor embolus could shed in the neighboring branches of vessels and form the microsatellite.[20–23] Partial hepatectomy especially anatomic resection removed at least 1 cm rim of normal liver parenchyma together with the original lesion macroscopically, and thus theoretically eliminated both the primary tumor and possible venous tumor thrombi.[24,25] This was impossible to be achieved by any local ablation modalities. Furthermore, in the RFA procedure, repeated insertion and overlapping the ablation areas were necessary when encountering tumors larger than one single session ablative area. Via the guidance of 2D ultrasonography, a viable seam could be possibly left undetected in the actual lesion area which existed in a three-dimensional formation during the process of overlaying the ablation sessions. This hypothesis had actually been proved by colleagues from Japan.[24]

In cases of solitary HCC≤3 cm, overlaying ablation was usually not necessary because the necrosis area produced by one session of a single-needle electrode was closed to a sphere with a diameter of 3 cm.[26] The viable tumor nest was consequently hard to survival due to homogeneously heat effect. This might at least in part explain why no significant difference in recurrence-free survival between RFA and surgical resection for HCC less than 3 cm was found. However, in the subgroup of solitary HCC≤3 cm, the overall survival and tumor-free survival of surgical resection group were significantly better than the RFA group. This might be due to the recurrent patients in the surgical resection group had a larger proportion amenable to radical treatment, which might confound the overall and tumor-free survival results. Furthermore, we found that, in multivariate analyses (radical or non-radical), recurrence intervention was a significant predicting factor for overall and tumor-free survival.

The patients' liver cirrhosis in our study were mainly caused by hepatitis virus. In subgroup survival analyses of HBV and HCV infection, HCV-infected patients had significantly inferior survival in overall, recurrence-free, and tumor-free survival when compared with HBV-infected patients. This might reveal a trend that HCC patients with HCV-related cirrhosis had poorer prognosis and higher incidence of tumor relapse than HBV-infected patients.

The current study showed a lower incidence of complications and adverse events in the RFA group. In addition the length of hospital stay was significantly shorter in the RFA group. These results were likely explained by the less invasive nature of RFA compared with surgical resection.

When facing recurrent HCC amenable for radical treatment, the frequency of applying RFA was significantly higher than excision. The contraindications for surgical resection might increase in patients with recurrent HCC with histories of surgery because of poor liver functional reserve or inadequate liver remnant, especially in distant intrahepatic recurrence cases. In contrast, RFA could be applied in most of these patients. As concluded by other groups,[27,28] RFA might even be superior to surgery when facing iterative recurrences. These results were likely due to the less invasive nature of RFA compared with surgical resection as well.

In multivariate analyses, intervention was an independent predictor for overall, recurrence-free, and tumor-free survival for all the 1,061 patients. Interestingly, in the subgroup of solitary HCC less than 3 cm, it was completely not related to any. This might reveal surgical resection was superior to RFA when treating HCC larger than 3 cm or multiple lesions, but when facing solitary small HCC, the effectiveness of the two modalities were comparable.

Serum AFP was the only significant predicting factor for all survival analyses in this study. A high AFP level was usually observed in a high-grade malignancy HCC, which was featured by high incidence of recurrence and poor prognosis.[29] Moreover, high AFP level was proved to be a risk factor for HCC occurrence in cirrhotic patients.[30,31]

This study clearly has limitation as a result of its retrospective cohort design. Baseline characteristics of the two groups showed slight differences in age of patients, gender distribution, and baseline AFP level. Furthermore, the rates of censorship were high in 87/648 in the surgical resection group and 33/413 in RFA group.

Conclusion

The current study demonstrated that when treating Childs A cirrhotic patients with solitary HCC larger than 3 cm but less than 5 cm, or with two or three lesions each less than 5 cm, surgical resection provides better overall survival, recurrence-free survival, and tumor-free survival. When treating Childs A cirrhotics with solitary HCC≤3 cm, RFA has a comparable recurrence-free survival benefit to surgical resection, but RFA is less invasive.

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ORIGINAL ARTICLE

Role of *p53* and *β-catenin* Mutations in Conjunction with CK19 Expression on Early Tumor Recurrence and Prognosis of Hepatocellular Carcinoma

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Abstract

Background Cytokeratin 19 (CK19), a molecular marker of hepatic progenitor cells and cholangiocytes, is expressed in hepatocellular carcinomas (HCC), but not in normal hepatocytes. However, role of CK19 in HCC progression, especially when interacted with *p53* and *β-catenin* mutations, remained largely unknown.

Materials and Methods From January 1983 to December 1997, 210 surgically resected, unifocal, primary HCCs were studied retrospectively. CK19 protein expression was detected by immunohistochemistry while mutations of *p53* and *β-catenin* genes were detected by direct DNA sequencing.

Results CK19 protein expression was detected in 35.7% (75/210), *p53* mutation in 47.2% (83/176) and *β-catenin* mutation in 14.5% (27/186). The tumor size ($p=0.0023$), grade ($p=0.00093$), tumor stage ($p=4\times10^{-7}$), high α-fetoprotein ($p=0.0004$), *p53* mutation ($p=0.024$), absence of *β-catenin* mutation ($p=0.0013$), and CK19 expression ($p=3\times10^{-5}$) were markers predictive of early tumor recurrence (ETR). CK19 expression, stage, and ETR were strong indicators of poor prognosis (all $p<0.0001$). Importantly, combination analysis showed an additive unfavorable prognostic interaction of CK19 expression and *p53* mutation. On the contrary, concurrent CK19 expression and *β-catenin* mutation was rare and CK19 expression abolished the suppression effect of *β-catenin* mutation on HCC progression.

Conclusions CK19 expression is associated with more aggressive HCC. CK19 cooperates with *p53* mutation towards advanced disease. In contrast, CK19 expression and *β-catenin* mutation play dramatic opposite roles in vascular invasion, ETR and the prognosis of HCC.

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Keywords CK19 · *p53* mutation · *β-catenin* mutation · Early tumor recurrence · Prognosis · Hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) is one of the most common fatal malignancies in Taiwan, southern Chain, Southeastern Asia, and sub-Saharan Africa, and the incidence is increasing in Western countries.[1,2] Surgical resection and various modalities of tumor ablation procedures have provided an opportunity for cure or prolonged life. Unfortunately, the outcome for patients with HCC remains generally grave mainly because of the advanced tumor stage unsuitable for surgical resection and the intrahepatic metastasis with frequent tumor recurrence after hepatectomy.[3] Therefore, the identification of molecular markers related to tumor progression, early tumor recurrence (ETR), and poor prognosis would facilitate a better evaluation of ETR and prognosis to help establish a better management plan that can benefit the patients.

The keratin family contains the intermediate filament proteins responsible for the structural integrity of epithelial cells and is subdivided into cytokeratins and hair keratins. Cytokeratin 19 (CK19) is the smallest acidic cytokeratin specifically expressed in the periderm. CK19 is a cell marker of hepatic biliary[4] and progenitor cells,[5] and not expressed in normal hepatocytes.[6] CK19 expression was detected in several types of human cancers, including papillary thyroid carcinoma,[7] breast cancer,[8] lung cancer,[9] intrahepatic cholangiocarcinoma,[10] and recently HCC.[11] CK19 expression in HCC was found to correlate with metastasis,[11] recurrence,[12] and prognosis of HCC.[13] However, the clinicopathological significance of CK19 in the tumor progression, in particular the vascular invasion with intrahepatic spread and ETR, which are the two most crucial prognostic factors in resected HCC,[3] warrants a larger series of cases for further clarification. Moreover, HCC has two major genetic mutations, *p53* and *β-catenin* mutations, which have opposing roles in tumor progression, ETR, and prognosis.[14–16] Mutations of *p53* are associated with more advanced HCC and poor prognosis,[14,16] whereas *β-catenin* mutations are associated with less-aggressive tumor and better prognosis.[15] Therefore, the role of CK19 expression in conjunction with the two critical gene mutations needs to be investigated to better understand its significance in HCC progression.

The aims of the present study are to consolidate the relationship between CK19 expression and poor prognosis in HCC, and to investigate the interrelationship between *p53, β-catenin* mutations, and CK19 expression in relation to vascular invasion, ETR, and prognosis in HCC.

Materials and Methods

Tissue Samples

From January 1983 to December 1997, 210 surgically resected, unifocal, primary HCCs, which received detailed pathological assessment at the National Taiwan University Hospital, and had adequate paraffin blocks of good quality, were selected for this study, as described previously.[17,18] Study was executed according to the regulations of the Ethics Committee of the National Taiwan University Hospital. These patients included 171 men and 39 women, with a mean age of 56 years (range 14–88 years). Serum hepatitis B surface antigen (HBsAg) was detected in 146 cases, anti-HCV antibody in 61, including 16 positive for both. All the patients had adequate liver function reserve at the time of surgery, received curative liver resection, and had a complete clinicopathological and follow-up data. None of these patients had distant metastasis or received anticancer treatment such as transhepatic arterial chemoembolization, percutaneous ethanol injection therapy, radiofrequency ablation, or chemotherapy before surgery.

Histological Study

Surgically resected specimens were formalin fixed and paraffin embedded. Histological sections cut at 5-μm thickness were stained with hematoxylin–eosin and reviewed by one of the authors (H.C.H.) to determine tumor grade and stage. Based on the criteria proposed by Edmonson and Steiner,[19] tumor grade was divided into three groups: well differentiated (grade I, 48 cases), moderately differentiated (grade II, 90 cases), and poorly differentiated (grades III and IV, 72 cases). HCC tends to spread in the liver through portal vein invasion, and vascular invasion is a crucial unfavorable prognostic factor.[20] At the time of operation, no evidence of regional lymph node or distant metastasis was noted. The tumor stage of unifocal HCC was closely associated with prognosis, as described.[17,18,20,21] Stages I (≤2 cm) and II tumors had no vascular invasion, whereas stage IIIA to IV HCC exhibited vascular invasion and various degrees of intrahepatic metastasis. Tumor stages were classified as I (ten cases), II (64 cases), IIIA (56 cases), IIIB (28 cases), and IV (52 cases).

Immunohistochemical Analysis of CK19 Protein Expression

The CK19 protein in HCC and liver was detected on formalin-fixed, paraffin-embedded sections by the labeled streptavidin–biotin method after antigen retrieval, as previously described.[18,22] The antibody used was a monoclonal

antibody against CK19 (1:200 dilution, BA17, GeneTax, San Antonio, TX, USA). For control of non-specific binding, we replaced the primary antibody with 5% fetal bovine serum. In addition, hepatocytes and bile ducts of uninfected liver tissues from surgically resected hepatic hemangiomas were used as negative control and positive control, respectively. Two pathologists who did not know patient outcome determined the percentage of positive cells. Five independent microscopic fields (×400) were selected for each sample to ensure representativeness and homogeneity. All the tumor cells within each microscopic field were counted, and then the positive rates of CK19 cells were calculated. The proportion of tumor cells positive for CK19 immunostain varied considerably, ranging from diffuse positive (>50%), heterogeneous (25% to 50%), focal (5% to 24%), to positive in a small amount of tumor cells (<5%). CK19 protein is specifically expressed in HCC and not in the nontumorous liver cells, hence CK19 was considered positive if staining presented in ≥5% of the tumor cells.[12]

Analysis of *p53* and *β-catenin* Mutations

Mutations of the p53 tumor suppressor gene were analyzed in 176 tumors by direct sequencing spanning exon 2 to exon 11 as described previously.[23] Mutation of the *β-catenin* gene were analyzed in 186 cases by direct sequencing of exon 3 as described previously.[15]

Follow-up Observation and Early Tumor Recurrence

Among the 210 study patients, 208 cases (99%) had been followed up for more than 5 years or until death, 75 patients (36%) survived for more than 5 years, and 189 (90%) were eligible for the evaluation of ETR. After surgery, all patients received laboratory examinations such as serum α-fetoprotein (AFP) at 1- to 6-month intervals, and ultrasonography of liver at 3- to 12-month intervals. Computed tomography and/or magnetic resonance imaging were used to verify whether intrahepatic recurrence and/or distal metastasis had occurred for patients with test results suggestive of recurrence. Intrahepatic tumor recurrence or distant metastasis detected by imaging methods supplemented with elevated serum AFP within 12 months of tumor resection was defined as ETR, as previously described.[3,21]

According to the site, size, number of tumor, liver function, and patient condition, tumor recurrence was treated by second resection, percutaneous ethanol injection, transhepatic arterial chemoembolization, radiofrequency ablation, or chemotherapy. All the patients in Taiwan had equal opportunity to access all the therapeutic modalities supported by the National Health Insurance.

Statistical Analysis

The data analyses were carried out using Epi Info™ Version 3.5.1 software (Centers for Disease Control and Prevention, Atlanta, GA, USA). The $\chi 2$ and Fisher's exact tests were used for univariate analysis. The survival rates after tumor removal were calculated by the Kaplan–Meier method, and difference in survival curves was analyzed by the log rank test. Multivariate analyses were performed on all the parameters measured in univariate analysis. Analysis of stage and time to ETR were conducted by multiple logistic regression models, and then time to death was analyzed by the Cox proportional hazard regression model. Two-tailed p values of <0.05 were considered statistically significant.

Results

Expression of CK19 Protein in Hepatocellular Carcinoma and Liver

By the immunohistochemical stain, CK19 protein was detected in the tumor cell cytoplasm in 75 HCCs (35.7%), including diffuse positive in 21 cases (10.0%), heterogeneous in 18 (8.6%), and focal in 36 (17.1%), which were regarded as CK19 positive group. Those without CK19 expression or CK19 expression positive in less than 5% of tumor cells were considered as negative group (135 cases, 64.3%). No immunostaining was seen in the normal or adjacent nontumorous liver tissue.

Clinicopathological Significance of CK19 Expression in Hepatocellular Carcinoma and Correlation with *p53* and *β-catenin* Mutations

To elucidate the significance of CK19 in HCC, we correlated its protein expression with major clinicopathological features. As shown in Table 1, CK19 protein expression tended to occur in HCC with high serum α-fetoprotein level (AFP>200 ng/mL; $p=0.0004$), but did not correlate with other clinical parameters, such as age, gender, and serum HBsAg or Anti-HCV status. Histologically, CK19 expression closely correlated with high-grade HCC [grade II–IV; odds ratio (OR), 4.24; 95% confidence interval (CI), 1.69–11.05; $p=0.0005$] and high-stage HCC (stages IIIA–IV; OR, 6.99; 95% CI, 3.15–15.07; $p<1\times 10^{-8}$). Moreover, CK19 expression progressively increased as tumor stage advanced, 20.0% in stage I, 12.5% in stage II, 37.5% in stage IIIA, 46.4% in stage IIIB, and 59.6% in stage IV; $p=1.3\times 10^{-6}$. Notably, CK19 expression did not correlate with tumor size, which is also an important prognostic factor.

Table 1 Univariate analysis of CK19 protein expression with various clinicopathological features and aberrant gene expression in 210 patients with surgically removed unifocal primary hepatocellular carcinoma

Variables	CK19 protein expression			
	Total	Yes, *n* (%)	Odds ratio	*p* Value
Age				
>56	119	38 (32)	1.0	0.1909
≤56	91	37 (41)	1.46 (0.80–2.68)	
Gender				
Male	171	56 (33)	1.0	0.0604
Female	39	19 (49)	1.95 (0.91–4.18)	
HBsAg				
Negative	54	18 (33)	1.0	0.1286
Positive	146	57 (39)	1.64 (0.83–3.26)	
Anti-HCV				
Negative	134	48 (36)	1.0	0.6802
Positive	61	20 (33)	1.14 (0.58–2.28)	
α-Fetoprotein (ng/ml)				
≤200	107	26 (24)	1.0	0.0004
>200	103	49 (48)	2.83 (1.51–5.31)	
Tumor size (cm)				
≤5	90	30 (33)	1.0	0.5329
>5	120	45 (38)	1.20 (0.65–2.22)	
Tumor grade				
I	48	7 (15)	1.0	0.0005
II~IV	162	68 (42)	4.24 (1.69–11.05)	
Tumor stage				
I~II	74	10 (14)	1.0	$<1\times10^{-8}$
IIIA~IV	136	71 (52)	6.99 (3.15–15.07)	
Early tumor recurrence				
No	105	23 (22)	1.0	3×10^{-5}
Yes	84	43 (51)	3.74 (1.90–7.39)	
p53 mutation				
No	93	30 (32)	1.0	0.3827
Yes	83	32 (39)	1.32 (0.68–2.57)	
β-Catenin mutation				
No	159	65 (41)	1.0	0.0008
Yes	27	2 (7)	0.12 (0.02–0.53)	

The tumor suppressor gene *p53* and *β-catenin* are the two major genes most commonly mutated in HCCs. In this series, *p53* mutation was detected in 83 of 176 cases examined (47.2%), and β-catenin mutation in 27 of 186 tumors (14.5%). In contrast to the lack of correlation between CK19 expression and *p53* mutation, CK19 expression showed a strong correlation with absence of *β-catenin* mutation, $p=0.0008$ (Table 1).

CK19 Expression is an Important Predictive Marker for ETR and Poor Prognosis

ETR is the most critical, early clinical factor predictive of poor prognosis of HCC after hepatectomy.[3,21] We found that ETR occurred about 2.3 times higher in HCC with CK19 expression than in HCC without the expression ($p=3\times10^{-5}$; Table 1). To further elucidate the impact of CK19 expression in the occurrence of ETR, its expression and major clinicopathological factors were analyzed. We found that tumor size ($p=0.0023$), tumor grade ($p=0.00093$), and particularly tumor stage (OR, 5.50; 95% CI, 2.63–11.66; $p=4\times10^{-7}$) were important histopathological risk factors for ETR.

We then analyzed the four molecular markers, CK19 expression, serum AFP level, and mutations of *p53* and *β-catenin*. As shown in Table 2, all the four molecular markers were related to the risk of ETR. Notably, CK19 expression had the highest risk for ETR (OR, 3.74; 95% CI, 1.90–7.39; $p=3\times10^{-5}$), as compared with high AFP ($p=0.0004$), *p53* mutation ($p=0.024$), and absence of *β-catenin*

Table 2 Univariate analysis of clinicopathological variables and CK19 protein expression with ETR in 189 patients with surgically removed unifocal primary hepatocellular carcinoma

Variables	ETR			
	Total	Yes, *n* (%)	Odds ratio	*p* Value
Clinical features				
Age				
>56 (years)	106	39 (37)	1.0	0.0167
≤56 (years)	83	45 (54)	2.03 (1.09–3.81)	
Gender				
Male	152	64 (42)	1.0	0.1896
Female	37	20 (54)	1.62 (0.74–3.54)	
HBsAg				
Negative	52	22 (42)	1.0	0.2877
Positive	132	62 (47)	1.41 (0.71–2.79)	
Anti-HCV				
Negative	125	54 (43)	1.0	0.8775
Positive	54	24 (44)	1.05 (0.53–2.10)	
Histopathological variables				
Tumor size (cm)				
≤5	84	27 (32)	1.0	0.0023
>5	105	57 (54)	2.51 (1.32–4.77)	
Tumor grade				
I	44	10 (23)	1.0	0.00093
II~IV	145	74 (51)	3.54 (1.54–8.32)	
Tumor stage				
I~II	69	14 (20)	1.0	4×10^{-7}
IIIA~IV	120	70 (58)	5.50 (2.63–11.66)	
Molecular markers				
α-fetoprotein (ng/ml)				
≤200	97	31 (32)	1.0	0.0004
>200	92	53 (58)	2.89 (1.53–5.49)	
p53 mutation				
No	83	30 (36)	1.0	0.0240
Yes	78	42 (54)	2.06 (1.05–4.08)	
β-Catenin mutation				
No	145	75 (52)	1.0	0.0013
Yes	26	4 (15)	0.17 (0.05–0.56)	
CK19 (↑)[a]				
No	123	41 (33)	1.0	3×10^{-5}
Yes	66	43 (65)	3.74 (1.90–7.39)	

mutation (p=0.0013). Consistent with the close correlation of CK19 expression with high tumor stage and ETR, HCC with CK19 expression had lower 5-year survival than those without the expression (p<0.0001; Fig. 1). ETR did not correlate with patient age, gender, and chronic HBV or HCV infection status (Table 2).

For further clarification, we performed a multivariate analysis using the Logistic regression model. As listed in Table 3, AFP (p=0.022), *p53* mutation (p=0.0015), tumor grade (p=0.042), and tumor size (p=0.005) were significant independent risk factors for high-stage tumor. Furthermore, absence of *β-catenin* mutation (p=0.033), large tumor size (p=0.011), and high-stage tumor (p=0.0006) were significant independent risk factors for ETR. Importantly, we found that CK19 expression was an independent risk factor associated with both the high-stage tumor (p=0.0002) and ETR (p=0.0398); which are two most crucial unfavorable prognostic factors leading to poor survival of the patients (Table 3). However, stage was the most crucial risk factor for ETR, and ETR and high tumor stage were two factors contributory to poor prognosis, ps<0.0001 (Table 3). Hence, CK19 expression did not exert prognostic impact independent of tumor stage. This indicates CK19 contributes to poor prognosis indirectly through tumor stage and ETR.

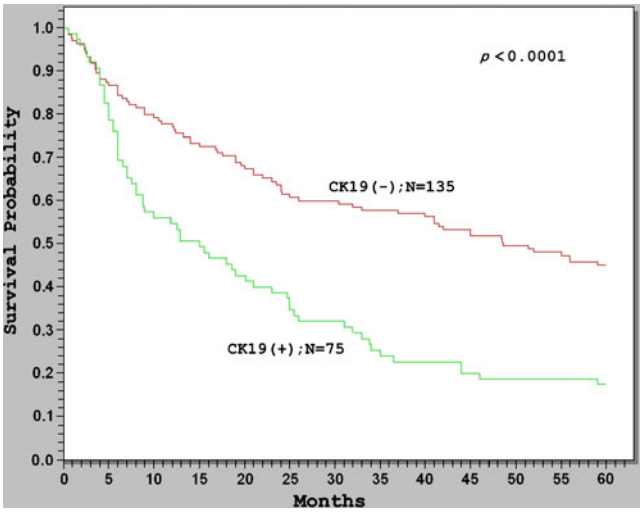

Fig. 1 Kaplan–Meier analysis of overall survival in 210 patients with hepatocellular carcinoma (HCC). (**a**) HCCs harboring CK19 protein expression was associated significantly with lower 5-year survival rate than those without CK19 protein expression, $p<0.0001$. (+), designated present of cytoplasmic CK19 expression. (−), designated absent of CK19 expression

Interaction of CK19 Expression with *p53* and *β-catenin* Mutations Exerts an Important Role in HCC Progression, ETR, and Prognosis

Tumor suppressor *p53* is the most commonly mutated gene in HCC,[23] and is known to correlate with advanced HCC and an unfavorable prognosis of HCC.[14,16] To better understand the role of CK19 expression in the HCC progression, we analyzed the interplay between CK19 expression and *p53* mutation. As shown in Table 4, an additive interaction between these two important independent unfavorable prognostic molecular markers in the tumor stage and ETR was found ($p=4\times10^{-8}$ and $p=0.00028$, respectively). Notably, HCCs with concomitant CK19 expression and *p53* mutation had the highest frequencies of vascular invasion with various extents of intrahepatic spread (stage IIIA to IV) and ETR, 97% and 76%, respectively, more than twofold higher than HCCs without any of the two events, 41% and 28%, respectively, $p=2\times10^{-7}$ and $p=0.000025$, respectively. Hence, HCCs with concomitant CK19 expression and p53 mutation had the lowest 5-year survival, followed by HCCs with either CK19 expression or p53 mutation, while HCCs without any of the two events the highest, $p=0.0001$ (Fig. 2a).

In contrast to *p53* mutation, *β-catenin* mutation is associated with low-grade, low-stage HCC, and better 5-year survival, and may possess tumor metastasis suppression activity.[15] Consistently, we showed a correlation between CK19 expression and absence of *β-catenin* mutation in HCCs (Table 1, $p=0.0008$). Notably, *β-catenin* mutation was rarely accompanied by concomitant CK19 expression, and encountered only in two cases (Table 4). Of the remaining three groups, HCCs with CK19 expression alone had the highest frequencies of vascular invasion (stage IIIA to IV, 92%) and ETR (66%), followed by HCC without any event (60% and 43%, respectively), while HCC with *β-catenin* mutation alone the lowest frequencies (32% and 8%, respectively), $p<1\times10^{-7}$ and $p<1\times10^{-5}$, respectively. HCCs with CK19 expression alone had vascular invasion and ETR 3- and 8-times higher than HCC with *β-catenin* mutation alone, $p<1\times10^{-8}$ and $p=0.0000078$, respectively (Table 4). Hence, the non-*β-catenin*-mutated HCCs with CK19 expression had the lowest 5-year survival, whereas HCCs with *β-catenin* mutation alone, the highest, $p=0.0002$ (Fig. 2b). These findings suggest that CK19 expression is an important risk factor for vascular invasion and ETR in both p53-mutated and non-p53-mutated HCC, and hence poor prognosis.

Table 3 Multivariate analyses of risk factors associated with ETR, tumor stage, and survival of patients with unifocal hepatocellular carcinoma

Covariate	Coefficient	S.E.	Z statistic	O.R./H.R. (95% C.I.)	*p* Value
High stage (stage III–IV; vascular invasion; yes)[a]					
CK19	1.8462	0.4889	3.7764	6.3359 (2.4304–16.5175)	0.0002
AFP	0.9495	0.4134	2.2969	2.5844 (1.1495–5.8107)	0.022
p53 mutation	1.3069	0.4118	3.1736	3.6947 (1.6483–8.2814)	0.0015
Grade	0.9762	0.4794	2.0363	2.6545 (1.0373–6.7931)	0.042
Size	1.1204	0.4011	2.7936	3.0661 (1.3970–6.7295)	0.005
ETR (yes)[a,b]					
CK19	0.7838	0.3813	2.0557	2.1899 (1.0372–4.6237)	0.0398
β-catenin mutation	−1.3580	0.6361	−2.1348	0.2572 (0.0739–0.8947)	0.033
Size (>5cm)	0.9512	0.3752	2.5354	2.5888 (1.2410–5.4006)	0.011
Stage (III–IV)	1.8325	0.4042	3.4267	3.9957 (1.8093–8.8243)	0.0006
Survival time (death)[c]					
ETR[b]	1.6514	0.2176	7.5891	5.2140 (3.4037–7.9871)	<0.0001
High stage	1.1410	0.2260	5.0485	3.1300 (2.0098–4.8745)	<0.0001

S.E. standard error; *O.R.* odds ratio; *H.R.* hazard ratio; *C.I.* confidence interval; *AFP* α-fetoprotein

[a] Logistic regression model

[b] Tumor recurrence within 12 months after hepatectomy

[c] Cox proportional hazards model

Table 4 Interaction between CK19 expression with *p53* mutation or *β-catenin* mutation in the tumor progression of hepatocellular carcinoma

Feature	CK19 expression/p53 mutation				
	Yes/yes	Yes/no	No/yes	No/no	*p* Value
Stage					
I~II	1 (3%)	4 (13%)	16 (31%)	37 (59%)	4×10^{-8}
IIIA~IV	31 (97%)*·***	26 (87%)**	35 (69%)*	26 (41%)**·***	
ETR[c]					
Presence	22 (76%)****·******	14 (54%)*****	20 (41%)****	16 (28%)*****·******	0.00028
Absence	7 (24%)	12 (46%)	29 (59%)	41 (72%)	
	CK19 expression/*β-catenin* mutation				
	Yes/yes	Yes/no	No/yes	No/no	*p* Value
Stage					
I~II	0	6 (8%)*******	17 (68%)*******	38 (40%)	2×10^{-7a}
IIIA~IV	2	59 (92%)	8 (32%)	56 (60%)	$<1\times10^{-7b}$
ETR[c]					
Absence	0	20 (34%)********	22 (92%)********	50 (57%)	0.00001[a]
Presence	2	38 (66%)	2 (8%)	37 (43%)	$<1\times10^{-5b}$

NS not significant; *ETR* early tumor recurrence

Asterisks designate comparison between the indicated two groups

p values: * <0.005; ** 0.0001; *** 2×10^{-7}; **** 0.0027; ***** 0.0234; ****** 0.000025; ******* $<1\times10^{-8}$; ******** 0.0000078

[a] *p* value indicative of all of the four groups

[b] *p* value indicative of cases with both CK19 expression and *β-catenin* mutation (Yes/Yes) were excluded from the statistical analysis due to small number of this group

[c] tumor recurrence within 12 months after hepatectomy

Discussion

HCC is a dreadful disease difficult to treat. Despite the significant improvement of earlier diagnosis and better management, the outcome of HCC after tumor resection remains unsatisfactory because of the high tumor recurrence rate.[3,24–26] We have shown that ETR is the most crucial, unfavorable, clinical prognostic factor for surgical

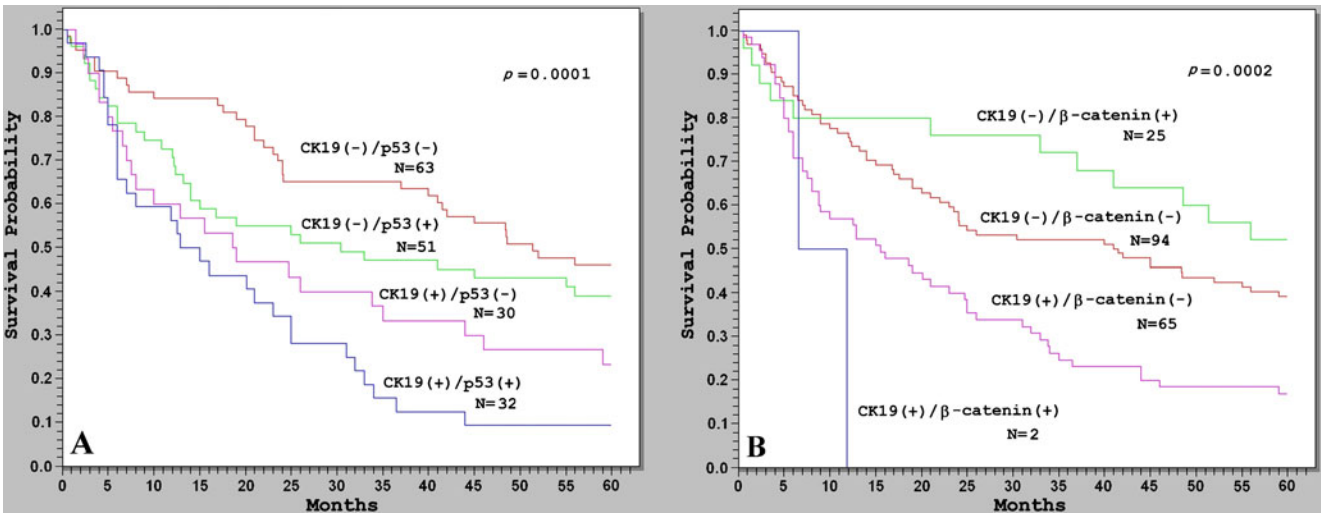

Fig. 2 Kaplan–Meier analysis of overall survival of patients with hepatocellular carcinoma (HCC) in relation to the conjunction of CK19 protein expression with *p53* mutation (176 patients) or *β-catenin* mutation (186 patients). (**a**) HCCs harboring CK19 protein expression with concomitant *p53* mutation was associated with the lowest 5-year survival rate (p=0.0001), even worse than HCCs with *p53* mutation alone (p=0.0051). (**b**) HCCs with *β-catenin* mutation alone had the best 5-year survival rate, while HCCs with CK19 expression alone had the worst 5-year survival rates (p=0.0002). In Fig. 2b, cases with both CK19 expression and *β-catenin* mutation were excluded due to small number of this group. (+), designated present of CK19 expression, *p53* mutation, or *β-catenin* mutation. (−), designated absent of CK19 expression, *p53* mutation, or *β-catenin* mutation

HCC patients; less than 20% of patients with ETR survive 5 years, compared to more than 50% survival of patients without ETR.[3] Hence, ETR can be regarded as a crucial clinical event before death, and needs more predictive and useful markers for better postoperative patient management planning. Cytokeratin 19 (CK19), which has been detected in several types of human cancers,[7–10] has been recently shown to be expressed in HCC.[11] In this study, we showed that CK19 protein expression in HCC was closely correlated with high AFP ($p=0.0004$), high-grade HCC ($p=0.0005$), and in particular high-stage HCC ($p<1\times10^{-8}$), with progressively increased CK19 expression as tumor stage advanced. These findings were consistent with the observations separately reported by other investigators. A correlation of CK19 expression with poorly differentiated HCC has been demonstrated by Uenishi et al.[12] Our previous study has shown that high serum AFP, which is the most widely used diagnostic marker, is associated with poorly differentiated and more aggressive HCC.[21] Ding et al. showed that CK19 expression correlated with intrahepatic metastasis.[11] These findings suggest that CK19 expression in HCC plays a role in facilitating tumor cell proliferation, leading to high-grade and high-stage HCC, with high AFP level.

To further elucidate the impact of CK19 expression in the occurrence of ETR, its expression and major clinicopathological factors were analyzed. We found that high tumor stage was the most important histopathological risk factor for ETR, while CK19 was the most significant molecular factor for ETR as compared with AFP, and mutations of *p53* and *β-catenin* genes. The multivariate regression analysis further confirmed that CK19 expression was an independent risk factor of ETR. Importantly, we found that HCC with CK19 expression had 2.3 times higher risk for ETR than in HCC without the expression ($p=3\times10^{-5}$). This finding was consistent with observation of Uenishi et al. who found that because of the association with increased invasiveness, CK19 expression was a predictor of ETR.[12] Furthermore, we showed that HCC with CK19 expression had lower 5-year survival rate than those without the expression ($p<0.0001$), in accord with the observation of Yang et al. who showed that CK19 was a predictor for poor prognosis in HCC.[13] These findings suggest that HCCs with CK19 expression harbor enhanced invasion/metastasis potential, leading to higher tumor stage and frequent ETR, and hence poor prognosis.

Besides the close association with ETR and prognosis in HCC, the significance of CK19 in the tumor progression of HCC, in particular the interaction with the two major gene mutations in HCC, *p53* and *β-catenin* mutations,[14,15,23] needs to be clarified. The mutations of *p53* and *β-catenin* genes contribute to two distinct pathways of hepatocarcinogenesis,[27] and are known to exert opposite role in HCC progression and patient prognosis.[14–16] Inactivation of p53 leading to aberrant mitosis and chromosome instability and hence more aggressive behavior of HCC with poor prognosis,[14,16,28] whereas *β-catenin* mutation is associated with low-grade, low-stage HCC, and may possess metastasis suppression activity, and hence better patient survival.[15] In this study, we showed that CK19 protein expression did not correlate with *p53* mutation, but was closely associated with absence of *β-catenin* mutation. Because of the importance of *p53* mutation in HCC progression, we further analyzed the potential interaction between *p53* mutation and CK19 expression, and found that these two independent molecular factors showed a positive interaction with additive effects in the tumor progression. Our findings suggest that CK19 expression is associated with HCC progression regardless of p53 mutation status, but also interacts positively with *p53* mutation and contributes to more advanced disease. This observation is similar to our previous report that stathmin expression was associated with advanced HCC regardless the status of *p53* mutation.[23] On the other hand, concomitant CK19 expression and *β-catenin* mutation was rare and encountered only in two cases, in accord with the observation of Durnez et al. who did not find HCC with concomitant CK19 expression and *β-catenin* mutation.[6] The rare concurrence of CK19 expression and *β-catenin* mutation suggests that CK19 plays a minor role in *β-catenin*-mutated HCC, in which the tumorigenesis is distinct from p53-mutated HCC.[27] More investigation is warranted for further clarification. Of the remaining three groups, HCC with CK19 expression alone had the highest frequencies of vascular invasion (92%) and ETR (66%), three- and eightfold higher than HCC with *β-catenin* mutation alone, which had the lowest frequency of vascular invasion (32%), and ETR (8%). HCCs negative for both events was in between. These findings indicate that CK19 expression and *β-catenin* mutation appear to play opposing roles in vascular invasion, ETR, and prognosis of HCC.

In conclusion, CK19 expression is associated with more aggressive HCC with vascular invasion and intrahepatic spread, and hence is an important risk factor for ETR, and an unfavorable prognostic factor, regardless of the presence or absence of *p53* or *β-catenin* mutation. Moreover, CK19 expression, in conjunction with *p53* mutation and the absence of *β-catenin* mutation, appeared to discriminate for advanced disease, high ETR, and poor prognosis. Our results highlight the potential combination of CK19 expression with p53 and *β-catenin* mutations for molecular staging of HCC to help identify the high risk patients of the same pathologic stage.

Conflicts of Interest There are no potential and real conflicts of interest in the subject of this study.

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ORIGINAL ARTICLE

Hospitalization for Complications of Cirrhosis: Does Volume Matter?

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Abstract
Introduction Close to 30,000 people die of cirrhosis in the USA each year. Previous studies have shown a survival advantage with high-volume (HV) hospitals for complex surgical procedures. We examined whether a volume benefit exists for hospitals dealing with specialized disorders like complications of cirrhosis.
Methods Using the Nationwide Inpatient Sample, we identified all cases of cirrhosis-related complications (n=217,948) from 1998 to 2006. Hospital volume was divided into tertile-based admissions for cirrhosis per year.
Results The primary outcome was in-hospital mortality, and secondary endpoints included length of stay (LOS) and hospital charges. The number of admissions for cirrhosis increased over time ($p<0.0001$). HV centers were more likely to be large (86.8%) and teaching (81.5%) hospitals compared to lower volume centers. The average LOS and hospital charges were greater at the HV centers, but hospitalization at a HV center resulted in an adjusted mortality benefit (HR 0.88; 95% CI 0.83–0.92) compared to care at lower volume hospitals.
Conclusion Despite increased LOS and hospital cost, a mortality benefit exists at HV centers. Future studies are necessary to determine other processes of care that may exist at HV centers that may account for this survival benefit.

Keywords Cirrhosis · Volume · NIS · Hospitalizations · Length of stay

Introduction

Cirrhosis is one of the leading causes of death in the USA in hospitalized patients.[1] There is no curative medical treatment for cirrhosis, and liver transplantation remains the only definitive cure. Prevention and treatment of complications such as variceal hemorrhage, hepatorenal syndrome, encephalopathy, and ascites is the most effective care for these complicated patients until liver transplantation is available. With a shortage of donor organs, the liver transplant waiting list is increasing, implying that more people are forced to live with cirrhosis and its subsequent complications.[2,3] Trends in care of these individuals can help us understand some of the ways we can improve the treatment standard in the future. The mortality for patients with cirrhosis is highest in the first year following initial diagnosis.[4]

The goal of this study was to assess if a benefit exists for cirrhosis patients treated at high-volume (HV) centers using a nationwide patient database. Attempts at understanding trends and referral patterns for these complex medical disorders may aid in optimizing care and overall patient outcome.

Methods

A retrospective analysis was performed using discharge records from the Nationwide Inpatient Sample (NIS) from 1998 to 2006 for all patients who had been hospitalized for

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cirrhosis or one of its related complications including ascites, variceal bleeding, hepatorenal syndrome, and encephalopathy. The methods for data extraction and analysis have been previously described.[5,6] The Healthcare Cost and Utilization Project supports the database, which is the largest US all-payer database for inpatient medical records comprising 100% of patient discharges from participating hospitals. This database collects information on approximately seven million hospital discharges per year from a stratified sample of 20% of nonfederal US community hospitals every year. This database includes both academic and specialty hospitals. Each record in the NIS represents a single discharge and includes a unique identifier.

Study Population

The Clinical Modification of the International Classification of Diseases, 9th revision, (ICD-9-CM) diagnostic and procedural codes was used to identify diagnoses and procedures. Patients who were discharged from the hospital with primary diagnosis of chronic liver disease and cirrhosis were identified and included only if hospital data were available. This included alcoholic cirrhosis (571.2), cirrhosis of the liver without mention of alcohol (571.5), biliary cirrhosis (571.6), esophageal varices (456.0 and 456.2), hepatic coma (572.2), portal hypertension (572.3), and ascites (789.5). There were 217,948 patients discharged from hospitals in the USA from 1998 to 2006 with primary diagnosis of cirrhosis. Those with secondary diagnosis of cirrhosis were not included in the study.

Hospitals were divided into tertiles based on volume of admissions with primary diagnosis of cirrhosis before any analysis was performed. The hospitals were split into three equal groups: low volume (LV; 1–40 admissions/year), medium volume (MV; 41–87 admissions/year), and high volume (HV; >87 admissions/year). We excluded all patients under age 18.

Variables

Patient demographic characteristics compiled in the NIS were used. Age was incorporated as a continuous variable. Race was categorized by the following groups: white, black, Hispanic, or other (Asians, Pacific Islanders, and Native Americans). Race was missing in 21.8% of cases in this cohort. Payer was categorized as Medicare, Medicaid, private, or other. Payer was missing in 0.3% of the cases. Mortality was defined as death during hospitalization.

Comorbidity was assessed using the method described by Elixhauser et al.[7,8] This is a previously validated index that uses ICD-9 codes and Diagnosis Related Groups to identify comorbid conditions such as cardiovascular disease, chronic pulmonary disease, malignancy, diabetes, renal disease, liver disease, neurologic disease rheumatologic disease, and AIDS. The benefit of this method is that it excludes diagnoses that are likely to be complications of care rather than true comorbid conditions. Scores between 0 and 3 were created based on how many comorbid diseases patients had.

Outcomes

Mortality was the primary endpoint examined in this study and was defined as death due to any cause prior to discharge. Secondary endpoints included specific complications during hospital stay, length of stay, and hospital charges. The specific complications related to liver disease

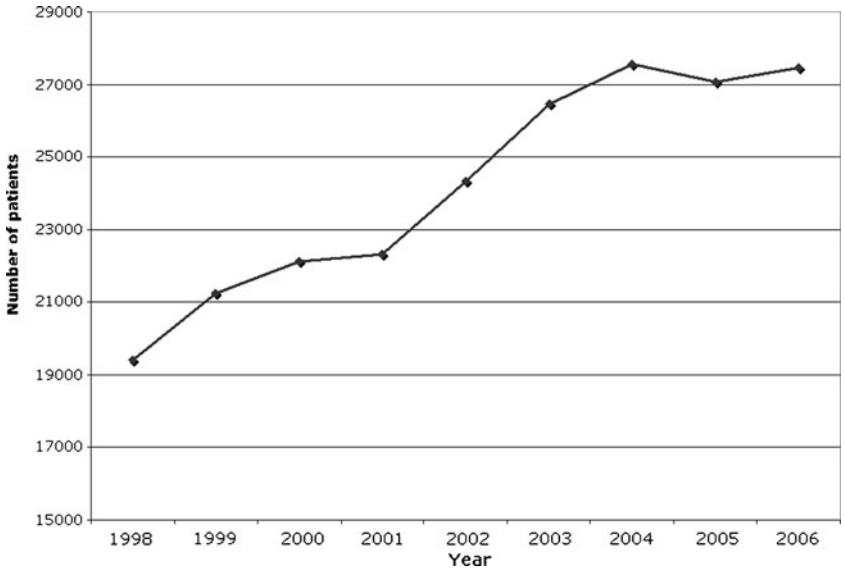

Fig. 1 Number of hospitalizations for cirrhosis from 1998 to 2006 ($p<0.0001$)

during the hospital stay were ascites, hepatorenal syndrome, variceal bleeding, and encephalopathy.

Statistical Analysis

SAS software (SAS Institute, Cary, NC) was used to analyze data. Continuous variables were evaluated using the Shapiro–Wilks test to determine if the sample came from a normally distributed population. Categorical variables were tested with χ^2 analysis. Statistical significance was defined as $p<0.05$.

Univariate predictor variables with a $p<0.05$ were included in the multivariate analysis. The probability of in-hospital mortality for cirrhosis admissions in each hospital volume tertile was calculated using a logistical regression while controlling for confounding variables. Variables assessed by logistic regression included: age, sex, race, primary insurance, admission type, Elixhauser comorbidity score, hospital volume tertile, hospital bed size, and hospital teaching status. Data were then tabulated as hazard ratios and 95% confidence interval, with $p<0.05$ statistically significant.

Results

Demographics

Over the 9-year period, 217,948 admissions with primary diagnosis of cirrhosis were included in this cohort from the NIS. The number of admissions for complications of cirrhosis has increased over time from 19,417 in 1998 to 27,451 in 2006 (Fig. 1), representing a 3.7% annual increase over the 9-year period.

Patient demographics are shown in Table 1. Overall, patients with liver disease were more often white (64.5%), male (63.3%), and from the South (41.3%). Patients were cared for most commonly at large (63.0%), teaching hospitals (48.6%). Many patients (44.3%) had more than three comorbidities. Ascites was the most common complication of cirrhosis for which patients were admitted (41.3%). This was followed by hepatic encephalopathy (34.2%), variceal bleeding (15.2%), and hepatorenal syndrome (2.4%)

Table 2 shows the breakdown of patient demographics by volume. Lower volume centers tended to care for a larger percentage of white patients compared to HV centers (74.3% vs. 65.9% vs. 54.9%, $p<0.0001$). There were more carriers of public insurance at the LV than HV hospitals (63.2% vs. 60.5% vs. 56.4%, $p<0.0001$). HV centers were more likely to be large (86.8%) and teaching (81.5%) hospitals compared to low-volume centers (38.7% vs. 19.5%, $p<0.0001$). Elixhauser comorbidity index did not show a significant difference in the amount of comorbid conditions between different volume centers. The percentage of patients who underwent transjugular intrahepatic portosystemic shunting (TIPS) procedure increased with higher volume centers (1.2% vs. 2.5% vs. 5.4%, $p<0.0001$). There was not as clear a trend with endoscopic variceal repair (LV, 13.0%; MV, 15.4%; HV, 13.4%; $p<0.0001$).

Primary Outcomes

The overall mortality rate for the entire cohort was 9.5%. The unadjusted mortality of patients in HV hospitals was not significantly lower than the lower volume centers (9.5% vs. 9.6% vs. 9.3%, $p=0.08$; Table 3). The mean length of stay increased with increasing volume (5.9 vs. 6.0 vs.

Table 1 Demographics of 217,948 admissions with primary diagnosis of cirrhosis from 1998 to 2006

Characteristic	Patients	Percentage
Mean age ± SD (years)	56.7±12.8	
Male gender	138,048	63.4
Race		
White	110,002	64.5
Black	16,530	9.7
Hispanic	34,871	20.4
Other	9,103	5.3
Payer		
Medicare	80,431	37.0
Medicaid	49,857	23.0
Private	56,305	25.9
Other	30,634	14.1
Hospital region		
Northeast	40,150	18.4
Midwest	37,283	17.1
South	89,944	41.3
West	50,571	23.2
Hospital size		
Small	22,930	10.5
Medium	57,564	26.4
Large	137,287	63.0
Teaching Hospital	105,802	48.6
Elixhauser index		
0	15,023	6.9
1	46,565	21.4
2	59,807	27.4
≥ 3	96,553	44.3
Procedure		
TIPS	6,756	3.1
EGD	27,679	12.7
Endoscopic therapy	30,294	13.9

Table 2 Demographics of 217,948 admissions with primary diagnosis of cirrhosis stratified by volume group

Characteristic	Low volume	Medium volume	High volume	*p* value
Number	71,747	72,748	73,453	
Mean age (years)	58.3	57.1	54.6	<0.0001
Male gender (%)	61.7	63.0	65.3	<0.0001
Race				<0.0001
White (%)	74.3	65.9	54.9	
Black (%)	9.4	9.6	10.0	
Hispanic (%)	11.4	19.2	29.4	
Other (%)	4.9	5.3	5.8	
Payer				<0.0001
Medicare (%)	43.0	38.3	30.0	
Medicaid (%)	20.2	22.2	26.4	
Private (%)	24.3	26.3	27.1	
Other (%)	12.6	13.2	16.5	
Hospital region				<0.0001
Northeast (%)	19.0	17.2	19.0	
Midwest (%)	22.1	14.8	14.5	
South (%)	41.2	41.8	40.8	
West (%)	17.6	26.2	25.6	
Hospital size				0.016
Small (%)	23.6	6.8	1.4	
Medium (%)	37.7	30.2	11.7	
Large (%)	38.7	63.0	86.8	
Hospital type				0.0002
Non-teaching (%)	80.5	55.9	18.5	
Teaching (%)	19.5	44.0	81.5	
Elixhauser index				<0.0001
0 (%)	7.0	6.9	6.8	
1 (%)	21.1	21.5	21.4	
2 (%)	27.4	26.9	28.0	
≥3 (%)	44.5	44.6	43.8	
TIPS (%)	1.2	2.5	5.4	<0.0001
EGD (%)	11.8	13.2	13.1	<0.0001
Endoscopic therapy (%)	13.0	15.4	13.4	<0.0001

TIPS transjugular intrahepatic portosystemic shunt, *EGD* esophagogastricduodenoscopy

7.3 days, $p<0.0001$). In addition, volume appeared to have an impact on hospital cost. Hospital charges were nearly half at lower volume centers ($18,680 and $24,570, respectively) compared to HV centers ($41,440, $p<0.0001$).

In-hospital mortality was also determined based on complications of end-stage liver disease stratified by hospital volume (Table 4). Patients with ascites had the lowest mortality of the four groups, while patients with hepatorenal syndrome suffered the highest mortality. The largest disparity existed in the group with hepatorenal syndrome which showed significantly lower mortality rate in the HV tertile (LV, 45.7%; MV, 45.0%; HV, 40.4%; $p<0.0001$).

To further assess the impact of hospital volume on mortality in cirrhotic patients, logistic regression models were created incorporating all important variables available in the cohort. After controlling for age, gender, race,

Table 3 Unadjusted outcomes for patients hospitalized for cirrhosis

Variables	Low volume	Mid volume	High volume	*p* value
LOS (days)	5.9±7.6	6.0±7.6	7.3±7.6	<0.0001
Hospital charges	$18,680±52,979	$24,570±52,979	$41,440±52,979	<0.0001
In-hospital mortality (%)	9.5	9.6	9.3	0.08

LOS length of stay

Table 4 Mortality rates when at least one complication is present

Complication	Low volume (%)	Middle volume (%)	High volume (%)	*p* value
Ascites	8.5	8.3	7.6	<0.0001
Hepatic encephalopathy	18.1	18.6	18.1	<0.0001
Variceal bleeding	9.0	9.5	10.2	<0.0001
Hepatorenal syndrome	45.7	45.0	40.4	<0.0001

primary insurance, and non-liver comorbidities, admissions at HV centers were associated with decreased in-hospital mortality (Table 5). Patients treated at a HV center experienced lower adjusted mortality when compared to those treated at LV centers (HR 0.88; 95% CI 0.83–0.92). Female gender was also protective (HR 0.85; 95% CI 0.82–0.88). Mortality was increased with black race (HR 1.15; 95% CI 1.09–1.21), Medicaid (HR 1.23; 95% CI 1.17–1.30) and private insurance (HR 1.22; 95% CI 1.16–1.28), and teaching hospitals (HR 1.13; 95% CI 1.08–1.17).

Table 5 Logistic regression of in-hospital mortality for 217,948 patients admitted with cirrhosis

Variables	Hazard ratio	95% CI	*p* value
Age	1.02	1.01–1.02	<0.0001
Female gender	0.85	0.82–0.88	<0.0001
Payer			
Medicare	Ref		
Medicaid	1.23	1.17–1.30	<0.0001
Private	1.22	1.16–1.28	<0.0001
Other	1.41	1.34–1.50	<0.0001
Race			
White	Ref		
Black	1.15	1.09–1.21	<0.0001
Hispanic	0.81	0.77–0.85	<0.0001
Other	1.10	1.03–1.18	0.007
Comorbidities (Elixhauser)			
0	Ref		
1	1.00	0.93–1.08	<0.0001
2	1.02	0.95–1.09	<0.0001
3	1.00	0.94–1.01	<0.0001
Hospital volume			
LV	Ref		
MV	0.97	0.93–1.01	0.18
HV	0.88	0.83–0.92	<0.0001
Hospital bed size			
Small	Ref		
Medium	1.05	0.99–1.12	0.10
Large	1.12	1.05–1.19	0.0002
Teaching hospital	1.13	1.08–1.17	<0.0001

Discussion

Despite an increased length of stay and hospital cost, an in-hospital mortality benefit exists at HV centers specializing in liver disease when treating patients with complications of cirrhosis. Admissions for cirrhosis and associated complications are increasing in the USA by approximately 3.7% per year. Reasons for this increase include increased rates of hepatitis C in the USA, longer waiting list for transplantation, and better access to care. It was our hypothesis that after adjusting for potential confounding variables, in-hospital mortality would be lower in HV centers due to better processes of care at these centers. This may include the availability of surgical interventions, experience and expertise in dealing with adjunctive therapies, and intensive care treatment. In this study, we have shown that an in-hospital mortality benefit exists at HV centers defined as more than 87 admissions per year.

Previous studies have used large databases to help describe trends in patients with cirrhosis in the USA.[1,9,10] We have previously reported the impact of cirrhosis and portal hypertension on outcomes after elective surgery using the NIS.[11] This study is one of the first to show a hospital volume effect in the care of cirrhotic patients. In this study, the in-hospital mortality was improved at HV centers, but only after adjusting for confounding factors. We tried to decipher the differences between the different volume groups to better understand why the outcomes are different. We found that procedures such as TIPS are performed more commonly at HV centers, but did not find the same trend with endoscopic variceal therapy. High-volume centers may have cared for more complex cases evidenced by longer length of stay and higher hospital charges compared to the lower volume groups. Despite this, an in-hospital mortality benefit was attained with treatment at HV centers.

High provider volume has been associated with improved outcomes for various procedures and diagnoses; thus, when possible a volume-based referral has been advocated.[12] To date, the studies focused on volume–outcome relationship in hepatobiliary disorders have focused on surgical procedures.[6,13–15] Very few studies have been performed on medical diseases and admission volume. This is probably because tangible endpoints may not be

easy to define or obtain. Myers et al.[9] found that the subset of cirrhotic patients that present with esophageal variceal bleeding did not benefit from treatment at a high-volume center. Our results did support the volume benefit, but also incorporated a much larger cohort as we included all patients with any complication of cirrhosis.

TIPS is a procedure to lower the pressure in the portal vein and is often used as treatment for ascites or variceal bleeding that is refractory to medical therapy. It was found that in this cohort of patients, a significantly larger percentage received this procedure at the HV centers than at the LV centers. This procedure had the largest difference and may be one of the reasons for the difference in the adjusted mortality rate. Was it performed because the patients were more refractory to medical therapy or was there better access to specialized procedures like TIPS at HV centers? Patients who were treated at HV hospitals for hepatorenal syndrome had a significant survival advantage over those treated at low- and mid-volume centers. It has been postulated that TIPS exerts beneficial effects in patients with HRS. A few small studies have found some benefit; however, larger studies are needed to more clearly define the role of TIPS in HRS.

There are several limitations that should be considered when interpreting the results of this study. One possible limitation of this study is the uncertainty of the procedure codes used in the database. Because the validity of these data relies on administrative data, this could result in a small percentage of improper diagnosis codes. There is a potential for underreporting of events, complications, and diagnoses. However, given the size of the study, it is unlikely that this has an appreciable effect on the data. Another possible limitation is the construction of the NIS database. Each record in the NIS is for a single hospitalization, not for one individual; therefore, a single patient may have had several admissions. It is impossible to link individual patient information with the NIS database; thus, this could have led to bias in our outcomes. Our data contain no information about surgeon specialty, training, experience, or other factors that may impact patient outcome. Our study used population-based data with only limited information on patient and treatment factors, thereby limiting our evaluation of medical factors such as presence of cancer, diabetes, antibiotic use, mechanical ventilation, and prior surgery. Also, this study does not follow up patients after discharge from the hospital, and it is not possible to determine any post-discharge mortality. Other studies have shown good correlation between in-hospital and 30-day mortality.[16] Despite being the largest all-payer database of hospital discharge records in the USA, there is no guarantee that our cohort is representative of local demographics and medical practices which may vary by state and community.

The hospitalizations for cirrhosis are increasing in the USA. Optimizing care and defining hospital processes should be at the forefront of our care of these specialized patients. This report describes a hospital volume–outcome relationship for in-hospital mortality after admission for cirrhosis. While the true reasons for this improvement in outcome are unknown, the volume effect does not apply to only surgical procedures. The role of referral patterns and streamlining this care to high-volume hospitals may provide the best care of this increasing group of hospitalized patients in the USA.

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ORIGINAL ARTICLE

Therapeutic Efficacy of Combined Intraoperative Ablation and Resection for Colorectal Liver Metastases: An International, Multi-institutional Analysis

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Abstract
Background Only 10–25% of patients presenting with colorectal liver metastases (CRLM) are amenable to hepatic resection. By combining resection and ablation, the number of patients eligible for surgery can be expanded. We sought to determine the efficacy of combined resection and ablation for CRLM.
Methods Between 1984 and 2009, 1,425 patients who underwent surgery for CRLM were queried from an international multi-institutional database. Of these, 125 patients underwent resection combined with ablation as the primary mode of treatment.
Results Patients presented with a median of six lesions. The median number of lesions resected was 4; the median number of lesions ablated was 1. At last follow-up, 84 patients (67%) recurred with a median disease-free interval of 15 months. While total number of lesions treated (hazard ratio (HR)=1.47, p=0.23) and number of lesions resected (HR=1.18, p=0.43) did not impact risk of intrahepatic recurrence, the number of lesions ablated did (HR=1.36, p=0.05). Overall 5-year survival was 30%. Survival was not influenced by the number of lesions resected or ablated (both p>0.05).
Conclusion Combined resection and ablation is associated with long-term-survival in a subset of patients; however, recurrence is common. The number of lesions ablated increases risk of intrahepatic recurrence but does not impact overall survival.

Keywords Colorectal cancer · Metastasis · Resection · Ablation · Recurrence · Outcomes

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Introduction

Colorectal cancer is the third most common type of cancer worldwide and the second most common cause of cancer-related death in North America and Western Europe.[1,2] Up to one fourth of patients with colorectal carcinoma have synchronous hepatic metastasis at the time of presentation, while another one in five patients develops metachronous metastasis to the liver during the course of their disease.[3,4] The median survival of patients with unresectable colorectal liver metastasis (CRLM) is 21–24 months.[5,6] When feasible, surgical resection is the gold standard in the treatment of CRLM. Following resection of CRLM, 5-year survival rates of up to 58% have been reported.[7–12]

Unfortunately, only 10–25% of patients with CRLM are amenable to hepatic resection. Many patients are not candidates for resection due to the number and distribution of the hepatic lesions. Due to recent advances in both surgical and, more importantly, medical oncology, the

criteria for resectability of CRLM have expanded.[13] Certain patients can be treated with preoperative chemotherapy in order to decrease the tumor burden in the liver.[14,15] Other patients who may have an anticipated small future liver remnant may be candidates for portal vein embolization.[16,17] Still other patients who have multiple bilateral lesions may be candidates for a two-stage approach.[18] Another therapeutic option for patients with multiple intrahepatic CRLM can involve the combination of hepatic resection with ablation.

By utilizing combined modality approaches such as interstitial ablative techniques simultaneous with hepatic resection, the number of patients eligible for curative intent surgery may be expanded.[13] Most published data on CRLM and ablation have focused on outcomes comparing patients who exclusively underwent either resection versus ablation only.[19–21] The data on combining resection with ablation for the primary treatment of advanced CRLM have been more limited. Specifically, most previous data on combined resection and ablation for primary hepatic treatment of CRLM have come from single-institution series and were limited by small sample sizes ($n<75$ patients).[22–29] In addition, previous studies failed to examine pattern of disease recurrence relative to the number of lesions resected versus ablated.[30] As such, the purpose of the current study was to determine the therapeutic efficacy of combined resection and ablation for CRLM as well as determine factors predictive of survival in a large multicenter cohort of patients. In addition, we sought to identify those factors predictive of recurrence, with a particular emphasis on how the number of lesions ablated impacted the risk of recurrence.

Methods

Data on 1,425 patients who underwent liver directed therapy for CRLM from 1984 to 2009 were indentified from an international, multi-institutional hepatobiliary database (Johns Hopkins Hospital, Baltimore, USA; Maastricht University Medical Centre, Maastricht, the Netherlands; Ospedale Mauriziano Umberto I, Turin, Italy; and Cliniques Universitaires Saint-Luc, Brussels, Belgium). The study was approved by the Institutional Review Boards of the respective institutions. Patients who were operated on with a palliative intent, who had <6 months of follow-up, or who were lost to follow-up were excluded. Only patients who underwent initial hepatic resection combined with simultaneous intraoperative ablation as the primary mode of treatment for CRLM were included; patients who underwent percutaneous ablation were excluded. Only patients who were operated on with curative intent and who had planned complete extirpation/destruction of all known hepatic disease were included. A total of 125 (8.6%) patients were identified and were the subject of the current study.

At the time of surgery, all patients were treated with both resection and ablation during the same operation. At the time of laparotomy, following mobilization of the liver, intraoperative ultrasound was performed to identify and characterize the nature and location of the CRLM. In general, the surgical approach involved resection of the larger/dominant lesions combined with ablation of the lesser disease. Lesions were considered resectable if at least two adjacent hepatic segments could be spared, vascular inflow and outflow could be maintained, and adequate biliary drainage could be preserved while maintaining an adequate liver remnant while achieving an anticipated R0 resection.[13,31] Resection was classified as a minor resection (less than three liver segments) or a major hepatic resection (three or more liver segments).[32] For those CRLM that were considered unresectable, due to location, inadequate future liver remnant, or proximity to vascular structures, ablation was utilized. In general, radiofrequency ablation ($n=101$) was performed using a radiofrequency generator (RITA model 1500X Rita Medical Systems, Inc., Fremont, CA, or RF 2000 with LeVeen; Radio Therapeutics, Mountain View, Corporation, CA) and when applicable a saline-enhanced device (Starburst XL or XLi, Rita Medical Systems, Inc.). A small minority of patients underwent cryoablation (Cryotech LC52000; Candela Laser, Wayland, MA; $n=21$) or microwave ablation (Microsulis Tissue Ablation; Microsulis Medical Limited, Denmead, Hampshire, UK; $n=3$). Ablation of CRLM was performed at the time of laparotomy according to a previously described standardized treatment approach.[33,34] In short, intraoperative ultrasonography was used to place the needle into the lesions to be treated. Ablation was only considered to be curative in intent when the probe could be optimally positioned under intraoperative ultrasound guidance to achieve complete destruction of the tumor and at least a 1-cm zone of normal liver parenchyma. In most cases, postoperative cross-sectional imaging was obtained prior to discharge to ensure adequate ablation and, moreover, to establish a new baseline image for future follow-up.

All patients were followed regularly based on established algorithms at each respective institution. In general, follow-up consisted of outpatient evaluation along with appropriate cross-sectional (i.e., abdominal and thoracic computed tomography scan) imaging as well as the serum tumor marker carcinoembryonic antigen (CEA) every 3–4 months following surgery up to 2 years and then every 6 months thereafter. Recurrence was defined as a lesion that was biopsy-proven recurrent adenocarcinoma or a lesion that was deemed suspicious on cross-sectional imaging in the setting of an elevated CEA level.

Data Collection

In addition to standard demographic data, the following data were collected for each patient: primary tumor characteristics (TNM stage and location of primary tumor); CRLM details (details on hepatic metastasis location, number, and size); tumor marker CEA; treatment-related variables; and presence of extrahepatic metastasis. Data on vital status and recurrence (including locations of recurrence) were noted. Recurrence was defined as intra- or extrahepatic.

Statistical Analyses

Summary statistics were obtained using established methods and presented as percentages or median values. Time to recurrence and survival were estimated using the nonparametric product limit method. Differences in survival were examined using the log-rank test. Factors associated with survival were examined using univariate and multivariate Cox regression analyses. The hazard ratio (HR) and the 95% confidence intervals (CI) were estimated, and a p value of <0.05 was considered significant. All statistical analyses were performed using SPSS version 17.0 (Chicago, IL).

Results

Patient and Tumor Characteristics

The patient and tumor characteristics of the 125 patients who underwent simultaneous resection plus ablation are detailed in Table 1. Over time, the combination of resection plus ablation was utilized in an increasing number of patients after 2000 ($p<0.001$). Among patients with metachronous disease, the median time from the primary tumor diagnosis to the development of liver metastasis was 13.9 months.

With regard to the extent of CRLM, about one half of patients had bilateral disease ($n=59$, 47.2%). The median size of the largest lesion was 3.0 cm. The median number of treated CRLMs was six lesions. A small subset of patients ($n=12$, 9.6%) had extrahepatic metastatic disease at the time of liver-directed surgery. The site of extrahepatic metastasis was pulmonary in most patients ($n=5$, 41.7%).

Overall, 109 individual patients (87.2%) received chemotherapy. Preoperative chemotherapy was administered to 85 (68.0%) patients, whereas 74 (59.2%) patients received adjuvant chemotherapy. Among those subjects for which the exact preoperative chemotherapy regimen was known, 19 (22.4%) patients received monotherapy with 5-fluoruracil, while 26 (30.6%) patients received an oxaliplatin-based

Table 1 Patients and tumor characteristics

Variable	No. of patients (%), $n=125$
Patient characteristics	
Median age (range, years)	59 (29–83)
Sex (male)	80 (64.0)
Primary tumor site	
Location of primary tumor, colon	89 (71.2)
AJCC T stage, T3/T4	99 (79.2)
Lymph node disease	85 (72.6)
Hepatic metastasis	
Presentation, synchronous	74 (59.2)
Size of largest metastasis [median (range), cm]	3.0 (0.4–9.2)
No. of metastasis [median (range)]	6 (2–19)
Location (unilobular)	66 (52.8)
Details of surgical procedure	
Total number of resected tumors [median (range)]	4 (1–16)
Total number of ablated tumors [median (range)]	1 (1–8)
No. of ablated tumors per patient	
1	65 (52.0)
2	22 (17.6)
3	16 (12.8)
≥4	22 (17.6)
Extent of hepatic resection	
Minor hepatectomy	89 (71.2)
Major hepatectomy	36 (28.8)

Table 2 Summary of the combinations of extent of hepatic resections and number of lesions ablated

Extent of hepatic resection	No. of patients (%), n=125			
	No. of lesions ablated per patient			
	1 (n=65)	2 (n=22)	3 (n=16)	≥4 (n=22)
Minor hepatectomy (n=89)	39 (60.0)	16 (72.7)	13 (81.2)	21 (95.5)
Major hepatectomy (n=36)	26 (40.0)	6 (27.3)	3 (18.8)	1 (4.5)

regimen and another 26 (30.6%) patients received an irinotecan-based regimen. Regarding adjuvant chemotherapy, among those cases for which the exact chemotherapy regimen was known, 16 (21.6%) patients received monotherapy with 5-fluoruracil, while 20 (27.0%) and 15 (20.3%) received oxaliplatin- or irinotecan-based regimens, respectively.

Details of Liver-Directed Surgery

At the time of surgery, the majority of patients (n=89, 71.2%) underwent a minor hepatic resection (less than three segments; Table 1). The majority of these patients underwent multiple minor resections. Overall, the median number of lesions resected was 4 (range 1–6), whereas the median number of lesions ablated was 1 (range 1–8). The exact combinations of resection and ablation are summarized in Table 2. Patients who had ablation performed of only one lesion (n=65, 52.0%) were more likely to have undergone a major hepatic resection (n=26, 40.0%) compared with patients who had more than one lesion ablated (n=10, 16.7%, p=0.004).

Postoperative death within 90 days of treatment occurred in two (1.6%) patients, both of whom underwent a major hepatic resection combined with ablation. One patient developed portal vein thrombosis, liver failure, and multisystem organ failure and died on postoperative day 10. The second patient developed fulminant liver failure with associated intractable metabolic acidosis and died on postoperative day 14.

Recurrence and Overall Survival

Following liver-directed surgery, 84 (67.2%) patients recurred after a median disease-free interval of 14.7 months. Overall, 3- and 5-year disease-free survival was 24.2% and 14.7%, respectively. At the time of last follow-up, the pattern of recurrence was intrahepatic only in 43 (34.4%) patients, extrahepatic only in 22 (17.6%) patients, and intra- and extrahepatic in 18 (14.4%) patients. Compared with patients who underwent resection only (n=1,292) or ablation only (n=35), patients who underwent concomitant resection plus ablation had a worse disease-free survival (Fig. 1a). Patients who underwent resection plus ablation, however, also had an increased likelihood of other adverse clinicopathologic factors. Specifically, patients who underwent combined resection and ablation more often presented with synchronous disease, a greater number of hepatic metastases, and bilateral hepatic involvement (all p<0.05). On univariate analysis, patients who had more than one lesion ablated had a higher risk of any-site recurrence compared with patients who had only one lesion ablated

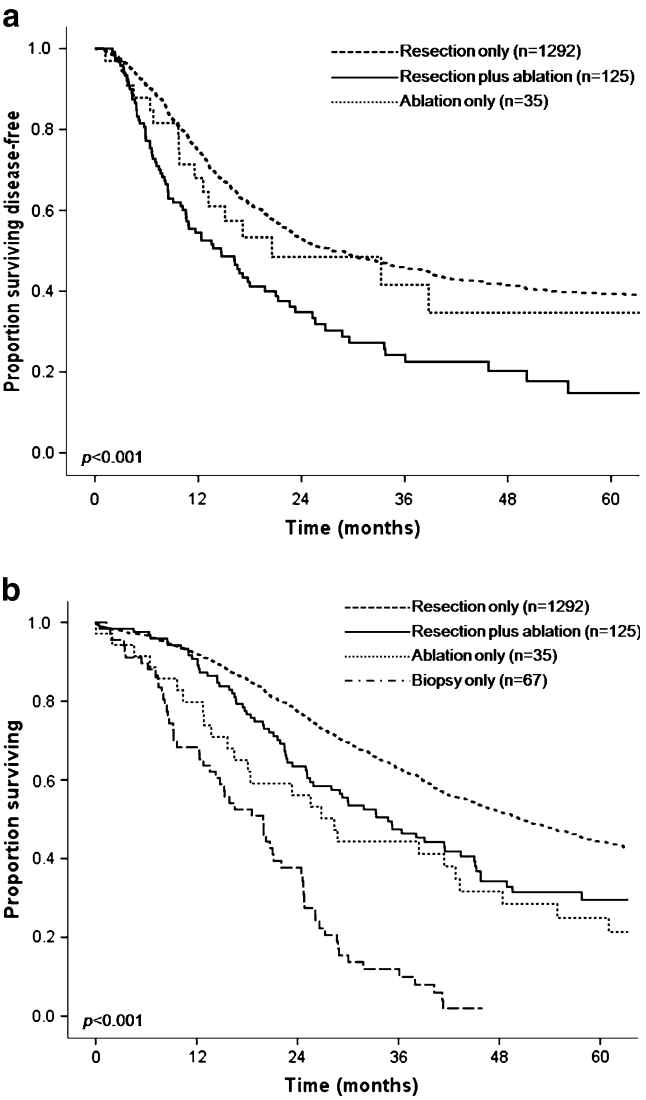


Fig. 1 Kaplan–Meier curves showing disease-free (**a**) and overall survival (**b**) stratified by mode of curative intent surgery: combined resection and ablation versus resection only versus ablation only

(HR=1.14, p=0.04). On multivariate analysis, after controlling for competing risk factors, the number of lesions ablated was no longer associated with any-site recurrence-free survival (p=0.12; Table 3). Moreover, when these analyses were performed excluding the 12 patients who presented with concomitant extrahepatic disease, the same results were observed.

Among all patients who underwent resection plus ablation, the total number of lesions treated (p=0.23) and the number of lesions resected (p=0.43) were not associated with risk of intrahepatic recurrence. In contrast, there was an associated trend with the number of lesions ablated and the risk of intrahepatic recurrence (HR=1.36, p=0.05; Fig. 2). In examining the entire cohort of patients who had four or more lesions (n=192), the subgroup of patients who had four or more lesions treated with resection plus ablation (n=95, 77.6%) had a higher risk of intrahepatic recurrence than patients who had four or more lesions treated by resection only (n=97, HR=1.87, p=0.002). However, among patients who had four or more lesions treated with resection plus ablation, the risk of intrahepatic recurrence was higher among patients who had more than one lesion ablated versus patients who had only one lesion ablated (HR=1.93, p=0.04). In fact, the risk of intrahepatic recurrence was similar among patients who underwent resection alone versus resection plus a single ablation (Fig. 3a).

The overall median survival following liver-directed surgery for patients treated with resection plus ablation was 34.8 months, with a 3- and 5-year overall survival of 47.3% and 29.5%, respectively. While overall survival was better among patients treated with resection only (median 50.5 months), patients who did not have extirpation of their disease (i.e., biopsy only) had a worse survival compared with patients treated with resection plus ablation (19.9 months, p=0.001; Fig. 1b). Among those patients treated with resection plus ablation, the total number of lesions treated, the number of lesions resected, and the number of lesions ablated were not associated with overall survival (all p>0.05; Table 4). Excluding the 12 patients with extrahepatic disease at time of presentation had no difference on these results.

To control for tumor number, a stratified analysis was then performed examining survival of patients who had four or more lesions. Among all patients with four or more lesions (n=192), patients treated with resection only (n=97) were noted to have a similar overall median survival and 5-year survival compared with patients who underwent resection plus ablation (35.6 months (30.3%) versus 31.9 months (25.0%), respectively; both p>0.05). Patients who had four or more lesions treated with resection plus ablation had no difference in 5-year survival whether one lesion was ablated (25.1%) versus more than one lesion ablated (23.7%, p=0.36; Fig. 3b).

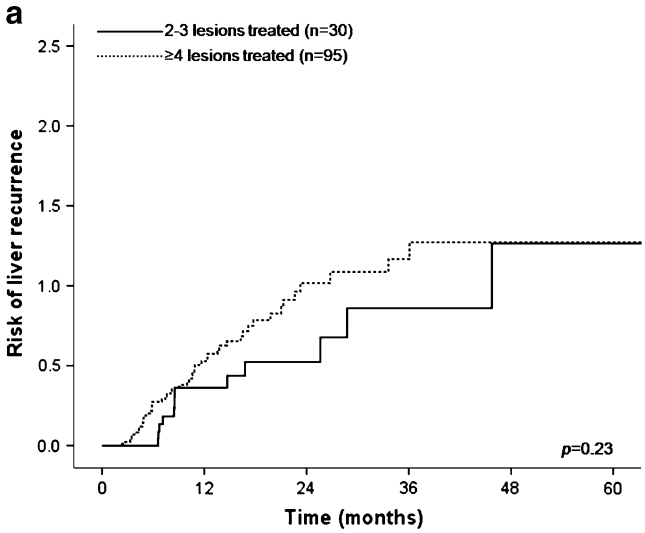
Discussion

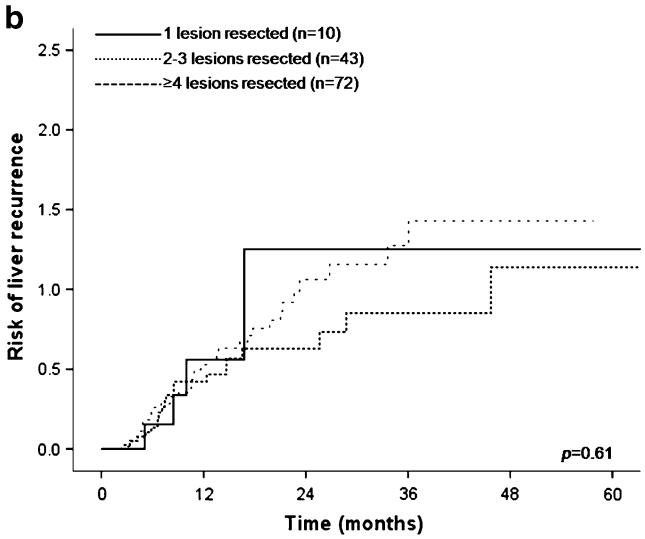
Combining resection with ablation has been proposed as a means to increase the number of patients with CRLM eligible for liver-directed therapy as it may allow the surgeon to remove the bulk of disease while ablating any smaller residual disease. While data on the combination of resection and ablation are important, very limited data exist in the literature. Most studies are single-institution series

Table 3 Univariate and multivariate analyses of factors proposed to be associated with recurrence-free survival

Prognostic factor	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	p value	Hazard ratio	95% CI	p value
Gender (male)	1.12	0.70–1.78	0.65	–	–	–
Location of primary tumor (rectum)	1.12	0.70–1.78	0.65	–	–	–
AJCC T stage (T3 or T4)	1.08	0.55–1.10	0.83	–	–	–
Node-positive primary tumor	1.73	1.03–2.91	0.040	1.86	1.07–3.24	0.029
Serum CEA >200 ng/mL	2.00	0.86–4.68	0.11	1.97	0.82–4.74	0.13
Synchronous presentation	1.23	0.79–1.91	0.37	–	–	–
Bilobar disease	1.02	0.66–1.58	0.91	–	–	–
Size of largest lesion	1.00	0.88–1.12	0.96	–	–	–
No. of CRLM resected	1.05	0.98–1.13	0.20	–	–	–
No. of CRLM ablated	1.14	1.00–1.29	0.043	1.11	0.97–1.27	0.12
Total no. of CRLM treated[a]	1.05	0.99–1.11	0.072	–	–	–
Extent of hepatic resection	1.49	0.90–2.43	0.12	1.33	0.76–2.30	0.32
Presence of concomitant extrahepatic disease	1.83	0.87–3.84	0.11	1.59	0.73–3.47	0.24

[a] Not included in multivariate analysis due to collinearity





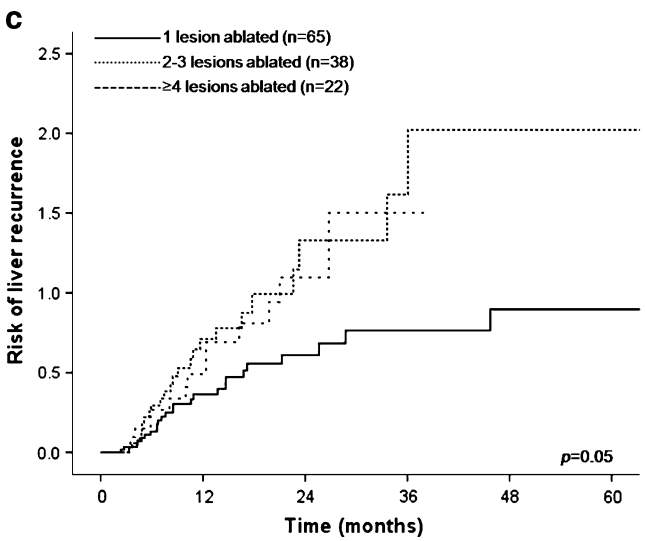
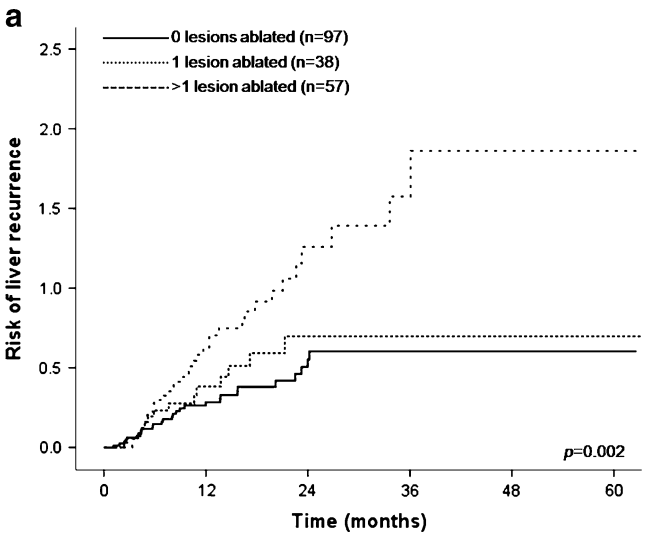


Fig. 2 Hazard curves showing the risk of developing an intrahepatic recurrence, stratified by total number of lesions treated (**a**), total number of lesions resected (**b**), and total number of lesions ablated (**c**)

comprising small numbers of patients.[22–29] Our data show that combined resection plus ablation is a relatively infrequent therapeutic approach to patients with CRLM (8.6%). The reason for this is probably multifactorial, but undoubtedly reflects, in part, the authors' collective inclination to resect CRLM when possible. The current study is, to our knowledge, one of the largest series of patients treated with combined resection and ablation specifically for CRLM. Perhaps more importantly, the current study not only examined recurrence and overall survival but also investigated the impact of ablation number on outcome.[30] In treating patients with combined resection and ablation, the relative impact of an increasing number of ablations has not been well defined. Our data suggest that an increasing number of ablations increased the risk of intrahepatic recurrence, but did not impact overall survival.



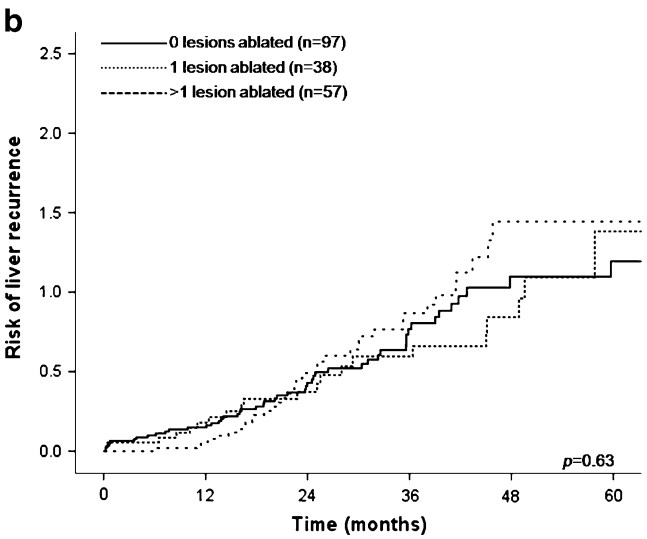


Fig. 3 Hazard curves showing the risk of intrahepatic recurrence (**a**) and disease-specific death (**b**) among patients with four or more lesions treated stratified by number of lesions ablated

Table 4 Univariate analyses of factors proposed to be associated with overall survival

Prognostic factor	Univariate analysis		
	Hazard ratio	95% CI	*p* value
Gender (male)	0.84	0.53–1.34	0.47
Location of primary tumor (rectum)	1.22	0.74–2.01	0.50
AJCC T stage (T3 or T4)	1.07	0.51–2.23	0.87
Node-positive primary tumor	1.71	0.98–3.00	0.060
Serum CEA >200 ng/mL	0.48	0.12–1.93	0.30
Synchronous presentation	0.83	0.52–1.31	0.43
Bilobar disease	1.12	0.70–1.79	0.42
Size of largest lesion	1.04	0.92–1.19	0.64
Number of CRLM resected	1.01	0.93–1.09	0.52
Number of CRLM ablated	1.12	0.99–1.27	0.080
Total number of CRLM treated	1.03	0.97–1.08	0.38
Extent of hepatic resection	1.54	0.90–2.63	0.11
Presence of concomitant extrahepatic disease	1.48	0.68–3.25	0.32

De Haas et al.[35] had previously reported that R1 margin status following surgical resection of CRLM was associated with risk of intrahepatic recurrence, but not disease-specific death. The current data are important because for the first time, we report that – analogous to data on R1 resection of CRLM – the number of ablations for CRLM is associated with an increased risk of intrahepatic recurrence, but not a worse survival.

There has been concern that surgery for extensive hepatic disease may be associated with increased perioperative mortality. Previous publications, however, have shown that ablation combined with hepatic resection does not necessarily increase perioperative mortality.[33,36] Resection plus ablation is generally well tolerated and comparable with the mortality associated with resection alone.[29,33] Our data would corroborate the low mortality associated with resection plus ablation as our reported postoperative mortality was only 1.6%. However, it is important to note that two patients did die following resection plus ablation. In both cases, ablation was combined with a major hepatic resection (i.e., right hepatectomy) and the patients succumbed to liver failure. Other investigators have similarly reported death secondary to liver failure in patients undergoing resection combined with ablation.[28,33,37] Similar to considering a major extended hepatic resection, when combining resection of the right liver with ablation of the left liver, the anticipated size of the *viable* remnant liver must be considered in light of the risk of possible liver insufficiency.

In the past, four or more colorectal liver metastases were considered a relative contraindication to surgery.[38,39] Now, few surgeons would consider tumor number alone to be a contraindication to surgery.[40] Managing patients with multiple hepatic metastases can be challenging, and it is in this subset of patients where combined therapy with resection plus ablation is most applicable. Although patients treated with combined resection plus ablation have a worse long-term survival compared with patients treated with resection alone, these patients also had a greater number of hepatic metastases as well as an increased risk of other adverse clinicopathologic factors. As such, comparison of these groups may be inappropriate and lead to unreliable causal inferences as the two groups are inherently not comparable.[41] Therefore, to help control for tumor number, a stratified analysis was performed to examine survival. Among all patients with four or more lesions, patients treated with resection only had a similar 5-year survival compared with patients who were treated with resection plus ablation. Perhaps more interestingly, we found that among patients who had four or more lesions treated with resection plus ablation, there was no difference in survival whether one lesion was ablated versus more than one lesion ablated. As such, when planning the surgical approach for patients with multiple lesions, the relative number of lesions to be resected versus ablated does not appear to impact overall survival. Rather, in patients with multiple tumors and advanced CRLM, the inherent tumor biology of the underlying disease is more likely to be the important factor dictating long-term outcome.

Recurrence among patients who underwent resection combined with ablation was common (actuarial 5-year disease-free survival, 14.7%). While on multivariate analysis the number of lesions treated or ablated was not associated with any-site recurrence, the number of lesions ablated did impact the risk of intrahepatic recurrence. Interestingly, among patients who had four or more lesions treated with resection plus ablation, patients who had more

than one lesion ablated had nearly a twofold increased risk of intrahepatic recurrence compared with patients who had only one lesion ablated. Other investigators have suggested that the use of ablation relative to resection may increase the risk of intrahepatic recurrence while not impacting overall survival.[10] The current study provides data that specifically define the relation of multiple ablations with the increased risk of intrahepatic recurrence.

The current study had several limitations. The current study did not specifically examine the rate of "true" local intrahepatic failure at the site of ablation. Rather, we only reported the incidence of "any-site" intrahepatic recurrence. The local recurrence rate of ablation has previously been well documented.[42–45] Given the multicenter, international nature of the current study, a re-review of cross-sectional imaging to document "true" local recurrence was not feasible. In addition, the goal of the current study was not to determine rates of local recurrence following ablation. As with virtually all retrospective analyses, selection criteria and surgical technique could not be standardized. However, the international, multi-institutional nature of our study instead provides a comprehensive "real-world" generalizeable experience of how resection combined with ablation is being used at major hepatobiliary centers worldwide.

In conclusion, although resection remains the gold standard treatment in most patients, a subset of patients with CRLM may benefit from hepatic resection and simultaneous ablation. While patients may derive a long-term survival benefit, recurrence is common. The number of ablations performed did not appear to impact long-term survival, but an increasing number of ablations were associated with an increased risk of intrahepatic recurrence.

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ORIGINAL ARTICLE

The Cholecystokin Provocation HIDA Test: Recreation of Symptoms is Superior to Ejection Fraction in Predicting Medium-Term Outcomes

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Abstract
Background The ^{99m} technetium labelled hepato imino diacetic acid (HIDA) scan is widely used in the investigation of patients with typical biliary pain but whose trans-abdominal ultrasound scan (US) is normal. Although the standard measure by which the HIDA scan is deemed positive is the presence of an ejection fraction (EF) of <35% following provocation with cholecystokinin (CCK), there still remains debate as to the usefulness of this measure. The aim of this study was to compare the roles of EF and symptom provocation following CCK infusion in relation to the outcome following laparoscopic cholecystectomy (LC). More specifically, we aimed to review the resolution of symptoms for our significant population of patients with normal HIDA scan EFs for whom surgery has traditionally been deemed inappropriate.
Patients and Methods All patients undergoing LC for a presumed diagnosis of biliary dyskinesia were identified from a prospectively maintained database. Data were collected regarding pre-operative symptoms, EF and symptom provocation during the CCK HIDA scan, histological findings, early symptomatic outcome, and medium-term follow-up.
Results During the period from March 2006 to October 2009, 42 patients with biliary symptoms but a negative US were referred for assessment by a single surgeon. There were 31 women and 11 men with a mean age of 39.0±12.6 years. All underwent a CCK HIDA scan of which 17 were positive with an EF <35% and the remaining 25 were negative. All patients reported recreation of symptoms following administration of CCK. All gallbladders were delivered intact for histological assessment and all but one showed evidence of chronic cholecystitis. At each postoperative visit, approximately 2 weeks following the procedure, all patients reported resolution of symptoms. After a mean of 18.7±12.1 months symptom recurrence had been noted in only one of 42 (2.4%).
Conclusions The CCK HIDA scan is a useful study in the investigation of acalcalous cholecystitis; however, we would suggest that recreation of symptoms following CCK provocation is superior to EF for the identification of underlying chronic cholecystitis. Indeed, a normal gallbladder ejection fraction does not necessarily rule out a biliary aetiology of symptoms for this patient population.

Keywords HIDA scan · Provocation test · Acacaluos cholecystitis · Cholecystectomy

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Introduction

Biliary dyskinesia is characterised by the presence of typical biliary pain in the absence of cholelithiasis on ultrasound examination of the gallbladder, the condition being defined by the Rome III criteria.[1] The prevalence of the condition is uncertain, varying in the literature from 2.4% to 20.7%.[2–4]

The standard means of diagnosis of biliary dyskinesia is the cholecystokinin ^{99m} technetium labelled hepato imino diacetic acid (CCK HIDA) scan. The technique of HIDA scanning was developed in 1977[5,6] and the concept of CCK provocation with calculation of an ejection fraction

(EF) was reported in 1981 by Krishnamurthy et al.[7] The principle behind the investigation is that the gallbladder contracts in response to cholecystokinin and that the rate of excretion of the radiolabelled HIDA is reduced in the presence of gallbladder dyskinesia.

There has been controversy as to methods used in the performance of the CCK HIDA scan in terms of dose and duration of infusion of the CCK,[8] and whether CCK is superior to a fatty meal in inducing gallbladder contraction.[9] The presently accepted EF fraction regarded as abnormal is also controversial. In Krishnamuthy's original study, the six asymptomatic patients had EFs varying from 0% to 78%.[7] The value of an EF <40%, which is used in the Rome III definition, was calculated on the basis of an assessment of only 40 asymptomatic individuals.[10] Furthermore, Zeissman et al. noted in their own study that 35% of asymptomatic patients had an EF <45%.[11]

Despite a body of evidence in support of CCK HIDA,[10,12–32] a number of authors have claimed that the EF is poor in predicting symptomatic outcome following cholecystectomy.[33–45] In addition to the variation in dose and administration, many of the current studies are of poor methodology and there is currently only one randomised controlled trial addressing this topic.

Given these difficulties with CCK HIDA, the aim of this study was to compare the predictive value of recreation of symptoms following provocation with CCK and EF in patients with presumed biliary dyskinesia, regardless of their calculated EF. Symptomatic relief was then determined in terms of short- and medium-term symptomatic outcome.

Methods

All consecutive patients referred to a single surgeon for consideration of laparoscopic cholecystectomy in whom a diagnosis of biliary dyskinesia had been established based on the Rome II criteria were entered into a prospectively maintained database.[1] Approval was obtained from the institutional review board prior to commencement of the study.

All patients underwent a CCK HIDA according to a standard protocol. Patients were administered 5.5 mCi of technetium 99 m intravenously. The biliary system was then imaged for 60 min following which 0.02 μg/Kg of Sincalide (Kinevac®, Bracco Diagnostics Inc., New Brunswick, New Jersey) was infused over a 30-min period. There then followed an additional 30 min of imaging. The ejection fraction was noted for each patient.

Following the procedure, patients were reviewed in the outpatient clinic and were specifically questioned as to whether or not the CCK injection recreated their typical pain.

All patients in whom their discomfort was recreated with the CCK HIDA underwent laparoscopic cholecystectomy with the gallbladders being extracted intact to avoid bile spillage. A histological examination of all gallbladders was performed to evaluate for the presence of chronic cholecystitis, gallstones, and additional pathological findings. There were no intra-operative or postoperative complications.

Patients were seen for a postoperative visit in the outpatient clinic at approximately 2 weeks to determine early symptomatic outcome. Subsequently, these patients were discharged from follow-up. A telephone consultation was then performed by the senior surgeon (SR) to determine medium-term follow-up.

The results of EF and CCK symptom provocation are presented as proportions (%) and the role of the two forms of assessment in predicting biliary dyskinesia was explored by comparison of sensitivity, specificity, positive (PPV), and negative predictive values (NPV) for the two groups. All statistical analyses were performed using the SPSS for Windows™ version 14.0 (SPSS Inc, Chicago, IL, USA), and statistical significance was taken at the 5% level.

Results

During the period of March 2006 to October 2009, 42 patients with biliary symptoms were referred for assessment by a single surgeon. All individuals had undergone transabdominal ultrasound which had not shown evidence of gallstones or other biliary pathology.

There were 31 (73.8%) women and 11 (26.2%) men with a mean age of 39.0±12.6 years.

All patients underwent a CCK HIDA scan according to a standard protocol of which 17 were positive based on an EF of <35%. Of note, the remaining 25 patients had normal studies based on this ejection fraction. Following the CCK HIDA scan, patients were reviewed in the outpatient clinic by the senior surgeon and all patients reported recreation of their symptoms following administration of CCK.

On the basis of symptom recreation, all 42 patients underwent laparoscopic cholecystectomy at which gallbladders were delivered intact to allow histological assessment and inspection of the bile for the presence of small calculi. Chronic cholecystitis was confirmed in 41 (98%) patients. The one exception was a patient who had adenomyomatosis as the sole pathological finding. Small calculi were identified in three (7%) and cholesterolosis in eight (19%) of patients.

At the postoperative visit in the outpatient clinic, all patients reported complete resolution of their symptoms. Telephone follow-up was conducted at a mean of 18.7± 12.1 months and symptom recurrence had been noted in only one patient (2.4%). This individual had only minor

symptoms and had not seen his family practitioner or sought a surgical consultation.

The sensitivity, specificity, PPV, and NPV for EF were 41%, 100%, 100%, and 4%, respectively, in predicting chronic cholecystitis. The sensitivity and PPV for symptom recreation following CCK were 100% and 98%; however, as all patients reported an exacerbation of symptoms following the CCK HIDA, it was not possible to calculate the sensitivity or NPV and thus a full comparison of EF and CCK provocation was not possible.

The fact that all patients reported complete resolution of symptoms in the early post-operative phase, with only one patient reporting symptom recurrence, prevented further comparison of the desired parameters for both test parameters.

Discussion

The primary finding of the study is that replication of symptoms following injection of CCK as part of a CCK HIDA scan appears to be superior to EF in predicting symptomatic improvement following cholecystectomy the presence of biliary pathology. The data would suggest that a low EF is predictive of the presence of biliary dyskinesia and associated histological chronic cholecystitis but that a so-called normal fraction is not reliable as all but one of the patients with an EF >35% had chronic inflammation evident on histological examination of their gallbladders.

While there is significant data in support of the use of EF in predicting outcome in patients with biliary dyskinesia,[10,12–32] there is also a sizeable volume of literature reporting the contrary[33–45] and thus there is need for some form of modification to the investigation to improve the diagnostic accuracy.

The use of symptom recreation is not a new concept. The CCK provocation test without a concomitant HIDA scan which involved infusion of CCK and assessment of symptom recreation was widely used prior to the widespread availability of HIDA. However, despite a large placebo-controlled crossover study with long-term follow-up supporting its use,[46] the literature, in a similar manner as it now is for CCK HIDA, was conflicting[38,47] and it was superseded by CCK HIDA. It was claimed that there was both subject and assessor bias and that the CCK would be stimulating organs other than the gallbladder and thus it was uncertain whether there was true symptom recreation.[38] The results of this study in which every patient fitting a clinical diagnosis of biliary dyskinesia and had symptom provocation with CCK regardless of EF would suggest that this test requires formal re-evaluation in a larger cohort of patients. If the provocation step is the most crucial, it may be reasonable that a fatty meal test could be used instead of CCK, there currently being limited recent literature in support of this application.[48,49] Another possibility, if a fatty meal were adequate, may be to omit the HIDA altogether and simply assess symptom recreation following ingestion of a fatty meal as this would represent a significant financial saving since the cost of a CCK HIDA scan is approximately $2,000 and would avoid unnecessary exposure to radiation.

The findings of additional biliary pathologies in patients undergoing cholecystectomy have been documented in previously reported series, with cholelithiasis seen in up to 5–15%[14,27,42] and cholesterolosis in 15% of patients.[43] It is uncertain as to the relationship between biliary dyskinesia and the presence of calculi or cholesterolosis. Velanovich[50] examined the bile of patients with an EF <35%, comparing it to the bile of patients with known gallstones and noted the presence of crystals in the bile or gallbladder wall, with no difference between the groups. The author hypothesised that biliary dyskinesia may be at one end of a spectrum of biliary disease with calculi developing later in its course of the process. Krishnamurthy et al. attempted to investigate the natural history of biliary dyskinesia by performing sequential HIDA scans in 27 patients with suspected acalculous cholecystitis.[51] They found that the mean EF reduced over time in patients with biliary dyskinesia but they did not identify the development of gallstones on ultrasound evaluation of the gallbladder of this cohort of patients.

The only patient in this series with no evidence of chronic cholecystitis on histopathological examination of the resected gallbladder demonstrated features of adenomyomatosis. This is a benign condition characterised by mucosal proliferation with Rokitansky–Aschoff sinus formation and is identified in 2–5% of gallbladder specimens.[52] It has been said that it is an asymptomatic condition but as it is seen in a significant proportion of resected gallbladders, it may be part of the spectrum of gallstone disease and it has, as in the current series, been reported to be the only pathological finding in patients with typical biliary pain.[53] Despite it being recognised as a benign condition, epithelial metaplasia may be seen, in particular when the disease demonstrates a segmental distribution and affects the fundal area.[54] For this reason, gallbladders demonstrating features of adenomyomatosis are often resected to prevent the development of neoplasia.

Conclusion

The CCK HIDA scan is a useful study in the investigation of acalculous cholecystitis. We would suggest that it be performed for all patients with symptoms typical of biliary dyskinesia in whom an ultrasound scan has failed

to demonstrate gallstones. Furthermore, this study has demonstrated that recreation of symptoms following provocation with an injection of CCK is superior to EF for the identification of underlying chronic cholecystitis.

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ORIGINAL ARTICLE

Solid Pseudopapillary Tumors of the Pancreas. Clinical Features, Surgical Outcomes, and Long-Term Survival in 45 Consecutive Patients from a Single Center

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Abstract
Background Solid pseudopapillary tumors of the pancreas (SPT) are rare neoplasms, and the natural history is poorly defined. The aim of this study was to define the natural history and compare patient and tumor factors between patients with malignant and non-malignant disease.
Methods Data for all patients with SPT who underwent surgical exploration at MSKCC between 1987 and 2009 were collected and analyzed. Patient, tumor, treatment, and survival variables were examined. Malignant tumors were defined as any tumor that was locally unresectable, metastatic, or recurrent. Differences between groups were analyzed by Fisher's exact, chi-squared, Wilcoxon, and log-rank tests.
Results Forty-five patients had an SPT during the study period. Median age was 38 years (10–63) and 38 (84%) were women. At the time of diagnosis, 38 were symptomatic, with the most common symptom being abdominal pain (n=35). The most frequent imaging characteristic was a solid and cystic tumor (n=29), most commonly located in the tail of the pancreas (n=23). Resection of the primary tumor (n=41) (41/2,919=1.4% of all resections) included distal pancreatectomy in 26, pancreatoduodenectomy in 11, central pancreatectomy in two, and enucleation in two. Nine patients had malignant disease defined by a locally unresectable tumor in three, liver metastases in three, locally unresectable tumor and liver metastases in one, local recurrence and liver metastases in one, and local recurrence in another. Patients with malignant disease presented with larger tumors (7.8 vs. 4.2 cm) (p<0.005). After median follow-up of 44 months, 34 patients were without evidence of disease, four patients were alive with disease, three patients died of disease, and four patients died of other causes.
Conclusions These results demonstrate that SPT occurs in young women, and the majority of patients will experience long-term survival following resection. The only feature associated with malignant disease was tumor size at presentation. The majority of patients are alive at last follow-up, and a low percentage experienced disease recurrence or death from disease.

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Keywords Solid pseudopapillary tumor · Surgical treatment · Survival

Introduction

Solid pseudopapillary tumors of the pancreas (SPT) are uncommon neoplasms with low malignant potential and which most frequently occur in young women.[1] Solid pseudopapillary tumors constitute 1–3% of pancreatic neoplasms and 10–15% of cystic tumors of the pancreas.[2,3]

The first presumed case of SPT was reported by Lichtenstein[4] in 1934. However, recent analysis of photo-

micrographs and gross pathology from this case reveal a lesion more consistent with a mucinous cystic neoplasm of the pancreas.[5] Because of this, most consider the first documented report of this disease to have been from Frantz in 1959.[6] Since that report, multiple small case series have been reported in the literature, and until this communication, no more than 1,000 cases have been communicated in the English literature.[1,7–12]

The natural history of these lesions has not been clearly defined. Following resection, recurrence of disease has been reported as uncommon; however, metastatic disease to regional lymph nodes and distant metastases to the liver have been reported. Long-term survival is to be expected even in the setting of metastatic disease; however, more biologically aggressive variants have been reported.[8,13,14]

The primary objective of this study was to further define the natural history of this uncommon neoplasm in patients who underwent surgical exploration at the Memorial Sloan-Kettering Cancer Center (MSKCC). Comparisons between patients with malignant disease and non-malignant disease were performed.

Material and Methods

Subjects and Data Collection

A prospectively maintained pancreatic database was queried for all patients who underwent surgical exploration for the diagnosis of SPT between 1987 and 2009. Patients were included whether or not they were resected. Approximately 20 patients previously communicated were included in this study.[13] Patient, tumor, and treatment-related variables were retrieved from the database and confirmed by chart review. Approval for this review was obtained from the Memorial Sloan-Kettering Cancer Center's Institutional Review Board.

Surgical Approach

Pancreatectomy was performed by either open or laparoscopic methods. Operative time, blood loss, and the requirement for blood transfusion were recorded. Postoperative complications were identified and recorded. Operative mortality was defined as death within 90 days of operation.[15]

Patient status was categorized at the time of last follow-up as follows: no evidence of disease, alive with disease, dead of disease (DOD), surgical mortality, or dead of other causes. The follow-up time was defined as the interval between the date of first operation and the date of last follow-up or death. Only DOD was considered an event in the analysis of disease-specific survival.

Pathologic Examination

Histopathology was reviewed at a monthly conference attended by surgeons and pathologists. All patients had hematoxylin and eosin slides and immunohistochemical stains that ruled out a ductal, acinar, or neuroendocrine tumors of the pancreas. Pathologic factors identified and recorded included tumor diameter, operative margin (positive or negative), presence of vascular or perineural invasion, the number of lymph nodes pathologically assessed, the number of positive lymph nodes, and immunohistochemistry analyses.

Malignant vs. Non-malignant Disease

Because SPT has been classically defined as a benign disease with malignant potential, an analysis comparing those patients with "malignant" disease from those with "non-malignant" disease was performed. Malignant disease was defined as locally unresectable tumor with invasion of portal/mesenteric vessels, metastatic disease to regional or distant sites, or recurrence of disease following resection.

Statistical Analysis

Differences between patients with malignant and non-malignant disease were assessed with Fisher's exact test (for binary variables) and chi-squared test (for polytomous variables) for categorical variables and Wilcoxon test for continuous variables. Survival curves were constructed by the Kaplan–Meier method and were compared using the log-rank test. All tests were two-sided, and statistical significance was achieved at $p < 0.05$. Statistical analysis was performed with SAS version 9.2.

Results

Patients' Characteristics

Between 1987 and 2009, 45 patients underwent surgical exploration for SPT. The median age at the time of presentation was 38 years (10–63), and 38 patients (84%) were women (Table 1). At the time of diagnosis, 38 of the 45 patients (84%) were symptomatic. The most common symptoms were abdominal pain in 35 patients, nausea/vomiting in 15, weight loss in eight, jaundice in three, back pain in two, fever in one, constipation in one, diarrhea in one, and fatigue in one.

Table 1 Demographic characteristics and tumor's information

Clinical characteristics	*n*=45
Gender	
Female	38
Age of presentation (years)	
Median	38
Range	10–63
Symptomatic	38 (84%)
Abdominal pain	35
Nausea/vomiting	15
Weight loss	8
Jaundice	3
Asymptomatic	7
Tumor characteristics	
Localization	
Head	15
Body	7
Tail	23
Size cm (*N*=43)	
Median	4.9
Range	1.4–20
Radiographic appearance (*N*=44)	
Solid cystic	29
Solid	12
Cystic	3
Others characteristics[a]	
Calcifications	7
Invasion of portal/mesenteric vessels	4
Liver metastases	4
Main pancreatic duct dilatation	2
Bile duct dilatation	2
Adjacent organs' compromise	2
Lymph node involvement	1

[a] Some patients had more than one factor

Preoperative Evaluation

Preoperative serum markers were obtained in seven patients (CA 19-9, CEA) and were normal. The most common preoperative imaging study was computed tomography (CT) which was obtained in 43 patients; MRI was obtained in 15 patients and endoscopic ultrasound in eight. Imaging characteristics could be determined in 44 patients and were consistent with a solid and cystic tumor in 29 patients, a solid tumor in 12 patients, and a cystic tumor in three patients. Calcifications were present in seven of 44 patients (16%) and dilation of the main pancreatic duct in two patients. Radiographic findings suspicious of malignant disease were present in nine patients (20%) with portal/mesenteric vessel invasion in four patients, liver metastases in three patients, invasion of adjacent organs and liver metastases in one patient, and invasion of adjacent organs and lymph node involvement in one patient (Table 1).

Preoperative tissue biopsy was obtained in 18 patients (transperitoneal biopsy in 10 patients and endoscopic biopsy in eight patients). In 10 patients, pathologic analysis confirmed the diagnosis of SPT (56% diagnostic accuracy); in three patients, neuroendocrine tumor was suspected, three had non-diagnostic biopsies, one was diagnosed as a mucinous tumor, and one was an undifferentiated neoplasm.

Surgical Treatment

Resection of the primary tumor was performed in 41 patients, and four patients were locally unresectable. Resection included distal pancreatectomy in 26 patients, pancreatoduodenectomy in 11, central pancreatectomy in two, and enucleation in two. Three patients underwent resection of hepatic metastases (during the resection of the primary tumor in one and in a second surgery in two), and a single patient underwent resection of local recurrence.

Postoperative complications occurred in ten out of 45 patients (22.2%). Complications included fever without cause (two), urinary tract infection (two), abdominal abscess (three), pancreatitis (one), portal vein thrombosis (one), pancreatic fistula (one), and transient atrial fibrillation (one). There was no mortality.

Pathologic Examination

The lesion was located in the head of the pancreas in 15 patients (33%), in the body in seven (16%), and in the tail in 23 (51%). The median size of the tumor was 4.9 cm (range, 1.4–20 cm). Final pathology confirmed the diagnosis of SPT in all patients (Figs. 1 and 2). Within the group of 41 resected patients, 32 had a complete resection (R0 resection), seven had a positive microscopic margin (R1 resection), and two patients had macroscopic residual disease (R2 resection). The median number of lymph nodes pathologically assessed was six (range 0–23 lymph nodes), and all examined lymph nodes were negative for SPT.

Immunohistochemical stains were performed in selected cases. CD56 was positive in 15 of 15, CD10 was positive in 13 of 13, beta-catenin was positive in 11 of 11, vimentin was positive in 22 out of 24, synaptophysin was positive in 14 out of 23, alpha-1-antitrypsin was positive in 12 out of 20, antichymotrypsin was positive in six out of 26, keratin was positive in four out of 12 patients, enolase was positive in one out three patients, and chromogranin was positive in one out of 27 patients.

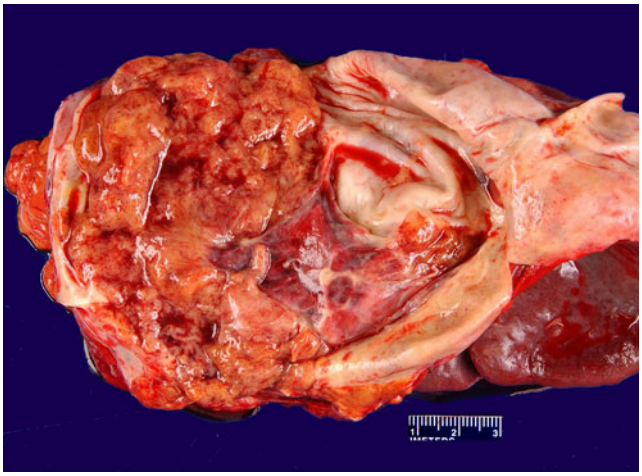

Fig. 1 Gross appearance of resected solid pseudopapillary tumor of the pancreas

Malignant vs. Non-malignant Disease

Nine patients presented a malignant disease. Three patients presented locally advanced tumors with invasion of portal/mesenteric vessels that precluded resection, three patients presented liver metastases, two patients presented local–regional recurrence after resection (with concurrent liver metastases in one case), and one patient presented a locally advanced tumor with invasion of portal/mesenteric vessels that precluded resection and liver metastases. There were no patients with positive lymph nodes. Table 2 compares and summarizes the characteristics between patients with malignant and non-malignant disease.

Follow-up and Survival

The median follow-up was 44 months (range 1–250 months). At the time of last follow-up, 34 patients were without evidence of disease (one of them had recurrence and it was resected), four patients were alive with disease (two patients with locally advanced diseased not resected, one with locally advanced disease and liver metastases not resected, and other with synchronous liver metastases resected at MSKCC and liver recurrence treated with chemoembolization), three patients died of SPT (one not resected due to locally advanced disease, one with liver recurrence after complete resection of the primary tumor and liver metastases, and other with resection of the primary tumor and progression of liver metastases), and four patients died of other causes. Disease-specific survival is presented in Fig. 3. The median survival of all patients was 44 months (1–250 months), and the median free recurrence survival was 40 months (1–250 months).

Discussion

Solid pseudopapillary tumors of the pancreas are uncommon malignancies that usually affect young women.[1,8,9,11] Most reported series describe a disease process that is incidentally discovered and is resectable at the time of presentation and following resection results in long-term survival. A more aggressive course has been reported in approximately 10% to 20% of patients with locally advanced tumors at the time of presentation, distant metastases, and local or distant recurrence.[1,5,14] The current study supports the previously

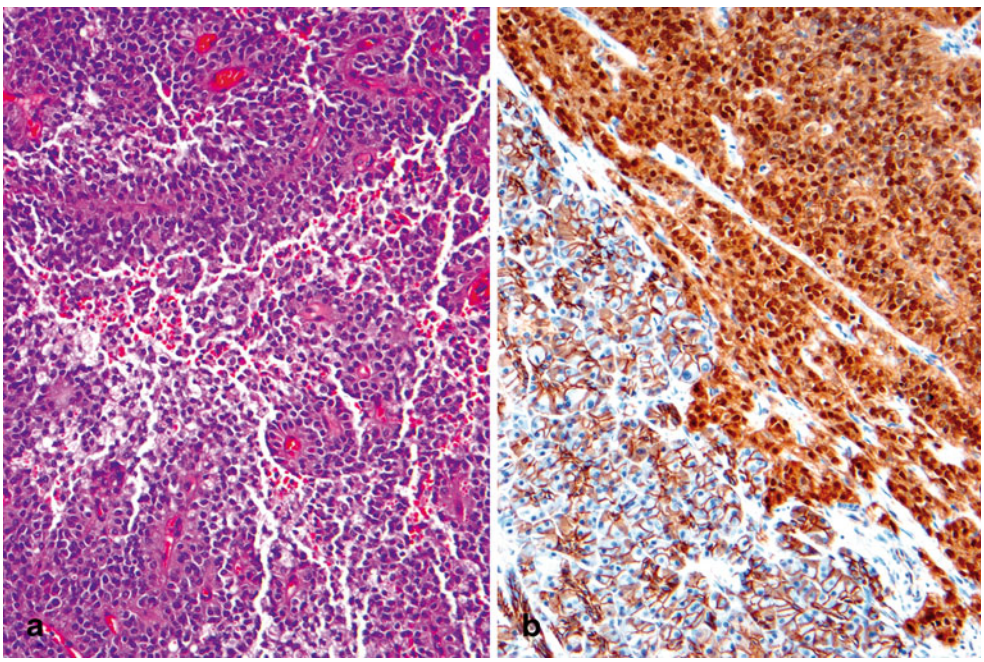

Fig. 2 **a** Distinctive morphologic appearance on hematoxylin–eosin stain. Loosely cohesive and epithelioid neoplastic cells are supported by capillary-sized blood vessels with formation of pseudopapillae. The nuclei are uniform and mitoses are rare. **b** Immunohistochemistry of β-catenin. Abnormal nuclear accumulation is seen in >90% tumors (*right*), and the adjacent non-neoplastic pancreas reveals a normal membranous labeling (*left*)

Table 2 Differences between patients with malignant (n=9) vs. non-malignant (n=36) disease

Variable	Malignant, n=9 (%)	Non-malignant, n=36 (%)	p
Gender			
Female	7 (77.7)	31 (86.1)	0.61
Male	2 (22.2)	5 (13.9)	
Age			
Median	42	33	0.16
Range	20–59	(10–63)	
Presentation			
Incidental	0	7 (19.5)	0.31
Symptomatic	9 (100)	29 (80.5)	
Symptoms			
Abdominal pain	7 (77.7)	28 (77.7)	0.1
Nausea/vomiting	4	11	
Weight loss	1	7	
Jaundice	2	1	
Imaging			
Localization			
Proximal	3 (33.3)	12 (33.3)	0.28
Distal	6 (66.7)	24 (66.7)	
Size (cm)			
Median	7.8	4.2	<0.005
Range	2–20	1.4–11	
Type (N=44)			
Solid	3 (33.3)	9 (25)	0.15
Cystic	2 (22.2)	1 (2.7)	
Both	4 (44.4)	25 (69.4)	
Calcification	1 (11.1)	6 (16.6)	1
Dilated pancreatic duct	1	1	
Dilated bile duct	1	1	
Suspicious of invasion of portal vein	2 (22.2)	2 (5.5)	
Suspicious of invasion of others organs	2 (22.2)	0	
Suspicious of lymph node metastases	1 (11.1)	0	
Liver metastases	4 (44.4)	0	
Surgery			
Splenectomy in distal pancreatectomy	5/5 (100)	12/21 (57.1)	0.12
Operative time	300	210	0.09
Blood loss	1,200	200	0.0035
Postoperative complications	2 (22.2)	8 (22.2)	1
Days of hospital stay (Median)	9	7.5	0.29
Pathologic examination			
Localization			
Head	3	12	0.28
Body	0	7	
Tail	6	17	
Positive margin	1	8	0.6
Invasion of normal pancreas	2 (22.2)	8 (22.2)	1
Perineural invasion	0	5 (13.8)	0.5
Vascular invasion	1 (11.1)	0	0.18
Lymph nodes resected			
Median	1.5	5	0.38
Range	(0–10)	(0–23)	
Positives lymph nodes	0	0	1

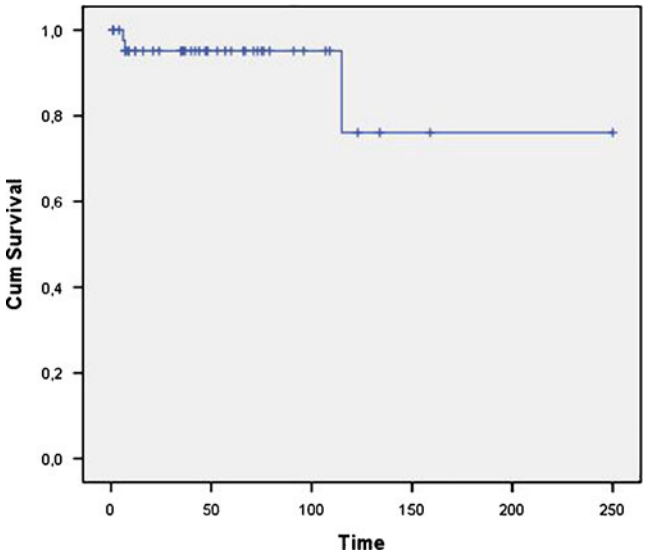

Fig. 3 Disease-specific survival in patients with solid pseudopapillary tumors of the pancreas (N=45)

reported natural history data.[1,8,11,16] Less than 2% of patients who underwent resection of pancreatic neoplasms during the study period had SPT; the majority of patients were young women (median age 38 years), and 80% experienced long-term survival.

In recent years, there has been a reported increase in the number of cases of SPT. This increase probably reflects an increase in incidental diagnosis associated with better-quality imaging studies.[11,17] Despite this, the majority of patients in the current study presented with symptoms. In this series, the most common symptom was abdominal pain. Other common symptoms included nausea/vomiting and weight loss. Although jaundice has been described infrequently,[5] three patients presented with jaundice.

Different imaging studies have been used in the diagnosis and staging of SPT.[1] CT findings include peripheral arterial enhancement of a solid and cystic tumor with central calcifications. Solid components typically enhance similar to pancreatic parenchyma on arterial and venous phases. This is different than hypoattenuation typically seen in adenocarcinomas in the venous phase and the enhancement of neuroendocrine tumors in the arterial phase.[5] In this analysis, the most common preoperative imaging study was abdominal CT. In the majority of patients, the lesion was localized in the pancreatic tail, the tumors' size had a high degree of variability, and the most common radiographic characteristic of the tumor was solid cystic. Despite these characteristic findings, preoperative diagnosis may be difficult.[1,5,8,9] This is highlighted in the current study where one third of patients presented with a solid or cystic tumor suggestive of another histopathologic type of pancreatic neoplasm.

In order to improve upon the accuracy of preoperative diagnosis, some have suggested the use of serum tumor markers and/or study of tumor fluid obtained through a percutaneous or endoscopic puncture. Goh et al.[18] studied serum tumor markers in 12 patients with CEA and 11 patients with CA 19-9 and observed that only one patient had an elevated CEA level and another patient had an elevated CA 19-9 level. In a more recent study, Reddy et al.[8] evaluated serum tumor markers in 13 patients with SPT with CA-125, CA 19-9, or CEA and observed that all patients had normal levels. In this study, six patients were studied with CA 19-9 and five with CEA, and all patients had normal levels. These results suggest that serum markers CEA and CA19.9 are not useful diagnostic or prognostic markers.

The utility of preoperative biopsy/cytology has been analyzed in several studies also with variable results. Papavramidis et al.[1] analyzed 713 patients from different studies, and they observed that 52 patients had preoperative cytologic confirmation of SPT. Unfortunately, it is not possible to evaluate the yield of this procedure because the number of patients in whom biopsy was performed was not reported. In a multicenter study, Jani et al.[19] analyzed 28 patients with cytology obtained through endoscopic ultrasound. Preoperative diagnosis was made in 21 patients (75%), and five patients were misdiagnosed with neuroendocrine tumor. In a more recent study, Reddy et al.[8] diagnosed SPT in eight out of 13 patients (61.5%) studied with cytology. In the current study, 18 patients (40%) underwent preoperative biopsy, and the diagnosis of SPT was confirmed in 56%.

In recent years, the histologic diagnosis has been supported by immunohistochemical analyses.[1,8,18,19] Most SPT stain for vimentin, CD10, neuron-specific, enolase, CD56, progesterone receptors, and α-1-antitrypsin. The neoplasm variably expresses synaptophysin and cytokeratins and is consistently negative for chromogranin, ductal, and acinar markers. Immunolabeling for B-catenin demonstrates abnormal nuclear labeling in more than 90%.[20] More recently, the expression pattern of claudins has been useful in distinguishing SPT from pancreatoblastoma, acinar, and endocrine tumors of the pancreas.[21] Other useful immunohistochemistry markers include CD56, CD10, and beta-catenins which are typically positive. On the contrary, chymotrypsin (acinar marker) and chromogranin (neuroendocrine marker) are generally positive in the minority of patients.

Table 3 summarizes the natural history of this disease observed in those studies with higher number of patients, which is consistent with this report; 85% of patients are females, more than 75% of patients have symptoms at the moment of diagnosis, the majority of them present with large tumors, almost all patients are treated with resection, and resection was associated with excellent long-term survival.[1,2,5,7–9,11,13,14,16,19,22–24]

All patients of this series underwent surgical exploration, and resection depended on the extent and presentation of

Table 3 Selected series of solid pseudopapillary tumors of the pancreas

Author	Year of publication	Number	Female	Age (years)	Symptomatic	Resection	Tumor size (cm)	Follow-up	Patients alive
Lee[22] (2 centers)	2008	62	57 (92%)	30 (mean)	44/62 (70%)	62/62	6.5 (mean)	47.5 months (mean)	62/62 (100%)
Reddy[8]	2009	37	33 (89%)	32 (median)	27/31 (87%)	36/37	4.5 (median)	4.8 years (median)	33/37 (89.2%)
Machado[11]	2007	34	27 (79%)	23 (median)	27/34 (79%)	34/34	7 (mean)	84 months (mean)	33/34 (97%)
Salvia[16]	2007	31	27 (87%)	34 (mean)	38/31 (90%)	31/31	5.4 (mean)	58.2 months (median)	31/31 (100%)
Chung[7]	2009	30	26 (87%)	38 (mean)	No information	30/30	5.3 (mean)	42 months	27/30 (90%)
Sun[12]	2005	28	23 (82%)	26.7 (mean)	23/28 (82%)	28/28	6 (mean)	66.9 months (mean)	28/28 (100%)
Jani[19] (5 centers)	2008	28	24 (86%)	35 (mean)	14/28 (50%)	28/28	4.2 (mean)	26 months (mean)	28/28 (100%)
Yang[9]	2009	26	22 (85%)	32.3 (mean)	17/26 (65%)	26/26	6.3 (median)	32.5 months (median)	25/26 (96%)
Martin[13] (previous publication)	2002	24	20 (83%)	39 (median)	17/24 (71%)	22/24	8 (median)	8 years (median)	22/24 (92%)
Choi[23] (only children)	2006	23	18 (78%)	13 (median)	20/23 (87%)	23/23	7.5 (median)	62 months (median)	22/23 (95%)
Matos[24] (2 centers)	2009	21	20 (95%)	34 (median)	17/21 (81%)	21/21	5.5 (median)	55 months (median)	21/21 (100%)
Current series		45	38 (84%)	38 (median)	38/45 (84%)	41/45	4.9 (median)	44 months (median)	38/45 (84%)

disease. Nine out 41 patients had an R1 (n=7) or R2 (n=2) resection, the tumor invaded the normal parenchyma of the pancreas in ten out of 41 patients, and no patient had identifiable metastatic disease to the regional lymph nodes. Those patients who underwent an R1 resection did not develop local recurrence or distant metastasis with a median follow-up of 37 months. Those patients who underwent an R2 resection did experience disease progression and ultimately died of disease. These findings suggest that in this disease microscopic margins are not a strong prognostic factor associated with disease recurrence. Incomplete gross resection (R2) however was associated with poor outcome, and therefore the ability to technically remove all gross disease should be considered prior to recommending operative exploration. Those patients not resected had locally advanced tumors with invasion of mesenteric vessels that precluded complete resection, suggesting a more aggressive behavior. Because these tumors are rare and the number of patients with malignant disease is even more uncommon, it is very difficult to determine the influence of resection of metastatic or locally recurrent disease.

In this series, nine patients had a malignant disease. Three patients presented a locally advanced tumor; three patients presented liver metastases; one patient presented a locally advanced tumor associated with liver metastases; one patient developed local recurrence and liver metastases; and another patient presented with local recurrence. Prognostic criteria for the prediction of malignant behavior are not well characterized.[5] Some studies have suggested male gender, younger patients, patients with tumors larger than 5 cm, venous invasion and advanced nuclear grade to be associated with malignant disease.[5,11,22,25] This study identified tumor size as being associated with more aggressive disease, and this should be suspected when patients present with larger tumors. The gender and the age were not associated with more aggressive disease.

After a median follow-up of 44 months, most of patients treated in this study have had an excellent outcome with 34 patients alive without disease recurrence. Death from disease occurred in 7% of patients, suggesting that in general these tumors have good prognosis. The definition of malignancy used in this study may be a method to select resected patients for more frequent monitoring for local recurrence or systemic metastasis.

In summary, this is the largest series of SPT published by a single center. The results confirm that SPT mainly occur in young women. The majority of patients in this study were treated with resection, with low morbidity and no postoperative mortality. The only feature associated with malignant disease was the tumor size. The majority of patients are alive at last follow-up, and low percentage experienced disease recurrence or death from disease.

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ORIGINAL ARTICLE

An Analysis of the Utility of Handheld PET Probes for the Intraoperative Localization of Malignant Tissue

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Abstract
Introduction The intraoperative localization of suspicious lesions detected by positron emission tomography (PET) scan remains a challenge. To solve this, two novel probes have been created to accurately detect the ^{18}F-FDG radiotracer intraoperatively.
Methods Nude rats were inoculated with mesothelioma. When PET scans detected 10-mm tumors, animals were dissected and the PET probes analyzed the intraoperative radiotracer uptake of these lesions as tumor to background ratio (TBR).
Results The 17 suspicious lesions seen on PET scan were localized intraoperatively (by their high TBR) using the PET probes and found malignant on pathology. Interestingly, smaller tumors not visualized on PET scan were detected intraoperatively by their high TBR and found malignant on pathology. Furthermore, using a TBR threshold as low as 2.0, both gamma (sensitivity, 100%; specificity, 80%; positive predictive value (PPV), 96%; and negative predictive value (NPV), 100%) and beta (sensitivity, 100%; specificity, 60%; PPV, 93%; and NPV, 100%) probes reliably detected suspicious lesions on PET scan imaging. They also showed an excellent area under the curve of 0.9 and 0.97 (95% CI of 0.81–0.99 and 0.93–1.0) for gamma and beta probes, respectively, in the receiver operating characteristic analysis for detecting malignancy.
Conclusion This novel tool could be used synergistically with a PET scan imaging to maximize tissue selection intraoperatively.

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Keywords PET probe · Minimally invasive surgery · Intraoperative probe · Beta rays · High-energy gamma rays

Introduction

The ability to detect tumor deposits is one of the most desired goals of the oncological field. Multiple imaging modalities have been developed and tested to solve this task in a non-interventional manner. These tests have had significant improvements over the last few decades and as a result, the finding of a suspicious lesion requiring further workup is increasingly seen in the medical field. Once such a lesion is found, its intraoperative localization becomes crucial for its proper diagnosis and treatment. It is at this stage that surgeons become involved to obtain a reliable biopsy of the lesion of interest. And even though, this is probably the most important step for its diagnosis, biopsies are

mostly obtained with nonspecific tumor tools such as needle localization, tissue palpation or direct intraoperative visualization. Thus, increasing advances in the radiological detection of malignancies have not yet seen parallel improvements in the surgical field. Therefore, the intraoperative localization of these suspicious lesions detected on imaging provides the rate limiting step in today's diagnostic workup equation.

The positron emission tomography (PET) scanning is one of the most commonly used imaging modalities by which cancer and recurrences are being diagnosed and monitored. This tomography detects different radiotracers attached to specific molecules of interest. In recent years, there have been major advances in radiotracer selection and usage.[1, 2] But although PET scanners have improved tumor detection, this test is currently not well suited for intraoperative use because of limitations in availability of intraoperative units, cost, and the cumbersome nature of such device in the operative environment. Furthermore, this tomographic test cannot delineate the precisely tri-dimensional locations of the tissues of interest.[3]

In response to these drawbacks, there has been a parallel development of novel molecular-guided technology in the form of handheld probes for use in the operating room. These devices are designed to detect either low- or high-energy particles emitted from previously selected radiotracers. As an example of their applications, the use of low-energy gamma probes to detect technetium is standard for lymphoscintigraphy and broadly used today in interventional procedures.

Other radiotracers have imposed greater challenges for their intraoperative detection, including the F-18-labeled fluorodeoxyglucose (^{18}F-FDG), which is the most currently used radioisotope for PET scan imaging. This compound has shown a high sensitivity and specificity for detection of malignant tissue, but the challenges for its use during operative procedures are due to its intrinsic characteristics. This isotope emits two rays, a low-energy beta ray and a high-energy gamma ray. It is the high-energy gamma particle which creates a significant surrounding interference and therefore substantial problems on its precise localization intraoperatively. Nonetheless, two novel intraoperative probes have been created to solve this issue and reliably detect this radioisotope. These probes are a handheld device and each can detect either of the two rays emitted by this radiotracer: gamma and beta. The ^{18}F-FDG emitted gamma radiation (the high-energy particle) travels a long distance and can even be detected outside of the body cavity. It is this characteristic that makes it appealing for the PET scan imaging. But for the intraoperative probe to reliably detect these gamma rays and avoid its surrounding radiation, it has to have a large amount of heavy shielding, and is therefore large and bulky. On the other hand, the beta rays only travel millimeters before annihilating into two high-energy gamma rays.[4] Therefore, this second rays can only be detected intraoperatively, and are affected to a much less degree by its surrounding radiation. In fact, the main advantage of the beta probe (the probe designed to detects the beta rays) is that it does not need the high degree of collimation needed on the gamma probe (the probe designed to detect the gamma rays), and is therefore smaller in diameter and more appealing for its intraoperative usage, especially for minimally invasive procedures.

The intraoperative use of this device is simple. It detects the amount of radiation emitted by a specific source, and gives the result as a number, which units are counts per seconds. This number is then easily standardized to the patient's background uptake and is interpreted as tumor to background ratio (TBR). As a result, this ratio is directly proportional to the amount of radiotracer uptake from that specific location and subsequently to its malignant potential. Thus, the higher the TBR, the more likely the lesion is malignant.

We designed a study to assess the ability of this intraoperative device to localize suspicious tissue previously seen on PET scan. Our first aim is to correlate the PET scan imaging findings with that of the intraoperative gamma and beta probes.

Our second aim is to define the limits of detection of the radiologic PET scan exam, as it is generally accepted that smaller tumors are not well detected using this test.[5] Similarly, we evaluated the limits of detection of these intraoperative probes and correlated tumor sizes with their radiotracer uptake.

Overall, our aims focus on defining the usefulness of these probes for the intraoperative guidance and selection of specific lesions when complemented with a preoperative PET scan imaging, taking into account different tumor sizes.

Materials and Methods

Animal Care

Nude rats described (averaged 250 g), all comply with the regulatory requirements of the Institutional Animal Care and Use Committee, the Research Animal Resource Center (RARC) of MSKCC, and the National Institutes of Health (NIH) "Guide for the Care and Use of Laboratory Animals".

They were all fed ad libitum, and maintained on broad spectrum prophylactic antibiotics upon their arrival to the

institution. All animal procedures were performed under proper inhaled anesthesia using 2% isoflurane. Animals were killed via CO_2 inhalation just prior to necropsy.

Cell Line

The human mesothelioma line was selected for its xenograph uptake quality in nude rats previously reproduced in our laboratory (unpublished data). This line was maintained with Roswell Park Memorial Institute Medium+10% FCS P+S+10 mM HEPES+2 mM fL-glutamine+1 mM sodium pyruvate and 1.5 g/L sodium bicarbonate+4.5 g/L-glucose. Cells were kept in a 5% CO2 humidified incubator at 37°C and subcultured twice weekly.

Irradiation

Nude rats although athymic, are immunocompetent to a certain degree and therefore resist a large variety of implanted tumors. To increase the uptake of our xenograft model, their immune function was further suppressed by external beam radiation.[6–8] Using the Gammacel 40 whole-body radiator, the animals received a one-time dose of 500 cGy. Desirable immunosuppression is obtained 4 days after this procedure, and xenograft implantation was performed then. Radiation produces no pain or discomfort to animals, and therefore no anesthesia was required.

For optimal preparation of this immunosuppression, animals were treated with prophylactic antibiotics upon their arrival to our institution. Antibiotic treatment was continued after whole-body radiation to avoid secondary, opportunistic infections.

Xenograft Implantation

After desired immunosuppression of the animals was achieved, 2e−7 cultured cells in 100 μl PBS suspension were intrapleurally injected over the right and left side of their chest wall. For this procedure, a 1 cm skin incision was performed in each site, with the animals under inhaled isoflurane anesthesia. The dissection was continued until the rib cage was visualized. Then, the syringe containing the suspended cells was carefully introduced intrapleurally, and the suspended cells injected. Each wound was closed using surgical clips, which were subsequently removed several days after the procedure. All animals tolerated the procedure well and were closely monitored with weekly nuclear imaging studies.

Radioisotope Production and Injection into Rats

^{18}F-FDG was obtained from the institutional radiopharmacy laboratory (Nuclear Medicine Department, MSKCC, New York, NY). A total volume of 0.15–0.20 ml containing 500 μCi of ^{18}F-FDG in sterile PBS was injected retro-orbitally in each rat under inhaled, isoflurane anesthesia.

MicroPET Scan Imaging

Animals were starved overnight to enhance the radiotracer uptake. After retro-orbital injection of 500 μCi of ^{18}F-FDG, a 1-h period was allowed for optimal radiotracer uptake,[9] and then the animals were placed in a prone position on the scanner.

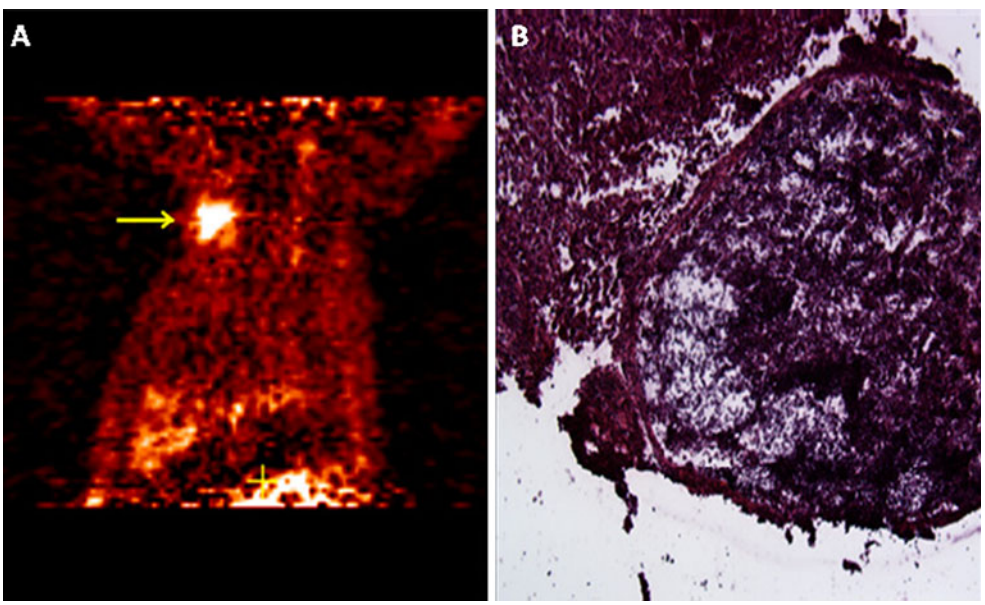

Fig. 1 PET scan imagine and pathological results. **a** Suspicious right chest wall mass. The high radiotracer uptake seen in this PET scan study correlated with the high TBR detected with the intraoperative probes. TBR of 11.0 and 8.24 were detected for gamma and beta probes, respectively. **b** H&E staining of the lesion shows mesothelioma

Scans were performed with transaxial fields of view of 10 cm and s axial views using the Focus 120 micro-PET™ dedicated small-animal PET scanners (Concorde Microsystems, Knoxville, TN). The transaxial field of view covered from the lower neck to the upper abdomen. Scans were collected with an energy window of 350–750 KeV and a coincidence timing window of 6 ns. Data was sorted into 2D histograms by Fourier re-binning and transverse images were reconstructed in a 128×128×63 (R4) or 128×128×96 (Focus 120) matrices by filtered back-projection. Images were corrected for non-uniformity of scanner response, and radionuclide decay to the time of injection.

Evidence of high ^{18}F-FDG uptake lesions was found 2 to 4 weeks after tumor implantation. Those lesions were followed until desired tumor size was reached (10 mm), and dissection with probe readings was performed then.

Procedure

Dissection

Once suspicious lesions where readily visualized on PET scan imaging, the animals were brought to the operating table. A retro-orbital injection of 500 μCi ^{18}F-FDG was performed and animals were then kept under proper inhaled anesthesia for a total of 30 min. Dissection was then performed, so that tissue sampling could take place 60–90 min after the injection for optimal radioisotope absorbance (as explained above). Animals were then killed for dissection. During the procedure, particular interest was given to the high ^{18}F-FDG uptake areas previously visualized on PET scan. The hand-held probe was placed perpendicularly over those areas and dissection was carried with the guidance of the high radioisotope counts obtained by the probes. Once the mass was directly visualized, in situ readings were recorded in triplicates. Afterwards, these lesions were dissected off the surrounding tissue and fresh frozen for subsequent pathological analysis.

Pet Probe and Counts

The high-energy gamma and beta probes (IntraMedical Imaging LLC, Los Angeles, CA) are designed to detect 511-keV photons from positron-emitting sources (gamma probe) and positrons (or beta rays) directly (beta probe). The probes were calibrated to accurately localize the point source of ^{18}F-FDG and the count rate was determined to optimize the detection of the 511 keV emissions.

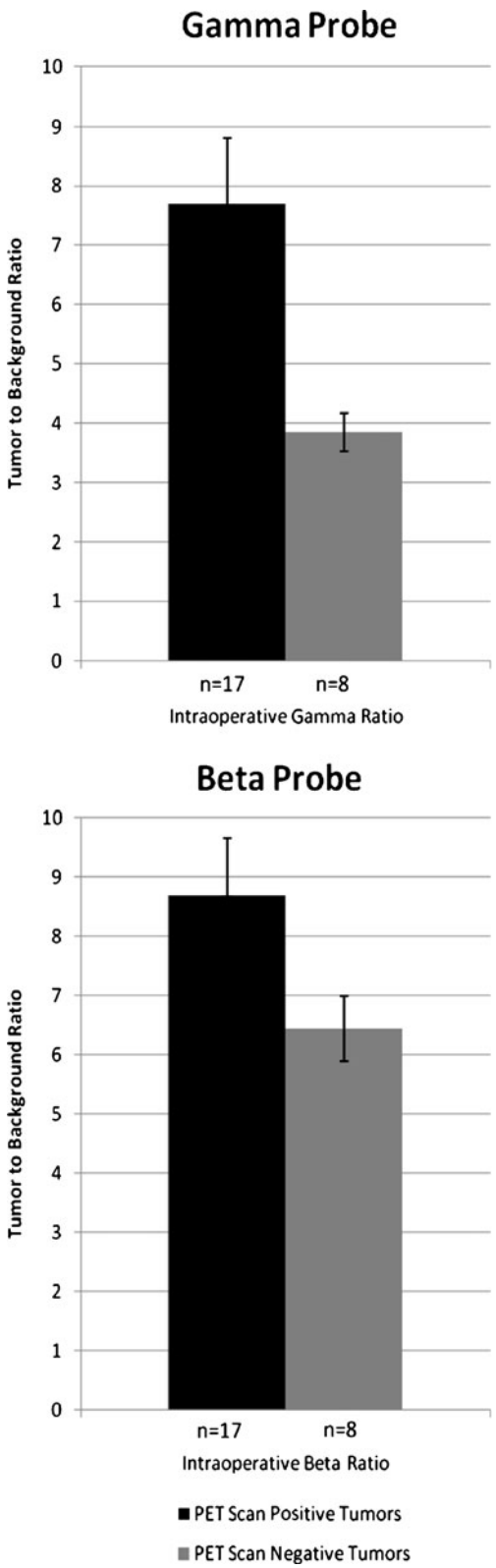

Fig. 2 Gamma and beta TBR of positive versus negative tumors on PET scan. Both probes detected an increased uptake on the PET-scan-positive group. SEM of both probes are shown for comparison. *n* number of tumors sampled, *SEM* standard error of the mean

Tumors were kept in situ for analysis. Radioactive emissions were measured in counts per second and recorded in triplicate for both beta and gamma probes.

A background tissue was obtained to correct for the background uptake of this radiotracer. The psoas muscle was selected as it is easily located inside the body cavity, and also is in close proximity to surrounding high FDG uptake organs, making it similarly affected to the surrounding radiation as the tumors to be biopsied. Readings were performed in triplicates in each animal, for TBR calculations.

Image Analysis

PET image analysis was done with ASIPro™ software (Concorde Microsystems Inc., Knoxville, TN). To verify ROI measurements, selected tissues were harvested, weighed, and counted in triplicate in a scintillation well counter calibrated for ^{18}F-FDG.

Statistical Analysis

Receiver operating characteristic (ROC) curves were utilized to assess the ability of each probe to detect PET-positive lesions as well as malignant tissue, and the area under the ROC curve (AUC) was used to summarize these measurements. Each ROC curve and its AUC was estimated non-parametrically and an optimal threshold was identified using the maximal Youden index.[10] A simple way to analyze the ROC graphs is the closer the AUC is to 1.0, in other words the closer the curves are to the left upper quadrant of the graph, the better the overall performance of the probes.

Other methods of finding an optimal threshold, such as the maximal chi-square method were not considered since their power would have been limited in this relatively small sample.

Results

After 2 to 4 weeks of monitoring, tumors reached desirable sizes (10 mm) in PET scan studies (Fig. 1). They were mostly located on the chest wall of the animals as well as in the intrapleural space. Some intrapleural tumors grew aggressively, and no anatomical distinction could be made between thoracic structures and tumor masses. On the other hand, other tumors as well as tumors on the chest wall were well delineated and amenable for precise surgical resection and probe analysis.

A total of 17 suspicious masses were found on PET scan imaging (named PET-scan-positive tumors), and all were subsequently localized intraoperatively with the use of either probe. Localization of tumors was sometimes facilitated by the evident tumor mass, but other times (on smaller tumors) by intraoperative explorations using the probes to guide the curse of the dissection. Probe readings, along with size measurements of the tumors were performed in situ, followed by tissue dissection and pathological analysis. Subsequently, all of these 17 lesions were found malignant on pathological examination.

Intraoperatively, all PET-scan-positive tumors were noted to have a higher TBR compared with their surrounding tissues. For the gamma probe, the average TBR value was 7.7, ranging from 4.4 to 23.4. The beta probe had a higher average of 8.7, ranging from 3.2 to 19. For comparison purposes, surrounding benign chest wall tissue TBRs was also calculated for both probes. The gamma probe had an average of 1.1, and a range from 0.72 to 1.6. Similar values for the beta probe averaged 1.4, ranging from 0.66 to 2.2. Benign pleural and peritoneal tissue

Table 1 Intraoperative probes detecting malignant tissue

Probes localizing malignancy (n=25)								
TBR	≥1.5		≥2.0		≥2.5		≥3.0	
Gamma probe	Sensitivity	100.0	Sensitivity	100.0	Sensitivity	95.8	Sensitivity	91.7
	Specificity	80.0	Specificity	80.0	Specificity	100.0	Specificity	100.0
	PPV	96.2	PPV	96.0	PPV	100.0	PPV	100.0
	NPV	100.0	NPV	100.0	NPV	83.3	NPV	71.4
Beta probe	Sensitivity	100.0	Sensitivity	100.0	Sensitivity	100.0	Sensitivity	100.0
	Specificity	60.0	Specificity	60.0	Specificity	100.0	Specificity	100.0
	PPV	92.6	PPV	92.6	PPV	100.0	PPV	100.0
	NPV	100.0	NPV	100.0	NPV	100.0	NPV	100.0

This table demonstrates the overall ability of the probes to detect malignant tissue regardless of their sizes. As shown, both probes had excellent sensitivities between TBR of 2.5 and 3.0. The beta probe had a more definite cut off value of 2.5 than the gamma probe

PPV positive predictive value, *NPV* negative predictive value, *n* number of samples

samples produced similar results. As seen, both probes were able to locate all suspicious tumors previously seen on PET scan, with a wide difference between their TBR and that of the other surrounding, benign tissue. In fact, using a TBR as low as 2.5, both probes reliably located all suspicious tissues previously seen on imaging.

Interestingly, we also encountered other small tumors with high intraoperative TBR, but not detected on the PET scan studies. A total 8 of these lesions were found, and ultimately proved malignant on pathological examination. These were defined as PET-scan-negative tumors. Their size and probe counts were analyzed in situ and recorded again in triplicate. TBRs on these malignant lesions were higher than that of their surrounding benign tissue, but somewhat lower than the previously described PET-scan-positive tumor group. Values on the gamma probe ranged from 2.4 to 5.6, with an average of 3.9. For the beta probe, values ranged from 3.1 to 7.8, for an average value of 6.44. Figure 2 compares the intraoperative TBR between the PET-scan-positive and PET-scan-negative tumors. Of note, the beta probe had a smaller difference between these two groups.

The overall ability of the intraoperative probes to detect malignant tissue regardless of the PET scan results or tumor diameters is shown on Table 1. Increasing the TBR from 1.5 correlated to an increased ability of both probes to differentiate between malignant and benign tissue. From a TBR of 2.0 to 3.0, both probes had their optimal results, suggesting that the cut off value for tissue sampling could be found in this range.

Of note, tumors detected on PET scan had larger diameters, with an average of 14 mm. These were significantly larger than the 8-mm average diameter found on the PET-scan-negative group. Interestingly, there is some overlapping between the two groups, especially between 9.0 and 11.9 mm. Below and above this diameter, the PET scan test was consistent in either not detecting them at all (if less than 9 mm), or reliably detecting them (if larger than 11.9 mm).

This finding is consistent with previous studies which show that tumors less than 1 cm in diameter are not accurately detected in PET scan imaging.[5] In our study group, we divided the tumors by size to better assess and compare the limits of detection of both the PET scan and the intraoperative PET probes. Table 2 shows the statistical results for the PET scan imaging for detecting tumor masses either larger than or smaller than 1 cm in diameter. For those over 1 cm, the PET scan had a sensitivity of 87% and a specificity of 100%. These results were significantly altered for tumors less than 1 cm in diameter, as the sensitivity of this imaging exam dropped to 40%.

Table 2 PET scan results for tumor detection

PET scan results for tumor detection			
Tumor size	<1 cm	≥1 cm	All tumors
Sensitivity	40	87	68
Specificity	100	100	100
PPV	100	100	100
NPV	80	92	76

This table shows the ability of the PET scan to detect tumors depending on their sizes. A significant decrease in sensitivity is observed on tumors less than 1 cm in diameter

PPV positive predictive value, *NPV* negative predictive value, *n* number of samples

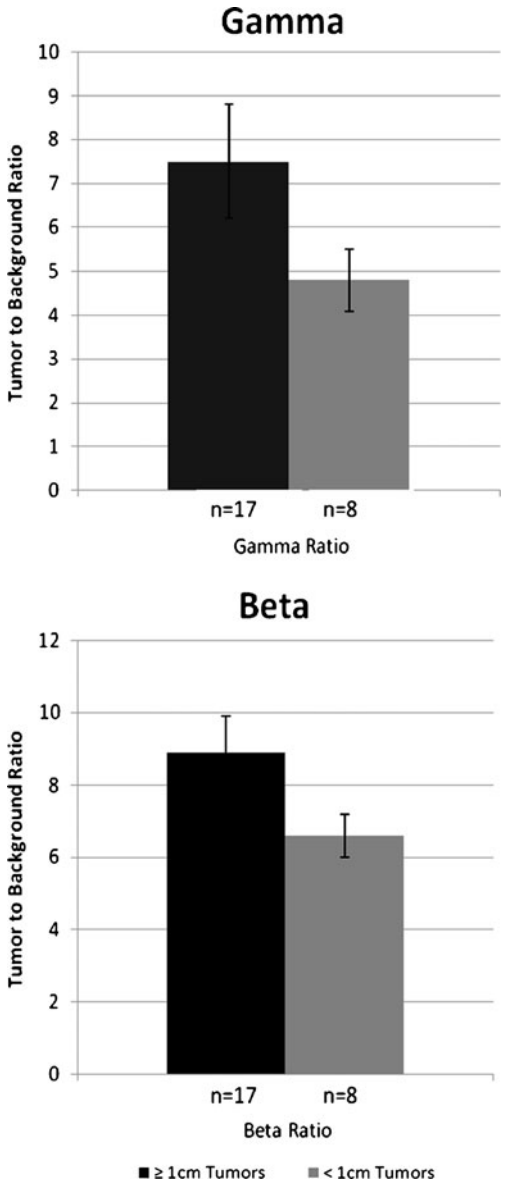

Fig. 3 Gamma and beta TBR of tumors larger versus smaller than 1 cm in diameter. Higher values are noted over the larger tumor group for both probes. A smaller difference between the groups is noted on the beta probe. This underscores the improved limits of detection that could be obtained by this probe. SEM of both probes are shown for comparison. *n* number of tumor sample, *SEM* standard error of the mean

On the other hand, the intraoperative probes showed better results for detecting tumors smaller than 1 cm. Figure 3 compares the corresponding TBRs of these two groups. For tumors less than 1 cm in diameter, the gamma probe had an average TBR of 4.8 (ranging from 2.6 to 10.6) and that for the beta probe was 6.6 (ranging from 3.2 to 9.0). Using a cutoff TBR of 1.5, both probes had a sensitivity and NPV of 100% for detecting these smaller sized tumors, with somewhat lower specificity for the beta probe (60% vs 80%). For gamma and beta probes, their corresponding PPV were 91 and 83, respectively.

For those larger than 1 cm in diameter, average TBR values for both gamma and beta probes were 7.5 (ranging from 3.3 to 23) and 8.9 (ranging from 3.6 to 19), respectively. Here, both probes had excellent results using a cutoff TBR of 2.5. In fact, for a TBR of 1.5, both probes had sensitivity and NPV of 100%. And similar to the results for the smaller tumors, the specificity of the gamma probe was somewhat higher (80% vs 60%), as well as the PPV (93% vs 88%).

But even though using this small TBR showed some benefit for the gamma probe, using the ROC curves, the overall consistency of TBRs in malignant tissues regardless of the tumor sizes showed better results for the beta probe (AUC of 0.90 and 0.97; 95% CI of 0.81–0.99 and 0.93–1.0 for gamma and beta probes, respectively).

Finally, we were able to correlate tumor diameters with intraoperative counts detected on both probes. Figure 4 demonstrates the positive correlation between size and counts per second detected, with an R^2 value of 0.48 and 0.43 for both gamma and beta probes, respectively. This again shows the ability of the probes to detect the higher ^{18}F-FDG uptake expected on larger tumor masses.

Discussion

The proper and reliable intraoperative detection of suspicious lesions seen on PET scan is essential for the correct diagnosis and treatment of cancer patients. By providing an intraoperative tool to better localize these tissues, a more accurate classification and staging could be obtained, with a secondary advantage of avoiding unnecessary tissue resection to obtain a reliable sample in such procedures. Furthermore, it will add an element to guide surgeons when an intraoperative assessment significantly changes operative planning, as is known to occur up to one third of cases.[11]

As mentioned before, ^{18}F-FDG is the most commonly used radioisotope in PET scan exams, and numerous studies have shown its high sensitivity and accuracy for evaluating both primary and metastatic diseases.[12–22] This molecule is a fluorinated glucose analog, and is internalized in cells using the GLUT transporters. It is then selectively concentrated in tumor tissue,[23] and from there emits two types of waves: gamma and beta. The first emitted wave (beta) is a positron that travels a short distance and eventually collides with a nearby electron to produce two gamma rays, 180° apart from each other.[4] This subsequent wave emitted is a high-energy ray (511 KeV) that can travel several centimeters in tissue.

The hand held PET probe is an intraoperative devise first described and developed by Daghighian et al.[24] in 1994, as a novel method to direct intraoperative tumor localization.

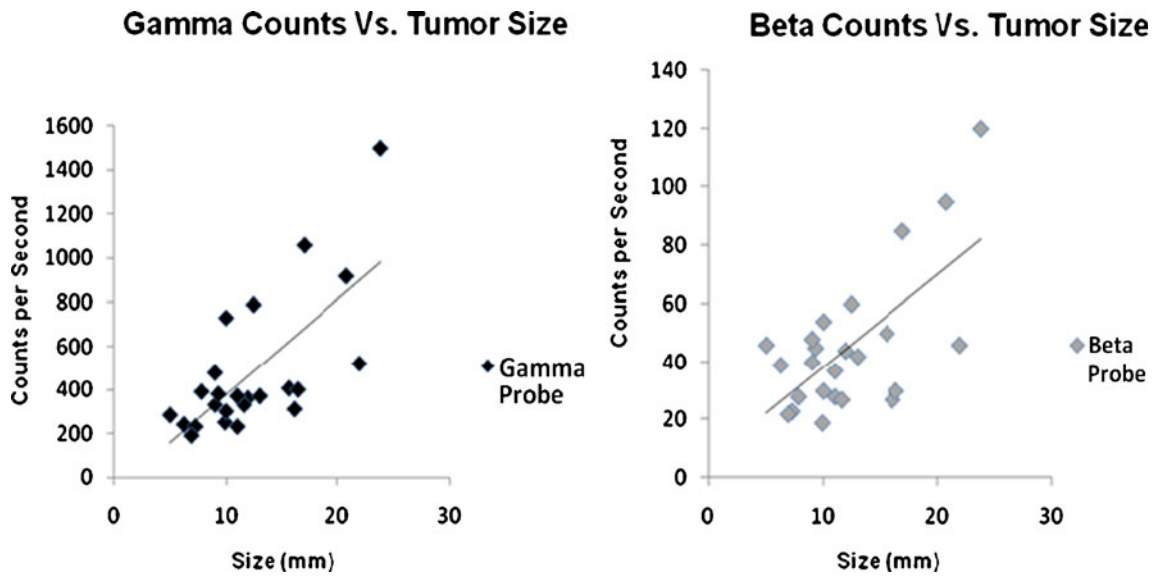

Fig. 4 Gamma and beta probe counts versus tumor size. A comparison between intraoperative counts obtained by the probes and the respective tumor sizes. This count is directly proportional to the degree of isotopic radiation emitted by the tissue being measured. As described, this number is easily calibrated to TBR after dividing it by the background's value. A direct correlation was seen, confirming the higher uptake detected on the larger sized tumors. Calculated R^2 resulted in 0.48 and 0.43 for gamma and beta probes, respectively

These positron detecting devices allow for direct localization of radiolabeled tumor cells by detecting both, gamma and beta rays. The high degree of collimation required to efficiently detect gamma rays, substantially increases the diameter of this devise and impedes its ideal mechanical manipulation intraoperatively. This is accentuated on procedures in small body cavities, or during minimally invasive surgeries. In contrast, the beta probe does not need such protection. This is because it is made from a thin crystal, sufficient to stop electron radiation, but too thin to be affected by the surrounding gamma rays. It therefore has a smaller diameter and is ideal for intraoperative manipulations as well as for minimally invasive procedures, as it very well fits in a 5-mm port used for laparoscopic surgery. Furthermore, the shorter path traveled by these rays makes it ideal for tumor detection at a closer range, as well as localization of smaller tumor deposits, as it is less affected by surrounding radiation than the gamma probe. These facts, along with its smoother intraoperative handling, may allow for better identification of metastatic foci,[24] and thus obviate unnecessary tissue resection in particular patients (such as those with pancreatic cancer and detectable peritoneal spread).

In this study, we focused on the importance of the intraoperative localization of tumors noted on PET scan imaging. As our results show, we were able to locate each of those suspicious lesions with either probe. Moreover, the direction of the dissection was guided on multiple occasions by the high counts detected by the probes towards the areas of interest.

PET scan imaging found 17 out of the total 25 tumors present. It failed to detect some tumors smaller than 1 cm in diameter. This is highlighted by the drop on its sensitivity from 87% to 40% when comparing tumors larger versus those smaller than one centimeter in diameter. On the other hand, the intraoperative probes were substantially better at detecting smaller tumors. The beta probe had consistently better results over the gamma probe in detecting tumors smaller than 1 cm in diameter, as shown in the ROC curves explained above. These suggest that improved limits of detection, as well as the possibility of analyzing the margins of a resected specimen could be attained using this novel, intraoperative tool.

Figure 2, shows a wider difference on the gamma probe between the two groups being compared. This shows a more direct correlation between the gamma probe and the PET scan findings. It may also disclose a somewhat better sensitivity for malignancy detection of the beta probe, particularly over the smaller tumor masses. In other words, the gamma probe may replicate better the results obtained by PET scan imagine, but the beta probe was somewhat more selective for malignant tissue, especially over the smaller tumors lesions. A proposed explanation of this finding is that the PET scanning was significantly affected by the size of the lesion. Below a certain threshold (in this case 9.0 mm) it was more likely to be unable to detect the malignant tissue. Similarly the gamma probe was less able to precisely locate these smaller tumors. On the other hand, the beta showed some advantages detecting smaller malignant lesions, possibly because it was affected to a lesser degree by its surrounding radiation.

Finally, the different tumor sizes (from 4.5 to 23.8 mm in diameter) were correlated with their intraoperative radioisotope emission obtained as counts per second. A direct, positive correlation was observed on both probes. This again shows the reproducibility of this intraoperative device for detecting different amounts of radiotracer uptake given by the various tumor sizes.

Based on our results, we suggest that the optimal TBR for localizing malignant lesions may be between 2.0 and 3.0 for both probes. That is about two times the isotopic radiation emitted from the background tissues. Within this range, the sensitivity of tissue selection was kept at its highest, and the specificity, as well as the PPV had the most substantial increase.

It is worth mentioning, that our comparison of the different probes was not intended to define one superior to the other. In fact, it is the synergism of the two what may be needed in most cases. While the gamma probe could easily guide you with certainty towards the PET scan findings, the beta probe might make possible the detection of smaller tumor foci, or an improved assessment of malignant tissues over an anatomically smaller areas. Furthermore, this later probe may guide surgeons to better select specific areas for tissue dissection, and even assess the margins of a resected specimen.

Conclusions

The intraoperative probes were able to localize suspicious lesions previously seen on PET scan. Each probe offers its own advantages and are thus designed to be easily interchanged during the surgical procedure. The reproducibility of these results over the multiple tumor samples demonstrates that this tool can be used with confidence in the operative environment. Furthermore, when this devise is complemented with a PET scan imagine, it exponentially improve our ability to efficiently localize malignancies during surgical procedures.

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CASE REPORT

Pylorus-Preserving Pancreaticoduodenectomy after Transhiatal Esophagectomy Sparing the Right Gastroepiploic Vessels and Gastric Tube

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Abstract
Introduction Pancreaticoduodenectomy after transhiatal esophagectomy is a technically demanding procedure in sense of preserving the blood supply to the gastric tube.
Case Report We report a case of pylorus-preserving pancreaticoduodenectomy for pancreatic head cancer, 13 years after a transhiatal esophagectomy, sparing the gastric tube and the right gastroepiploic artery and vein.
Discussion This type of operation is less time-consuming and less invasive, since no further reconstruction of the alimentary tract or the vascular system is applied.

Keywords Pylorus-preserving pancreaticoduodenectomy · Esophagectomy · Gastric tube · Gastroduodenal artery · Right gastroepiploic artery

Introduction

Pancreaticoduodenectomy (PD) is the procedure of choice in pancreatic head cancer. However, in patients who underwent transhiatal esophagectomy with the stomach being anastomosed to the cervical esophagus, choosing the best technique for the PD presents a great challenge.[1] The surgeon is usually confronted with two options: to preserve the blood supply to the stomach via the right gastric and gastroduodenal artery (GDA) or to sacrifice blood vessels and substitute the devascularized stomach with the colon. We herein present a case of pylorus-preserving pancreaticoduodenectomy (PPPD) for pancreatic head cancer, sparing the gastric tube and its unique vessels, the right gastroepiploic artery (RGEA), 13 years after transhiatal esophagectomy for esophageal cancer.

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Case Report

A 50-year-old Caucasian male was referred to our clinic with a 1-month medical history of painless obstructive jaundice, dark urine, and clay-colored stools (total bilirubin (Bil_t) 17 mg/dl). The patient had undergone transhiatal esophagectomy for esophageal cancer 13 years ago.

An abdominal contrast-enhanced computed tomography (CT) scan showed an ill-defined, almost iso-attenuating 2.5-cm mass in the pancreatic head with marked dilatation of the intra- and extrahepatic bile ducts (Fig. 1). The presence of the gastric tube in the posterior mediastinum

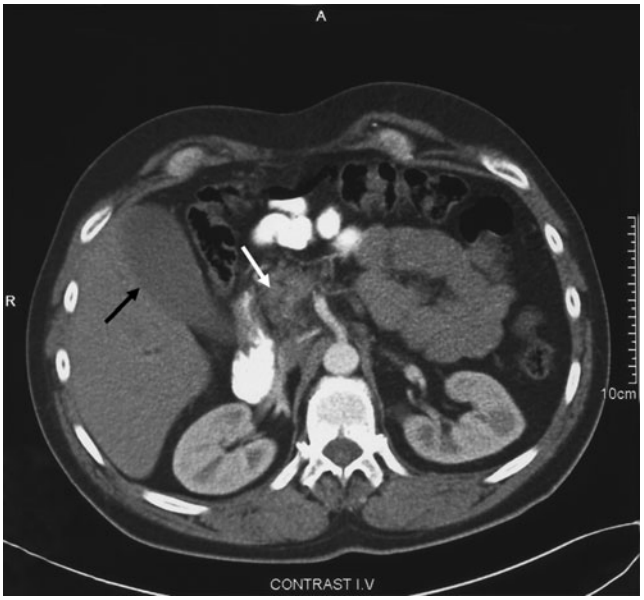

Fig. 1 Contrast-enhanced computed tomography scan of the abdomen. An ill-defined hypodensity is seen in the pancreatic head at the level of superior mesenteric artery origin (*white arrow*). Gallbladder dilatation is also noted (*black arrow*).

was also noted on CT images of the thorax. A plastic endoprosthesis was placed in the common bile duct (CBD), via endoscopic retrograde cholangiopancreatography, to restore the bile flow. Endoscopic ultrasonography-guided fine-needle aspiration biopsy and cytology revealed cells with high-grade dysplasia of the ductal epithelium indicative of ductal adenocarcinoma. An angiographic study of the Haller's tripod and superior mesenteric artery depicted the RGEA as the only vessel perfusing the gastric tube (Fig. 2).

During patient's preoperative management, laboratory evaluation showed aspartate aminotransferase 23 IU/L (normal, <45 IU/L), alanine aminotransferase 32 IU/L (normal, <45 IU/L), alkaline phosphatase 121 IU/L (normal, 40–150 IU/L), gamma-glutamyl transpeptidase 173 IU/L (normal, 10–55 IU/L), Bil_t 1.8 mg/dl (normal, 0.2–1.2 mg/dl), and direct bilirubin 1.2 mg/dl (normal, <0.5 mg/dl). Tumor markers such as carcinoembryonic antigen, carbohydrate antigen 19-9, and alpha-fetoprotein were found within normal range. Although the patient presented with two uncommon malignancies prior to 50 years of age, his family history was negative for familial cancer syndromes, and no further work up was performed.

Regarding the surgical technique, exploration after a median laparotomy revealed massive adhesions and fibrotic changes in the upper abdomen, without any evidence of metastatic disease. The proper hepatic artery and the GDA were identified. Typical antegrade cholecystectomy was performed followed by division of the common hepatic duct, approximately 1 cm before the bifurcation, and

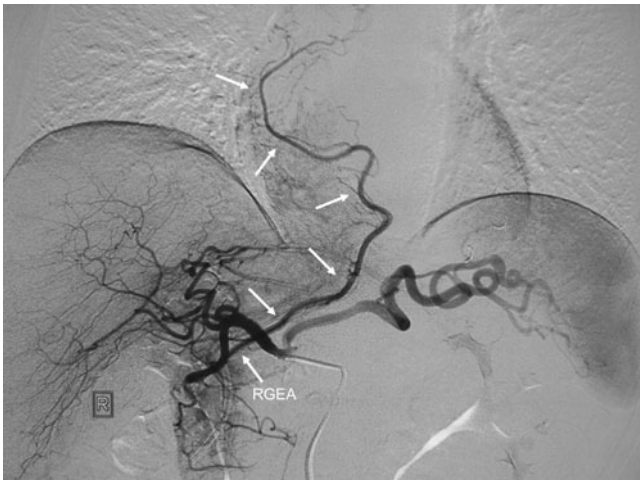

Fig. 2 Preoperative digital angiography of the celiac axis, demonstrating the cephalad course of the right gastroepiploic artery (RGEA, *arrows*). The distal half of the artery is located above the diaphragm into the thorax.

removal of the biliary stent. The duodenum was divided preserving the pylorus and the GDA. All branches of the GDA to the duodenum and pancreas (the anterior and posterior superior pancreatoduodenal and a few penetrating arteries) were identified, ligated, and divided at their roots taking care not to injure the RGEA which was the only one supplying the stomach (Fig. 3). Consequently, the GDA was completely detached from the head of the pancreas,

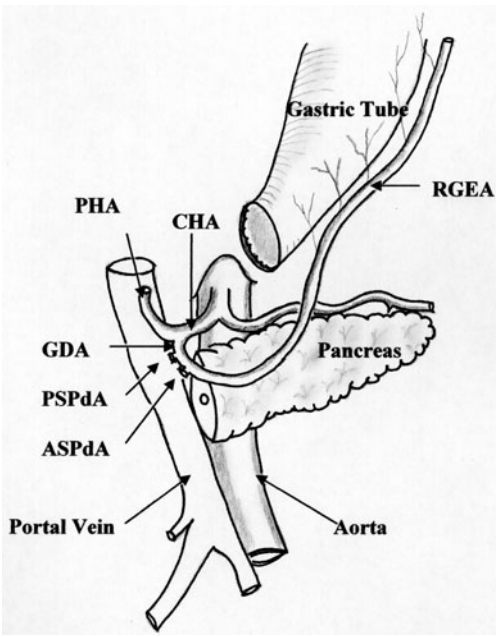

Fig. 3 A schematic illustration after removal of the specimen with preservation of the gastric tube, the gastroduodenal artery (GDA), and right gastroepiploic artery (RGEA). *PSPdA* posterior superior pancreatoduodenal artery, *ASPdA* anterior superior pancreatoduodenal artery, *PHA* proper hepatic artery, *CHA* common hepatic artery.

which was then divided between the neck and the body. The proximal jejunum was divided, and the distal loop was transposed through the mesocolon. Reconstruction of the gastrointestinal tract included an end-to-side duct-to-mucosa pancreatojejunostomy, an end-to-side hepaticojejunostomy, and an end-to-side gastrojejunostomy in that order, using a single jejunal loop. Finally, a side-to-side Braun anastomosis was performed between the afferent and efferent part of the jejunal loop involved in the gastrojejunostomy. The operative time and blood loss were 7 h and 800 mL, respectively.

Macroscopically, the pancreatic head contained a grayish tumor, 2.5×2×2 cm in size, which infiltrated the duodenum. Light microscopy revealed a well-differentiated adenocarcinoma of the pancreatic head that infiltrated the distal CBD and duodenum. Metastasis was found in two out of eight peripancreatic lymph nodes. Microscopically, surgical margins were negative for malignancy including bile duct, duodenum, pancreas specimen, and uncinate process (R0 resection). The overall AJCC stage of the tumor was IIb (T3 N1 M0).[2] The postoperative course was uneventful, and the patient was discharged on the 15th postoperative day. Following his recovery, adjuvant chemotherapy was started with Gemcitabine (Gemzar®, Lilly USA, LLC), 1,000 mg/m^2, on days 1, 8, and 15 out of every 28 days cycle, for six subsequent cycles. During his follow-up, a CT scan of the abdomen 8 months after the procedure showed multiple metastatic lesions into the liver, and the patient received a second line chemotherapy treatment with Erlotinib (Tarceva®, Genentech Inc.), 100 mg/d. Fourteen months after the procedure, the patient is alive in fair condition.

Discussion

The coexistence of esophageal and pancreatic cancer, either synchronous or metachronous, is rare. Therefore, there are few reports concerning the surgical management either in one- or two-stage procedure. In cases where PD and esophagectomy are performed in the same surgical procedure, there is an advantage of planning the operation ensuring adequate blood supply to the stomach.[3,4] Thus, careful selection and planning of the appropriate surgical procedure are indispensable when performing PD in a patient who has previously undergone transhiatal esophagectomy reconstructed with the gastric tube. To our knowledge, PD for pancreatic cancer after transhiatal esophagectomy with gastric tube reconstruction has been reported three times in the past.[5] In addition, a case of gastric tube-preserving PPPD for distal CBD cancer and three cases of surgically treated ampullary cancer after esophagectomy have also been reported.[1,6]

Advances in imaging modalities and other diagnostic tools, as well as in surgical techniques and perioperative management, are expected to increase the rate of secondary surgery for a metachronous primary carcinoma in the future. Moreover, the prognosis of patients with multiple cancers, including pancreatic carcinoma, depends largely on the prognosis of the pancreatic cancer.[7] Most cases of pancreatic cancer become clinically symptomatic when already at an advanced stage, making patient selection important in achieving long-term survival and effective palliation.[3]

In our case, surgery was indicated since there was no evidence of metastatic disease. Preoperative angiographic depiction of the Haller's tripod revealed that the gastric tube was perfused only by the RGEA without development of collateral pathways, rendering the operation very demanding. Therefore, it was obligatory to spare the RGEA to avoid ischemia of the gastric remnant. In the circumstance where sacrifice of the GDA and the RGEA were necessary, a vascular graft anastomosing the common hepatic or the proper hepatic artery to the remaining RGEA would have been utilized. Finally, viability of the stomach could not have been guaranteed, the ascending colon would be transposed and anastomosed to the cervical esophagus as most authors justify colon replacement only when the stomach is not available.[3]

The clinical effect of lymph node dissection around the pyloric ring and along the GDA and RGE vessels, especially on long-term survival after a PPPD for a pancreatic carcinoma, is vague. Available data from prospective randomized controlled trials indicate that PD and extended lymphadenectomy confers no survival advantage over PD only and may be associated with disabling diarrhea and malnutrition postoperatively.[8] In case of PPPD, despite the risk of lymphatic tumor spread around the pyloric ring, preservation of these lymph nodes does not seem to impair the radicality of resection and curability. In addition, based on various published retrospective and prospective studies, there is no superiority of PD compared to PPPD. Morbidity and mortality are similar in both procedures, and until now, there was no evidence for survival benefit for one of the two procedures.[9]

Conclusion

In conclusion, although performing PPPD after transhiatal esophagectomy sparing the RGE vessels is technically demanding, this approach is less time-consuming and less invasive since no further reconstruction of the alimentary tract or the vascular system is applied. Preoperative angiographic evaluation and meticulous surgical technique are prerequisites for satisfactory results.

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MULTIMEDIA ARTICLE

A Novel Technique of Partial Splenectomy Using Radiofrequency Ablation

Jan Jin Bong · Rajesh Kumar · Duncan Spalding

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Abstract
Introduction Partial splenectomy has frequently been advocated to avoid the risk of overwhelming postsplenectomy sepsis. Concerns over adequate haemostasis during partial splenectomy, however, have limited its widespread use. We have previously reported our experience of using radiofrequency (RF) ablation to minimise blood loss during hepatic and splenic resections.
Methods In this video, we illustrate the technique of partial splenectomy assisted by RF energy to minimise blood loss.

Keywords Radiofrequency ablation · Partial splenectomy · Minimal blood loss

Introduction

Symptomatic splenic cysts are usually treated with either a total splenectomy or with cyst fenestration and omentoplasty. However, because of concerns of compromised immunological function after splenectomy and high recurrence rates following cyst fenestration, partial splenectomy has increasingly been advocated as the standard of care.[1] Nevertheless, concerns over adequate haemostasis during partial splenectomy have limited its widespread use. We have previously reported our experience of using radiofrequency (RF) ablation in minimising blood loss during hepatic and splenic surgery.[2,3] In the present case, this novel technique is utilised to reduce blood loss in a partial splenectomy for a symptomatic traumatic cyst. As long as the splenic hilum is preserved and a clear resection margin can be achieved, this technique can potentially be used for any splenic lesion including parasitic cysts.

Methods

This video illustrates the technique of partial splenectomy assisted by RF energy. First, the spleen was fully mobilised by dividing the lienorenal ligament. Adhesions to the transverse colon and the short gastric vessels were then divided. Once the spleen was delivered into the wound, RF energy was applied to the planned resection margin, removing the cyst and preserving the residual healthy spleen. Coagulative desiccation was performed using a "cooled-tip" radiofrequency probe and a 500-kHz generator (Radionics Europe, NV, Wettdren, Belgium). Application of the RF energy began with the area deepest and furthest from the upper surface of the spleen. Once coagulative desiccation had been achieved, the probe was then withdrawn 3 cm and the process repeated until the surface of the spleen was reached. The probe was then advanced 1 cm along the resection margin. When haemostasis was secured with complete ablation of the resection margin, a scalpel was used to transect the coagulated plane. No vascular clamping of the vascular pedicles was necessary, and the estimated blood loss was less than 30 ml. Postoperative recovery was uneventful.

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Results

We have performed this procedure in seven patients with no postoperative morbidity or mortality. To date, few reports have been presented involving a relatively small number of patients. The major potential complication is that of bleeding from the transected parenchyma whilst morbidity includes insufficient arterial supply to the preserved splenic remnant.[4]

Conclusion

Radiofrequency ablation can be a useful adjunct in partial splenectomy. This safe, fast and simple technique allows for preservation of splenic function with minimum blood loss. A potential benefit is that as it is more easily accomplished, it is therefore easier to teach compared to traditional partial splenectomy requiring isolation of segmental vessels.

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HOW I DO IT

Laparoscopic Pylorus-Preserving Pancreatic Head Resection and Hybrid Open Reconstruction via Pancreatogastrostomy

Tobias Keck · Simon Kuesters · Ulrich Wellner · Ulrich Theodor Hopt · Wojciech Konrad Karcz

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Abstract
Introduction Laparoscopic pancreatic surgery is ambitious and should only be performed in institutions with expert knowledge in pancreatic surgery.
Methods Whereas pancreatic tail resection is routinely and safely performed in several institutions, the laparoscopic resection of the pancreatic head is only performed by a handful of surgeons.
Results In this article, we present our hybrid approach with complete laparoscopic pylorus-preserving pancreatic head resection and successive reconstruction via a small retrieval incision, which might combine the advantages of the laparoscopic resection with the safety of an open and routine pancreatic anastomosis.

Keywords Laparoscopic pancreatic surgery · PPPD · Pancreatogastrostomy · Cystic neoplasms

Introduction

Indication for surgery in benign or premalignant pancreatic lesions has significantly increased the percentage of patients who received prophylactic pancreatic surgery throughout the last years,[1] especially those patients with cystic pancreatic neoplasms who generally have long-term survival rates and unimpaired prognosis after receiving a prophylactic operation.[2] For these patients, faster recovery from the operation utilizing minimally invasive surgery has been the focus of interest for lesions located on the left side of the mesentericoportal axis.[3] There are now larger series available detailing laparoscopic pancreatic tail resection that demonstrate safety and feasibility of this technique.[4,5] Laparoscopic pancreatic head resection is technically far more demanding and has therefore only been applied by a handful of specialized surgeons.[6–8] Recently, a robot-assisted laparoscopic middle pancreatectomy has been described, which demonstrates the advancement of technical development in pancreatic surgery.[9] The main critique of laparoscopic pancreatic head resection is that one might risk serious complications arising from pancreatic fistula formation in trade off for a smaller incision. We therefore demonstrate our technique of hybrid approach with complete laparoscopic pylorus-preserving pancreatic head resection (Lap. PPPD) and successive conventional and routine reconstruction via a small 5-cm retrieval incision.

Indications

The indications for our hybrid approach are as follows: neuroendocrine tumors of the pancreatic head up to a size of 2 cm, main duct type intraductal papillary mucinous neoplasm of the pancreas (IPMN) or combined type IPMN, branch duct type IPMN larger than 2 cm (signs of an invasive component do not exclude the possibility of laparoscopic resection), and periampullary or duodenal tumors up to 2 cm. About one third of all patients who

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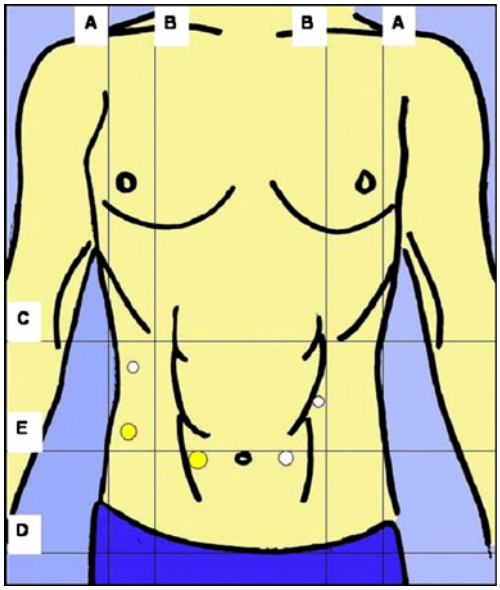

Fig. 1 Trocar placement. **a** Linea axillaris anterior, **b** linea clavicularis media, **c** linea subcostalis, **d** line between Spinae iliacae anteriores superiores. **e** Middle line between **c** and **d**. *Yellow dots* indicate 12-mm trocar positions for camera and staplers. *White dots* indicate 5-mm trocar positions

received a pancreatic head resection in our clinic qualify for the hybrid operation technique.

Technique

Laparoscopic Pylorus-Preserving Partial Pancreatoduodenectomy

The laparoscopic part of the operation is performed in special beach chair position with legs in abduction to allow the positioning of the surgeon or alternatively the first assistant between the legs of the patient. The trocars (all

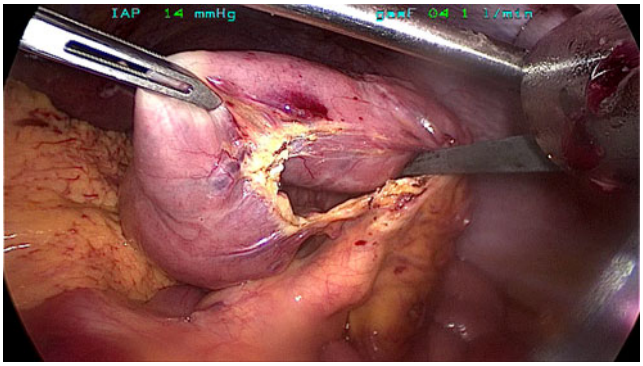

Fig. 3 Preparation of first jejunal loop

12 mm, Applied Medical, Rancho Santa Margarita, CA) are placed in a semilunar row (Fig. 1). The instruments consist of regular sharp and atraumatic laparoscopic instruments. For dissection, we used the Ligasure 5 mm Dissector (Covidien, Dublin, Ireland) and for transsection of the pancreatic neck, we used the Harmonic scalpel (Ethicon Endo-Surgery, Cincinnati, Ohio). HDTV Optical instruments (45 degree camera) and laparoscopic instruments were provided by Storz (Storz, Tuttlingen, Germany). The laparoscopic part of the operation is performed in two positions. Figure 2 demonstrates the positioning of the surgeon, the first and second assistants in positions A and B. The first part of the operation is performed in position A. The surgeon first gets access to the lesser sac by dividing the gastrocolic ligament with preservation of the gastroepiploic arcade. The right gastroepiploic vein is followed to the lower border of the pancreas. After division of the pancreas at the root of the transverse mesocolon, the superior mesenteric vein is liberated by circular dissection. Next, the right colonic flexure is liberated and the patient is turned to his left side. A complete Kocher maneuver is performed to free the duodenum from its retroperitoneal adhesions. The Kocher maneuver is continued to the

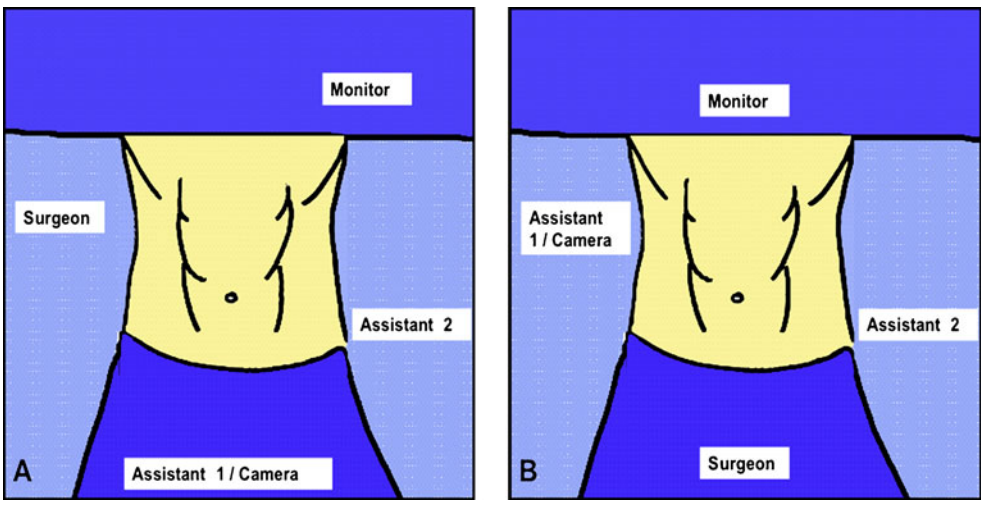

Fig. 2 Drawing demonstrates positions **a** and **b** from the laparoscopic operation. The surgeon in position **a** is standing on the right side, in position **b**, between the legs of the patient

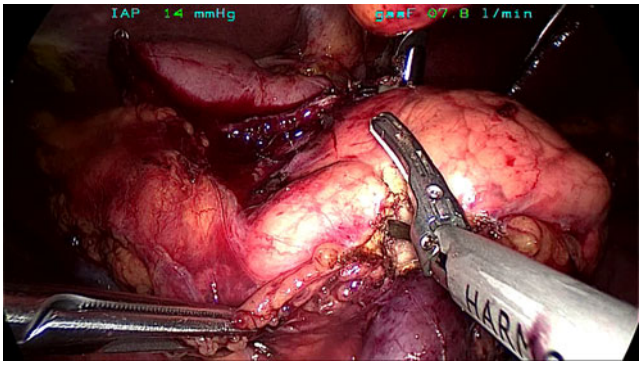

Fig. 4 Dissection of the pancreas with the harmonic scalpel

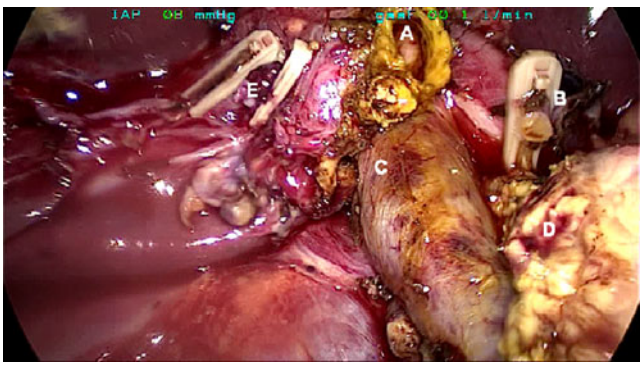

Fig. 5 Situs after resection. **a** Bile duct, **b** clip on art. gastroduodenalis, **c** portal vein, **d** pancreatic tail, **e** clips on art. cystica

ligament of Treitz from the right side to completely free the duodenum from these adhesions. After this, the colon is positioned upwards by the second assistant and the first jejunal loop is prepared by luminal dissection of the mesentery (Fig. 3). The devascularized gut is then transposed to the right side underneath the mesenteric root. The superior mesenteric vein is liberated further by dissection of the uncinate process and the superior mesenteric artery is identified and prepared. After transection of the gastroepiploic arcade close to the pylorus, the postpyloric duodenum is prepared by dissection of the minor omentum. The postpyloric duodenum is transected via the use of an endoscopic stapler device (Endo GIA, Covidien, Dubin, Ireland) and the stomach is placed in the upper left quadrant of the abdomen. The next step is the dissection of the gastroduodenal ligament. The lymph nodes of the gastroduodenal ligament are transected, the common hepatic artery and the gastroduodenal artery are prepared, the gastroduodenal artery is clipped with two proximal and one distal laparoscopic PDS clip (Autosuture/Covidien, Dublin, Ireland) and transected. The gallbladder is removed and the common hepatic duct is cut proximal to the cystic duct insertion. The lymphadenectomy is then continued on the upper rim of the pancreas and the portal vein is circularly liberated. After this step, the team changes to position B. In position B, the surgeon now carefully undermines the pancreatic head. The pancreas is elevated with a blunt instrument and transected with the Harmonic scalpel (Fig. 4). After this, the pancreatic head is carefully developed from the uncinate process along the mesenteric artery. The mesopancreas is divided by the use of a laparoscopic sealing dissector (Ligasure, Covidien, Dublin, Ireland). The specimen is then placed in the left upper quadrant of the abdomen and a 5-cm transverse incision is then performed in the right upper quadrant. Situs after resection is shown in Fig. 5.

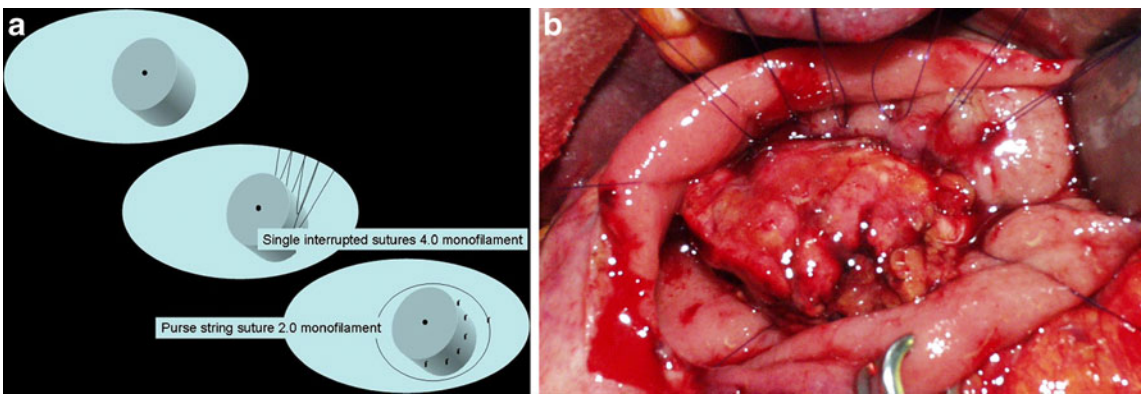

Fig. 6 Reconstruction via inverted pancreatogastrostomy. This reconstruction can be performed via a small 5–7-cm incision; **a** demonstrates the different steps of the anastomosis and **b** demonstrates the finished anastomosis before closure of the stomach

Small Access Open Reconstruction: Pancreatogastrostomy, Hepaticojejunostomy, Gastroenterostomy

After the resection, a 5-cm transverse retrieval incision is performed by dissection of the right straight abdominal muscle and a retractor system is placed in the abdomen (Alexis wound retractor; Applied Medical, Rancho Santa Margarita, CA) and Ulmer retractor system (Aesculap, Tuttlingen, Germany). The wound retractor and the retractor system allow a positioning of the incision to the area of interest for the anastomosis in the epigastrium. The access to the stomach is gained via a small posterior (1–2 cm) and a larger (5 cm) anterior working incision. An internal circular purse string suture (2.0 monofilament SH) is placed 1 cm from the posterior incision. The pancreas is inserted over 1–2 cm into the stomach via the posterior incision and an inverted circular end-to-side anastomosis is performed by single interrupted sutures (4.0 monofilament SH needle; Fig. 6). After the purse string suture of the stomach is knotted, the ventral incision of the stomach is closed by continuous running suture. This technique of pancreatogastrostomy allows the pancreatoenteric anastomosis on a minimal space. The incision is then pulled by the retractor to the right upper quadrant and an end-to-side hepaticojejunostomy is performed by single interrupted sutures (5.0 monofilament C1 needle). Finally, 40 cm distal from the hepaticojejunostomy, an antecolic end-to-side duodenojejunostomy is performed by continuous running suture. In conclusion, the anastomoses are drained via the trocar incisions. The skin is closed with an absorbable running suture, leaving a wound of approximately 6 cm.

Discussion

Laparoscopic operations have conquered several terrains of the surgery landscape. The proposed advantages are faster recovery from the operation and faster return to regular activity in the short term and less incisional hernias in the long term. In addition, smaller incisions might be of cosmetic relevance for the patients especially in operations that have a more elective indication. In pancreatic surgery, laparoscopic techniques have been viewed for a long time as being controversial due to potential limitations in lymphadenectomy or radicality in oncologic cases. In the last decade, indications for pancreatic surgery have shifted from operations for cancer or chronic inflammation to a high number of prophylactic operations for benign or premalignant precursor lesions in the pancreas, wherein cystic neoplasms of the pancreas comprise the majority of these cases.[1] Consecutively, in the last few years, several larger series of laparoscopic pancreatic resections for these indications have merged.[4,5,7] The performed laparoscopic operations on the pancreas are mainly restricted to the pancreatic tail or enucleations as they are technically less demanding and developing pancreatic fistula are generally less dramatic and of less clinical consequence compared to pancreatic fistula after pancreatic head resection.[10] There are only a few series from a handful of equally skilled pancreatic and laparoscopic surgeons that report their results with pancreatic head resections.[6,7] The main argument against laparoscopic pancreatic head resection is that one accepts compromises in performing the anastomosis in trade for a smaller incision. We therefore established a hybrid technique of laparoscopic and open surgery in which we can perform the anastomoses the exact same way as we do in open surgery but restrict the incision to 5–7 cm for retrieval of the specimen and for suturing the anastomoses. We do not expect the hybrid approach to replace open pancreatic surgery in the majority of cases. We do, however, propose a technique that needs consideration in the comparison to fully laparoscopic and open surgery, as we are convinced that hybrid techniques are likely to gain wider acceptance in complex operations. We speculate that the combination of laparoscopic resection and minimal access reconstruction combines the advantages of both approaches. We will therefore continue to evaluate our operative technique for selected indications such as small periampullary lesions, cystic neoplasms or small neuroendocrine tumors.

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REVIEW ARTICLE

Radiofrequency Ablation Versus Resection for Liver Tumours: An Evidence-Based Approach to Retrospective Comparative Studies

Gianpiero Gravante · John Overton · Roberto Sorge · Neil Bhardwaj · Matthew S. Metcalfe · David M. Lloyd · Ashley R. Dennison

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Abstract
Background Recently randomized controlled trials have been advocated to compare radiofrequency ablation (RFA) and hepatic resection (HR) in resectable tumours and determine whether differences in observed survivals result from the heterogeneity in previous studies between RFA (treating unresectable lesions) and HR (treating lesions deemed resectable). We reviewed the literature that directly compares the treatments and employed an evidence-based approach to examine the data.
Materials and Methods All studies comparing RFA and HR were included. Primary outcomes were the overall survival (OS) and disease-free survival (DFS) at 3 and 5 years. A subgroup analysis was conducted for solitary or small tumors (<4 cm for colorectal metastases (CRM) or <5 cm for hepatocellular carcinoma (HCC)).
Results Most studies were retrospective. For CRM, HR was markedly superior to RFA in respect of 3- and 5-year OS as well as 5-year DFS including tumours smaller than 4 cm and solitary lesions. For HCC, HR was markedly superior to RFA for 3- and 5-year OS as well as 3-year DFS, and produced a better OS at 3 years for solitary lesions and DFS at 3 years for small tumours.
Conclusions Multiple factors determine outcomes following treatment of liver tumours. Small or solitary lesions seem the most appropriate ones to study as this reduces the number of confounding variables, but even in these cases HR confers a better OS and DFS than RFA for both CRM and HCC. If our data are confirmed it will be important to examine other factors influencing the response.

The article has not been presented to any society or meeting.

Mr. Ashley R. Dennison had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Keywords Radiofrequency ablation · Hepatic resection · Palliation · Liver tumours

Introduction

Over the last two decades, improvements in preoperative assessment,[1] surgical technique, anaesthesia and postoperative intensive care have all contributed to a significant reduction of postoperative morbidity and mortality following liver surgery. These factors have also helped improve the long-term survival of patients undergoing hepatic resection (HR). In patients where surgical resection is not possible or appropriate, there has been considerable progress in the field of ablative therapies. In conjunction with adjuvant chemotherapy, these treatments aim to palliate by achieving some degree of disease control and it was hoped that these treatments would also prolong survival. These in situ techniques for the ablation of liver tumours have steadily increased in popularity and are now generally preferred to previous modalities such as chemoembolization and alcohol injection.

Cryotherapy was the first technique introduced for hepatic ablation and although the use of cold temperatures easily produced tissue destruction, cellular antigens were preserved; and in large volume, ablations produced massive activation of the immune system[2] and serious systemic effects (cryoshock).[3,4] As a direct result of these potentially fatal consequences, there was a gradual decline in the use of cryotherapy which was mirrored by the contemporaneous development and increasing popularity of safer techniques based on tissue heating. Developments in radiofrequency ablation (RFA) and more recently microwave ablation progressed rapidly in large part due to technical improvements which allowed for the evolution of generators and probes which produced reproducible tissue destruction which was safe and could be achieved quickly. To date, RFA remains the most widely used ablative technique worldwide and numerous RFA devices have been developed[5] each producing different shapes[6] and volumes of the ablated lesion. Initially, the wide range of generators and probes used (and the even wider range of combinations) produced results and data that were very difficult to compare; and in an attempt to overcome these difficulties, researchers adopted a common terminology[7] which has subsequently allowed results to be pooled (and resulted in a number of reviews and meta-analyses). These pooled results have demonstrated a mortality of 0.5% following RFA ablation (20/3,670 patients), a complication rate of 8.9% (327/3,670) and a local recurrence rate of 2–60%.[8–11] There is an overall survival (OS) at 5 years of 14–55% which is very encouraging especially when the initial poor prognosis of many of the patients is considered.[12]

Evidence from the literature also shows that local recurrences are highly dependent on the diameter of the initial lesion,[10] a characteristic shared by all in situ ablative techniques.[13–16] One centimetre is usually considered the minimum safe macroscopic margin for tumour ablation and a 5-cm ablation is required for the safe destruction of a tumour (including the transitional zone) with a diameter of approximately 3 cm.[10,17] These encouraging results have prompted some authors to advocated the use of a multicentre randomized controlled trial to compare RFA and HR in patients with resectable tumours;[12,18] but to date, this has not yet been performed. Our intention is to review critically the literature that directly compares the two treatment options, analyse the results with an evidence-based approach in order to determine whether a future large randomised study is justified.

Materials and Methods

Study Selection and Data Extraction

We followed the QUOROM guidelines for the development and description of this study.[19] All studies comparing RFA and HR for the treatment of primary and secondary liver tumours that reported the OS and disease-free survival at 3 or 5 years were included in the analysis. Given the shortage of prospective randomized trials that compared RFA and HR, retrospective studies (case controls) were also included in the analysis. No dates were used to limit the search. All available studies were included regardless of the number of patients treated. Excluded were those that evaluated only one of the treatments, either RFA or HR, those that did not report OS or disease-free survival (DFS) or that reported data for shorter follow-up (i.e. 2 years) and finally those studies that treated with RFA patients that had already undergone HR in the past or those who had a combined approach (resection+RFA). Studies were searched for and selected from the MEDLINE, EMBASE and Cochrane Library databases without language restrictions. Three sets of key words were used: the first were related to the liver disease (colorectal metastases (CRM), colon and rectal cancer, hepatocellular carcinoma (HCC), primary and secondary neoplasms, malignancy, tumours, and liver cancers), the second involved the treatment adopted (radiofrequency, ablation, surgery, resection, palliation, palliative therapy), the third the outcome (OS, DFS).

Potentially relevant studies were identified by the title and the abstract and full papers were obtained and assessed in detail. The methodological quality of studies could not be assessed according to the Jadad Score[20] as most of the studies found were retrospective (see "Results" section and Tables 1 and 2). A specifically designed data form was used

Table 1 Characteristics of comparative studies for colorectal liver metastases

Author	Year	Type of study	Patients	Age (years)	Sex (males; %)	Tumour characteristics		Treatment	Approach	DFS (years)		OS (years)	
						Number	Diameter			3 (%)	5 (%)	3 (%)	5 (%)
Abdalla[21]	2004	CC	190	60 (23–88)	–	–	–	Res.	–	–	–	73	58
			57	60 (23–88)	–	1 (1–8)	2.5	RFA	Open	–	–	37	–
Berber[22]	2008	CC	90	64±1	57 (63)	1	3.8±0.2	Res.	–	–	–	70	40
			68	64±1	43 (63)	1	3.7±0.2	RFA	Lap.	–	–	35	30
Elias[23]	2004	CC	40	–	–	2.4±1.8	4.4±2.6	Res.	Anat.	–	–	–	–
			64	–	–	2.5±2.5	1.4±1.3	Res.	Wegde	–	–	–	–
			88	–	–	2.9±2.5	1.5±1.1	RFA	Open	–	–	–	–
Oshowo[24]	2003	CC	20	63 (52–77)	10 (50)	1	4 (2–7)	Res.	–	–	–	55	–
			25	57 (34–80)	11 (44)	1	3 (1–10)	RFA	Perc.	–	–	53	–
Reuter[25]	2009	CC	126	62	69 (55)	2.1	5.3	Res.	–	–	–	–	23-
			66	63	46 (70)	2.8	3.2	RFA	–	–	–	–	21
Hur[18]	2009	CC	42	–	–	1	2.6 (0.6–8)	Res.	–	90	90	70	50
			25	–	–	1	2.5 (0.8–3.6)	RFA	Open/perc.	76	70	60	26
Aloia[26]	2006	CC	150	61 (23–88)	87 (58)	1	3.5 (0.5–17)	Res.	–	–	50	79	71
			30	61 (23–88)	23 (77)	1	3 (1–7)	RFA	Open/perc.	–	0	57	27
Otto[27]	2009	Prosp.	82	62 (38–80)	49 (60)	2 (1–11)	5 (1–15)	Res.	–	–	–	60	51%
			28	64 (42–78)	20 (71)	2 (1–5)	2.0 (1–5)	RFA	Perc.	–	–	67	48%
Lee[39]	2008	CC	116	58 (26–79)	76 (66)	1	<3 cm=55%; >3 cm=45%	Res.	–	88	85	–	66
			37	59 (28–75)	26 (70)	1	<3 cm=73%; 3-6 cm=27%	RFA	Open/perc.	53	43	–	49
White[40]	2007	CC	30	62 (42–81)	20 (67)	1	2.7±1.1	Res.	Wegde	51%	32%	82%	57%
			22	62 (48–77)	8 (36)	1	2.4±1.0	RFA	Perc.	–	–	26%	0%
Leblanc[33]	2008	CC	37	61 (25–88)	24 (65)	1 (1–10)	2 (0.3–18)	Res.	–	–	–	–	–
			34	67 (27–81)	17 (50)	3 (1–8)	1 (0.2–5)	RFA	Open/lap.	–	–	–	–

OS overall survival, *DFS* disease-free survival, *CC* case control, *Prosp* prospective study not randomized, *RCT* randomized control trial

[a] Data estimated from Kaplan–Meier curves

[b] Overall survival since treatment of the primary tumor

Table 2 Characteristics of comparative studies for hepatocellular carcinoma

Author	Year	Type of study	Patients	Age (years)	Sex (males; %)	Tumour characteristics		Treatment	Approach	DFS (years)		OS (years)	
						Number	Diameter			3 (%)	5 (%)	3 (%)	5 (%)
Ogihara[28]	2005	CC	47	60 (48–72)	29 (62)	1	7.4±5.2	Res.	–	–	–	65	31
			40	69 (59–79)	19 (48)	1	4.6±2.9	RFA	Open/Lap./Perc.	–	–	58	39
Guglielmi[29]	2007	CC	91	–	73 (80)	1=76%; >1=24%	<3 cm=34%; 3–6 cm=66%	Res.	–	56	27	64	48
			109	–	88 (81%)	1=59%; >1=40%	<3 cm=30%; 3–6 cm=70%	RFA	Perc.	22	22	42	20
Chagnon[30]	2007	RCT	90	18–75	–	–	≤5 cm	Res.	–	69	–	73	–
			71	18–75	–	–	≤5 cm	RFA	–	64	–	71	–
Ueno[31]	2008	CC	123	67 (28–85)	82 (67)	1=89%; >1=11%	2.7±0.1	Res.	–	47	38	92	80
			155	66 (40–79)	100 (65)	1=65%; >1=35%	2.0±0.1	RFA	Open/perc.	36	20	92	63
Santambrogio[32]	2009	CC	78	68 (60–76)	55 (71)	1	2.9±1.2	Res.	–	–	–	85	54
			74	68 (61–75)	59 (80)	1	2.7±1.1	RFA	Lap.	–	–	66	41
Chen[34]	2006	RCT	90	49±11	75 (83)	1	≤5 cm	Res.	–	69	–	73	–
			71	52±11	56 (79)	1	≤5 cm	RFA	Perc.	60	–	69	–
Cho[35]	2005	CC	61	57	48 (79)	<3	3.4±1.0	Res.	–	37	–	77	–
			99	58	76 (77)	<3	3.1±0.8	RFA	–	31	–	80	–
Hong[36]	2005	CC	93	49±10	69 (74)	1	2.5±0.8	Res.	–	55	–	84	–
			55	59±10	41 (75)	1	2.4±0.6	RFA	Perc.	40	–	73	–
Vivarelli[38]	2004	CC	79	65±8	57 (72)	1=83%; >1=17%	≤3 cm=27%; >3 cm=73%	Res.	–	50	–	65	–
			79	68±9	67 (85)	1=58%; >1=42%	≤3 cm=28%; >3 cm=72%	RFA	Perc.	20	–	33	–
Hasegawa[37]	2008	CC	2857	67 (48–77)	2114 (74)	1=84%; 2–3=16%	2 (1–3)	Res.	–	–	–	–	–
			3,022	69 (52–80)	1937 (64%)	1=72%; >1=28%	2 (1–3)	RFA	–	–	–	–	–

OS overall survival; *DFS* disease-free survival, *CC* case control; *Prosp* prospective study not randomized, *RCT* randomized control trial

to collect all the relevant data, including patients' demographics, technical aspects, and outcome measures. Data collection was carried out independently by two researchers (GG and OJ) and then compared. Primary outcome measures were the OS and DFS at 3 and 5 years of follow-up after treatment. A subgroup analysis was conducted when possible for patients affected by solitary tumours or where the maximal tumour diameter was less than 4 cm for CRM and 5 cm for HCC.

Statistical Analysis

Data analysis was performed using the Statistical Package for the Social Sciences Windows version 13.0 (SPSS, Chicago, IL, USA) and the meta-analysis with Interactive eXplanations (MIX–version 1.6) program. Descriptive statistics for qualitative variables was performed with occurrences and described with relative frequencies, for quantitative parametric variables with the mean and standard deviation and for the quantitative non-parametric variables with the median and range. The odds ratio and 95% confidence intervals in the RFA and HR group were evaluated. Results were considered significant if the probability of a chance occurrence was less than 5% ($p< 0.05$).

Results

Since 2003, numerous articles have compared the results of RFA and HR for CRM and HCC (Tables 1 and 2).[18,21–40] All studies were retrospective except for three which were prospective,[27,30,34] including two randomized trials.[30,34] Some studies reported specific data for solitary[18,22,24,26,28,32,34,36,39,40] or small tumours.[18,22,26,30–32,34–36,40] A study based on a theoretical mathematical analysis using the Markov modelling to simulate a randomized trial of RFA and HR for HCC less than 5 cm was also retrieved and discussed, but its numeric data were not included.[41] Two studies reported OS and DFS for shorter follow-ups,[33,37] one study had a significant higher percentage of patients that underwent previous HR in the RFA group and presented lower RFA survival rates compared to the others studies examined.[40] The descriptive data of these three studies are still presented for completeness (Tables 1 and 2) but have not been included (Tables 3 and 4). One article published in a Chinese journal was not available.[42]

Survival of Patients with Colorectal Metastases

At the moment, there are no 5-year survival data available for RFA employed for resectable CRM. All studies used RFA to treat unresectable liver tumours including those that presented specific data on solitary lesions or small tumours (Table 3). HR was markedly superior to RFA for 3- and 5-year OS as well as 5-year DFS (Table 3, Fig. 1). Results also confirm the superiority of HR over RFA for OS at 5 years of follow-up in tumours smaller than 4 cm and for solitary lesions (Table 3). There were not enough studies to provide results for the DFS at 3 years or for OS at 3 years in small tumours.[18,39]

Survival of Patients with Hepatocellular Carcinoma

HR was markedly superior to RFA for 3- and 5-year OS as well as 3-year DFS (Table 4, Fig. 2). The subgroup analysis showed better OS at 3 years for HR compared to RFA in solitary lesions and DFS at 3 years for small tumours (Table 4, Fig. 2). No significant differences were found at 3-year OS for small tumours (Table 4, Fig. 2). There were not enough studies to provide definitive results for 5-year DFS[29,31] or for the subgroup analysis of OS at 5 years and DFS at 3 years for solitary lesions.

Discussion

Currently, liver resection is the gold standard treatment for resectable liver tumours but is not possible or appropriate in up to 80% of cases due to a low predicted hepatic reserve, significant co-morbidity or technical issues related to the location, number or size of the lesions. Intuitively, RFA presents a valid alternative to hepatic resection on many levels, especially by improving the OS compared to standard chemotherapy or palliative treatments. Despite this, overall survivals at 5 years still do not match those of HR and these outcome differences have been attributed to the fact that HR patients had resectable lesions while those treated by RFA were unresectable.[12] It is this explanation, which has been taken by some authors to imply that in matched patients results with HR and RFA would be similar, that has resulted in some units advocating a randomized prospective trial for resectable lesions.[12] If proven, the advantage of a minimal invasive technique, with the greater preservation of liver, reduced complications and shorter hospital stays would expand the indications considerably. To date, there are a few sporadic reports of curative rather than palliative treatments with RFA for resectable liver lesions.[43,44] Two randomized studies on solitary HCC measuring less than 5 cm appear to confirm similar OS with HR and RFA, although the follow-up is only 3 years.[30,34] In the retrospective study of Hasegawa et al. [37] although for HCC higher recurrence rates were found for RFA, OS was similar to HR for tumours of less than 3 cm. We did not include this study due to the length of the

Table 3 Results of the meta-analysis for colorectal metastases

Parameter	Time interval	Tumour characteristics	RFA	HR	OR (95%CI)	*p*	Ref.
OS	3 years	–	46.8% (109/233)	71.4% (410/574)	0.390 (0.283–0.538)	<0.0001	18,21,22,24,26,27
		Solitary	46.6% (69/148)	73.5% (222/302)	0.375 (0.245–0.575)	<0.0001	18,22,24,26
		Small (<4 cm)	46.2% (43/93)	73.5% (97/132)	–	–	18,22
	5 years	–	31.5% (80/254)	51.3% (311/606)	0.525 (0.381–0.724)	<0.0001	18,22,25–27,39
		Solitary	33.1% (53/160)	60.3% (240/398)	0.401 (0.270–0.595)	<0.0001	18,22,26,39
		Small (<4 cm)	32.5% (40/123)	59.6% (168/282)	0.407 (0.258–0.642)	<0.0001	18,22,26
DFS	3 years	–	63% (39/62)	88.6% (140/158)	–	<0.0005	18,39
	5 years	–	35.9% (33/92)	68.5% (211/308)	0.095 (0.048–0.190)	<0.0001	18,26,39

HR hepatic resection, *RFA* radiofrequency ablation, *OR* odds ratio, *CI* confidence interval, *OS* overall survival, *DFS* disease-free survival. *Solitary* studies treating patients with one metastasis only. *Small* studies reporting data specific for tumours less than 4 cm in diameter

follow-up; it is worth noting that the survey involved 795 institutions and 7,185 patients and in the future will almost certainly produce interesting long-term results.

We conducted this study in an attempt to identify, among the criteria used to define respectability, those that could explain the difference in observed OS at 3 and 5 years between lesions treated by HR and unresectable lesions treated with RFA. The classic criteria which are employed to determine resectability include the number of metastases (three to four), the size of the largest tumour and a mandatory 1 cm margin of resection.[45] It is possible that in previous studies, lesions treated by HR had a better prognosis because of the significant difference in the number of patients with solitary tumours in the HR compared to the RFA groups. A number of studies report results for RFA and HR in patients who had solitary lesions,[18,22,24,26,28,32,34,36,39,40] but the pooled analysis consistently demonstrates increased survival rates for HR. It is also possible that this better prognosis following HR may result from differences between groups in respect of the size of the tumours treated and as a consequence the disease free margins (Ro resections) that were achieved. The data do not support this however, as even the case specific data available for small tumours[18,22,26,30–32,34–36,40] again demonstrated consistently higher survivals rates for HR compared to RFA. This appears to suggest that tumour characteristics other than the size or number of lesions influence the OS differences observed in these studies. Extensive disease is frequently not suitable for treatment by one or other treatment particularly when ablative techniques could damage vital inflow structures or major venous tributaries. However, extensive bilobar lesions or invasion of important vascular structures (vena cava, hepatic pedicle, two suprahepatic veins with proximity to the third) are generally contraindications for both HR and RFA and only a very small number of these cases are treated and are thus unlikely to have influenced the results.[46]

White et al.[40] reported rates of OS at 3 and 5 years following RFA that were markedly lower than the majority of series although OS following HR was in line with published results. Overall survival at 3 years was approximately 26% (as estimated from the Kaplan–Meier curves)

Table 4 Results of the meta-analysis for hepatocellular carcinomas

Parameter	Time interval	Tumour characteristics	RFA	HR	OR (95%CI)	*p*	Ref.
OS	3 years	–	67.1% (505/753)	76.6% (576/752)	0.578 (0.455–0.735)	<0.0001	28–32,34–36,38
		Solitary	67.1% (161/240)	78.2% (241/308)	0.581 (0.395–0.854)	<0.01	28,32,34,36
		Small (<4 cm)	78.1% (410/525)	81.5% (436/535)	0.739 (0.543–1.006)	NS	30–32,34–36
	5 years	–	43.7% (165/378)	58.7% (199/339)	0.482 (0.350–0.663)	<0.0001	28,29,31,32
		Solitary	40.3% (46/114)	45.6% (57/125)	–	–	28,32
		Small (<4 cm)	55.9% (128/229)	70.1% (141/201)	–	–	31,32
DFS	3 years	–	36.9% (236/639)	55.2% (346/627)	0.507 (0.402–0.639)	<0.0001	29–31,34–36,38
		Solitary	51.6% (65/126)	61.7% (113/183)	–	–	34,36
		Small (<4 cm)	43.7% (197/451)	56.0% (256/457)	0.671 (0.511–0.882)	<0.005	30,31,34–36
	5 years	–	28.1% (78/278)	24.5% (49/200)	–	–	29,31

HR hepatic resection, *RFA* radiofrequency ablation, *OR* odds ratio, *CI* confidence interval, *OS* overall survival, *DFS* disease-free survival. *Solitary* studies treating patients with one lesion only. *Small* studies reporting data specific for tumours less than 5 cm in diameter

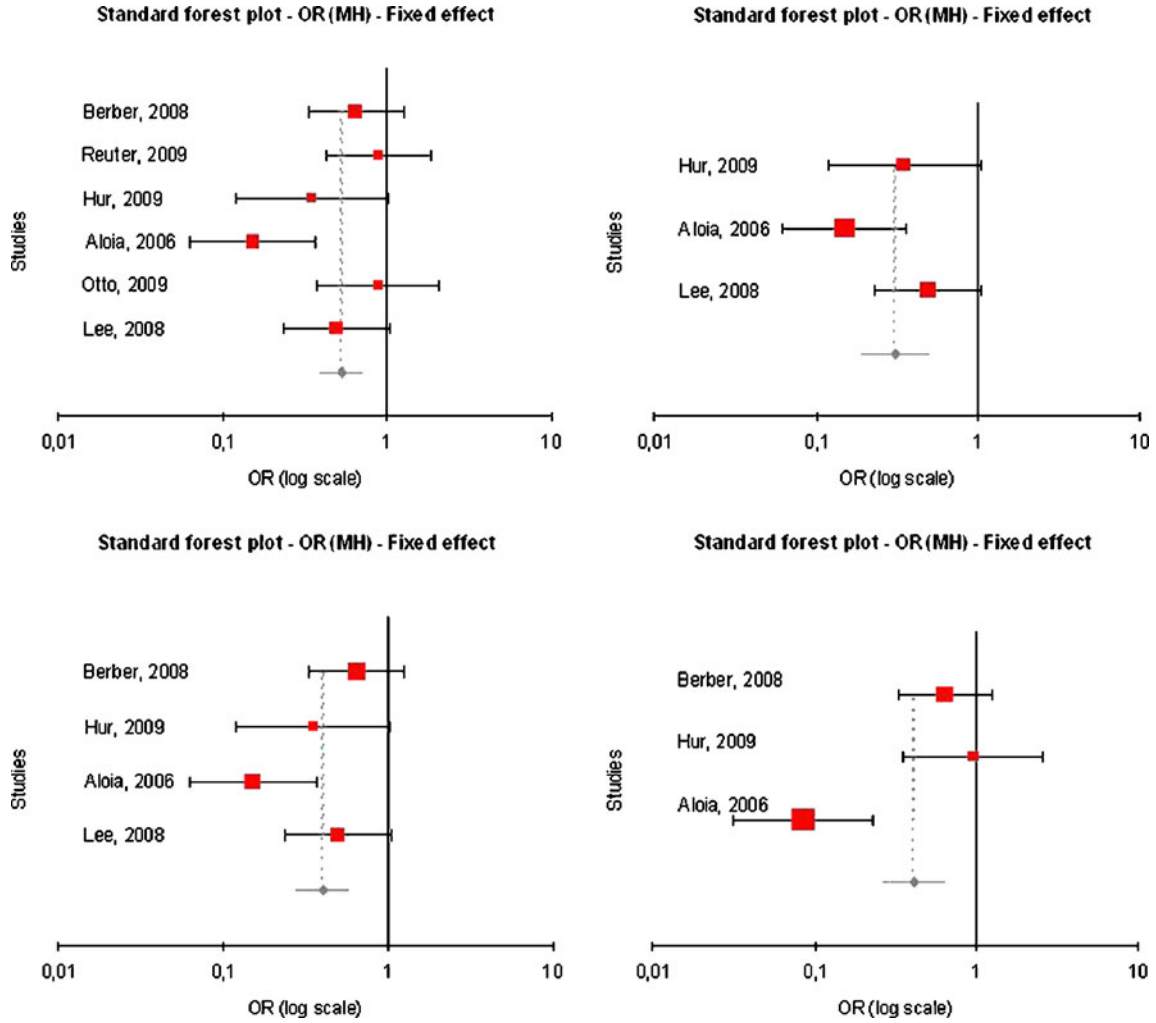

Fig. 1 Forest plot graphs showing results for colorectal metastases. *Left upper panel* overall survival at 5 years. *Right upper panel* disease-free survival at 5 years. *Left lower panel* overall survival for solitary metastases at 5 years. *Right lower panel* overall survival for small lesions (<4 cm) at 5 years

compared to 35–60% for the other reports[18,22] while at 5-year survival was 0% compared to 21–49% for the other reports.[25,39] The OS Kaplan–Meier curve shows that most of the RFA patients died within the first 36 months following the procedure. However as pointed out by the authors, patients in the RFA group were more likely to have undergone prior liver resection.[40] This implies more advanced or aggressive original tumours and reduced hepatic reserves, both characteristics that would predict a worse prognosis compared to the patients in the HR group. For this reason, the study was not considered consistent with the other evaluated series and has not been included. Interesting results have also been reported by Molinari et al.[41] using the Markov model. HR produced better survival for HCC less than 5 cm compared to RFA due to the increased risk of recurrent disease after RFA.[41] It is possible that HR, particularly when a formal anatomical (at least segmental) resection is possible, achieves better clearance margins and hence disease control with consequently lower recurrences than following RFA ablation. However, there were also survival differences relating to the patients' age at the time of treatment. HR is still the best option for patients younger than 75 years of age where the operative risk is low. In patients over 75 years of age, RFA is to be preferred as any survival advantage following treatment by HR is outweighed by the significantly increased perioperative risk.[41]

The current study has important limitations that need to be acknowledged for a critical appraisal of the results. The number of studies available was sufficient to draw general conclusions regarding OS and DFS, but not for all the subgroup analyses, for example DFS at 3 years for CRM or the OS survival at 5 years for solitary or small HCC. Hopefully, this problem can be overcome if results from

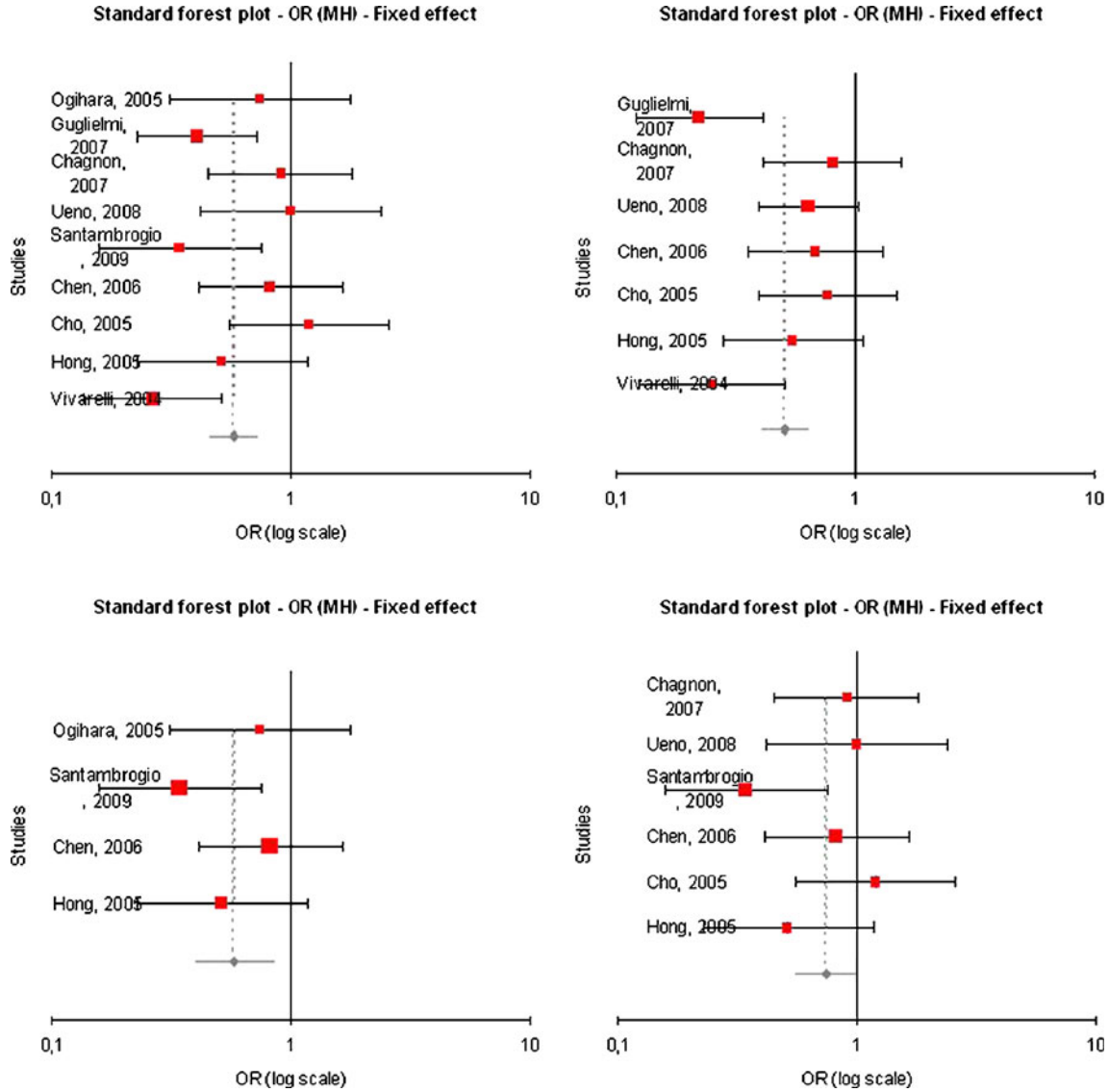

Fig. 2 Forest plot graphs showing results for hepatocellular carcinoma. *Left upper panel* overall survival at 53 years. *Right upper panel* disease-free survival at 3 years. *Left lower panel* overall survival for solitary metastases at 3 years. *Right lower panel* overall survival for small lesions (<5 cm) at 3 years

future series is reported in such a way that it can be added to the present data. In addition, the vast majority of the studies were retrospective in nature and these usually carry important confounders: patient selection, disease biology (extent of disease, disease-free interval), definition of resectability (or eligibility for transplant when dealing with HCC), intent of treatment, different histologic subtypes of tumor (especially HCC vs. CRM), liver function (for HCC), technical success of procedures (adequacy of ablation, pathology margins on resection specimens), approach for RFA (open, laparoscopic, percutaneous) and proximity to major vessels,[17] patient comorbidities (especially cirrhosis), and use of systemic treatments (chemotherapy and its efficacy rates). However, they are at present the only source of data which is available in order to determine whether a large prospective study (with all its risks and implications) is still justified.

Conclusions

Unfortunately, the majority of studies which are presently available for analysis comparing the treatment of liver tumours by HR or RFA are retrospective. There are only two RCTs available and they generally have short follow-ups.[30,34] HR appears to confer better OS and DFS than RFA for both CRM and HC even when results for solitary or small tumours are analysed. Some subgroups do not contain sufficient studies to furnish reliable OS results at 5 years and more series are required with specific data for

solitary or small lesions to enable definitive conclusions to be reached. With all the limitations derived from the heterogeneity of pooling data from retrospective studies, if these preliminary results are confirmed with the emergence of further series, it will be important to carefully examine other factors which may influence the response to different treatments and the consequent outcome.

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GI IMAGE

Plumstone Ileus as a Presentation of Crohn's Disease

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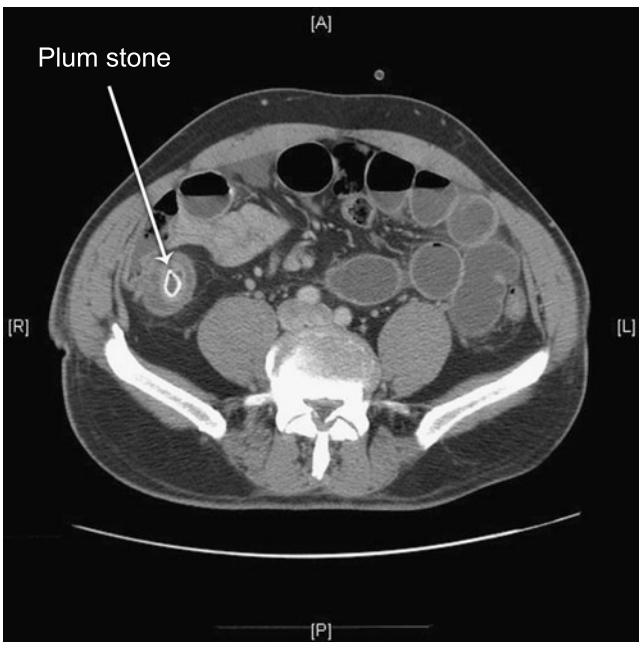

Fig. 1 CT abdomen demonstrating small bowel obstruction secondary to a plum stone.

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This 57-year-old gentleman was admitted with colicky abdominal pain, vomiting and signs of small bowel obstruction on abdominal X-ray. He confessed to swallowing a plum stone and so underwent laparotomy and enterotomy for plum stone ileus (Figs. 1 and 2). At laparotomy, fat-wrapping and other features consistent with Crohn's disease were noted in the region of impaction, but as he had been previously asymptomatic, no resection was undertaken. Unfortunately, he failed to settle and subsequently underwent right hemicolectomy, the histology from which confirmed Crohn's. On literature review, fruit stone impaction has been shown to be a not infrequent presentation of inflammatory bowel disease.

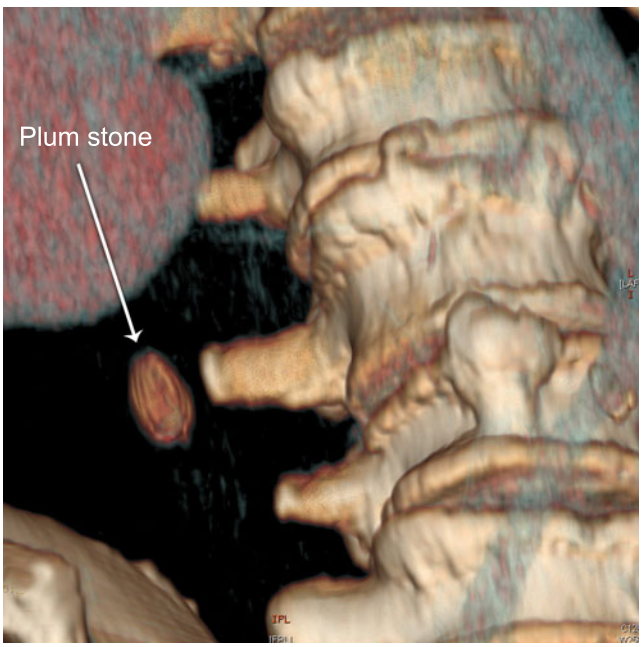

Fig. 2 CT reconstruction of plum stone position.