J Gastrointest Surg (2008) 12:1815–1821
DOI 10.1007/s11605-008-0668-7

ERCC1 RNA Expression in Peripheral Blood Predicts Minor Histopathological Response to Neoadjuvant Radio-chemotherapy in Patients with Locally Advanced Cancer of the Esophagus

Jan Brabender · Daniel Vallböhmer · Peter Grimminger · Andreas C. Hoffmann · Frederike Ling · Georg Lurje · Elfriede Bollschweiler · Paul M. Schneider · Arnulf H. Hölscher · Ralf Metzger

Received: 13 May 2008 / Accepted: 8 August 2008 / Published online: 3 September 2008

Abstract
Objective The aim of this study was to determine the gene is spelled excision repair cross-complementing gene 1 (ERCC1) RNA-expression in peripheral blood as a non-invasive molecular predictor of response to neoadjuvant radio-chemotherapy in patients with locally advanced cancer of the esophagus.
Background Only patients with locally advanced cancer of the esophagus with a major histopathological response to neoadjuvant radio-chemotherapy benefit from this treatment. No non-invasive molecular marker exists that can reliably predict response to neoadjuvant therapy in this disease. To improve the treatment of patients with cancer of the esophagus, molecular predictors of response are desperately needed.
Methods Blood samples were drawn from 29 patients with esophageal cancer prior to neoadjuvant radio-chemotherapy. After extraction of cellular tumor-RNA from blood samples, quantitative expression analysis of ERCC1 was done by real-time reverse transcription polymerase chain reaction.
Results Nineteen (65.5%) patients showed a minor and ten (34.5%) a major histopathological response to neoadjuvant therapy. ERCC1 expression in blood of patients was detectable in 82.8%. The median ERCC1 expression was 0.62 (minimum 0.00, maximum 2.48) in minor responders and 0.24 (minimum 0.00, maximum 0.45) in major responders ($p=0.004$). No significant associations were detectable between ERCC1 levels and patients' clinical variables. Relative ERCC1 levels above 0.452 were not associated with major histopathological response (sensitivity, 68.4; specificity, 100%), and 13 of 19 patients with minor response could be unequivocally identified.
Conclusion Minor responders to the applied therapy show a significant higher ERCC1 expression level in their blood compared to major responders. ERCC1 appears to be a highly specific non-invasive predictor of response to neoadjuvant therapy in esophageal cancer.

Presented at the Forty-Ninth Annual Meeting of The Society for Surgery of the Alimentary Tract, San Diego, California, May 17–22, 2008

J. Brabender (✉) · D. Vallböhmer · P. Grimminger · A. C. Hoffmann · F. Ling · G. Lurje · E. Bollschweiler · A. H. Hölscher · R. Metzger
Department of Visceral and Vascular Surgery,
University of Cologne,
Joseph-Stelzmann Str. 9,
50931 Cologne, Germany
e-mail: jan.brabender@t-online.de

P. M. Schneider
Department of Visceral and Transplant Surgery,
University of Zuerich,
Rämistr. 100,
8091 Zürich, Switzerland

Keywords Molecular markers · Response prediction · Cancer of the esophagus · ERCC1

Introduction

In recent years, neoadjuvant therapy strategies have been applied to improve survival in patients with locally advanced esophageal cancer.[1–3] However, it has been shown that only patients with a major histopathological response benefit from this treatment.[4] These regimens can be extremely grueling and might lead to many complications, including mucositis, pancytopenia, infection, tumor progression, and rarely, death.[1,5] Therefore, predictive molecular markers indicating response or non-response to neoadjuvant treatment would be extremely helpful for future individualized therapy strategies in cancer of the esophagus.

Several candidate molecular response markers to neoadjuvant therapy in esophageal cancer have been discovered in the last couple of years.[6–12] However, all of these potential markers are of invasive nature, meaning it is mandatory to obtain tumor tissue for molecular analysis by at least a biopsy during esophagogastroscopy. We have recently developed a method to quantify tumor-specific mRNA in peripheral blood of patients with gastrointestinal malignancies.[13] A non-invasive molecular marker would ultimately improve response prediction and enable on-line monitoring of therapy success or failure in neoadjuvant therapies.

One of the most promising molecular markers for response prediction is the excision repair cross-complementing 1 (ERCC1). ERCC1 mRNA expression has been reported to be associated with non-response to neoadjuvant *cis*-diamminedichloridoplatinum(II) (CDDP)-based chemotherapy in gastric cancer, colonic cancer, and non-small cell lung cancer.[14–16] More interestingly, high ERCC1 mRNA expression in tumor tissue of patients with locally advanced esophageal cancer has been significantly associated with histopathological minor response to neoadjuvant radio-chemotherapy (5-FU, *cis*-Platin, 36Gy) in this disease.[9]

The purpose of this prospective study was to investigate the potential of quantitative ERCC1 RNA expression in peripheral blood of patients with locally advanced, resectable esophageal cancers as a non-invasive molecular predictor of histopathological response to neoadjuvant radio-chemotherapy in this disease.

Materials and Methods

Study Population, Demographic Data, and Neoadjuvant Therapy All patients were recruited from an ongoing clinical trial on neoadjuvant radio-chemotherapy for esophageal cancer. None of the patients had prior radio- and/or chemotherapy. Twenty-nine consecutive patients (median age, 61 years; age range, 41–71 years; gender, 23 men and six women, 18 adenocarcinomas and 11 squamous cell carcinomas) with locally advanced, resectable esophageal cancers (cT2–4, Nx, M0) were offered standardized neoadjuvant radio-chemotherapy. Clinical staging was based on a barium swallow, endoscopic ultrasound, and computed tomography of chest and abdomen. CDDP (20 mg m^{-2} day^{-1}) was administered as a short-term infusion on days 1–5, and 5-fluorouracil (1,000 mg m^{-2} day^{-1}) was administered as a continuous infusion over 24 h on days 1–5. Radiation therapy was administered by linear accelerators with 10- to 15-MV photons. Radiation was delivered in daily fractions of 1.8 Gy (days 1–5, 8–12, 15–19, and 22–26) to a total dose of 36 Gy using a multiple-field technique. Surgical resection was performed 4–5 weeks after completion of chemo radiation after clinical restaging using the same procedures as for primary staging. Standardized transthoracic en bloc esophagectomy with two-field lymphadenectomy and reconstruction by gastric tube interposition with high intrathoracic anastomosis was performed in all patients.[17] Informed consent was obtained from each patient, and the scientific protocol was approved by the local ethics committee.

The degree of histomorphological regression was classified into four categories according to Schneider et al.:[4] (a) grade I, >50% vital residual tumor cells; (b) grade II, 10–50% vital residual tumor cells; (c) grade III, nearly complete response with <10% vital residual tumor cells; and (d) grade IV, complete response (pCR, ypT0). Regression grades III and IV were considered as major histomorphological response (MaHR) compared with grades I and II constituting minor histopathological response (MiHR).

Blood Procurement, Tumor Cell Enrichment, and RNA Extraction Twenty milliliters of whole blood was drawn prior to the start of the neoadjuvant therapy using 5 ml citrate tubes (Sarstedt, Numbrecht, Germany). Blood samples were immediately further processed for the enrichment of disseminated circulating tumor cells by density gradient centrifugation using a kit (OncoQuick1, Hexal, Frickenhausen, Germany) as reported by Hoffmann et al.[13] In brief, 20 ml of whole blood was transferred in supplied 50 ml polypropylene tubes containing a porous barrier and separation medium and centrifuged for 20 min (1,600×*g*, 48°C). Cells were separated according to their different buoyant densities, and the circulating tumor cells got enriched in a layer formed between plasma and separation medium. This cell fraction was transferred into polypropylene tubes containing 50 ml washing buffer followed by centrifugation for 10 min to eliminate

contaminating platelets. This washing step was repeated once, and according to the manufacturer's protocol, a detection limit of 1.46 tumor cells in 20 ml of whole blood could be achieved. Total cellular RNA from this pellet of enriched tumor cells was extracted using the Purescript1 kit (Gentra1, Hamburg, Germany) according to the manufacturer's recommendation.

Direct Quantitative Real-Time Reverse Transcription Polymerase Chain Reaction Generation of cDNA was performed using oligo (dT)18 primers and MMLV reverse transcriptase (Moloney Murine Leucemia Virus, Clontech AdvantageTM Kit, Palo Alto, CA, USA). Direct quantitative real-time reverse transcription polymerase chain reaction (RT-PCR) (TaqManTM, ABI PRISM 7900 HT Sequence Detection System Applied BiosystemsTM, Darmstadt, Germany) assays were performed in triplicates to determine ERCC1 mRNA expression levels.[18,19] The primers and probes for ERCC1 mRNA detection were designed as reported by our group:[9] ERCC1, 5′-AGC CGC CCA TGG ATG TAG T-3′, reverse primer: 5′-TGG GAA TTT GGC GAC GTA A-3′, TaqMan Probe: 5′-CCC TGT TCC TCA GCC TCC GCT ACC-3′. Thermal cycling conditions for ERCC1 and for b-actin were 2 min at 50°C and 10 min at 95°C for initial denaturation followed by 40 cycles of 95°C for 15 s and 60°C for 60 s. One microgram of human placental total cellular RNA (ClontechTM Lab, Palo Alto, CA, USA) was used to control each run of reverse transcription. This cDNA was used in serial dilutions as standard for the quantitative real-time RT-PCR. Triplicates of the blood samples were assayed in each run. ERCC1 levels were standardized for b-actin (ratio ERCC1/b-actin) to account for loading differences as extensively described.[13]

Statistical Analysis Gene expression levels were described using the median as a point estimator and the range of values. Cutoff values for discrimination of mRNA expression levels and histopathological response were derived from receiver operating curve data (ROC; area under the curve and the 95% confidence interval).[20] Associations between gene expression levels and clinicopathological parameters were evaluated using χ^2, Wilcoxon rank test, Mann–Whitney test, or *t* test applying Fisher's exact testing for significance (Software Package SPSS for Windows,Version 15.0; SPSS, Chicago, IL, USA). The level of significance was set to $p<0.05$. All *p* values are given for two-sided testing.

Results

RNA expression peripheral blood of patients was detectable for ERCC1 in 82.8% (24 of 29) and 100% (29 of 29) for beta-actin. The median relative ERCC1 RNA expression level standardized for beta-actin was 0.41 (range, 0–2.49).

The response frequencies for the 29 resected tumors were as follows: 34.5% (ten of 29) of the tumors demonstrated major (grades III and IV) histopathological response, and 65.5% (19 of 29) of the tumors demonstrated minor histopathological response (grades I and II) to our neoadjuvant treatment regimen. The median ERCC1 expression was 0.62 (minimum 0.00, maximum 2.48) in minor responders and 0.24 (minimum 0.00, maximum 0.45) in major responders and was significantly different ($p=0.004$ Mann–Whitney test, Fig. 1). No significant associations were detected between the median ERCC1 expression in patient's blood and clinicopathological variables (Table 1).

In Fig. 2, individual relative ERCC1 expression levels were blotted against the respective regression grades. ROC analysis was applied to determine an ERCC1 expression value that best segregates patients into minor or major responders. An ERCC1 expression level of 0.452 was determined as an optimal cutoff value to identify minor histopathological response to neoadjuvant therapy. Table 2 shows the association between major and minor histopathological response groups and dichotomized relative ERCC1 expression levels for the whole study group ($n=29$). The sensitivity for detection of a minor histopathological response was 68.4% with a specificity of 100% (area under the curve, 0.89; 95% confidence interval, 0.67–98). This association of dichotomized ERCC1 mRNA levels and histopathological response was highly significant ($p<0.001$) as shown in Table 2. There were no significant associations between dichotomized maximum cutoff values for ERCC1 expression and clinicopathological variables. Histopathological response was not significantly associated with clinicopathological variables (i.e., histology, gender, and tumor stage). In summary, quantitative ERCC1 RNA expression testing in peripheral blood unequivocally identified 13 of 29 (44.8%) patients whose tumors will not exhibit a major histopathological response to the applied neoadjuvant radio-chemotherapy with a specificity of 100%.

Discussion

In the current study, we identified high ERCC1 RNA expression in peripheral blood of patients with locally advanced esophageal cancer as a non-invasive molecular predictor of minor histopathological response to neoadjuvant radiochemotherapy in this disease.

Because DNA is the primary cellular target for both chemotherapy- and radiation-induced damage, DNA repair efficiency could be a limiting factor for therapeutic response,

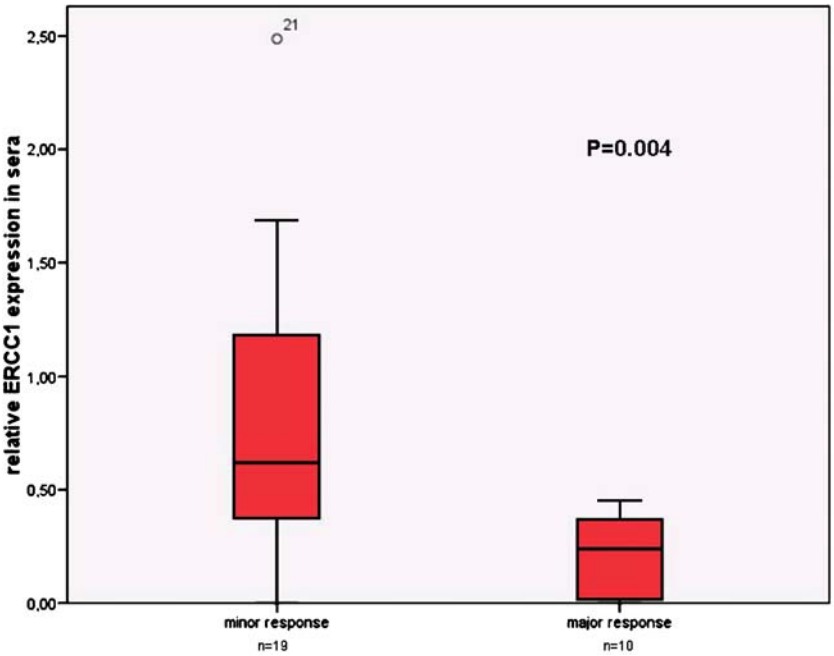

Figure 1 Box and whisker plots of relative ERCC1 expression levels in blood of minor and major responders to neoadjuvant therapy. The *boxes* show the 25th and 75th percentile (interquartile) ranges. Median values are shown as a *horizontal black bar* within each box. The whiskers show levels outside the 25th and 75th percentiles but exclude far outlying values, which are shown *above the boxes*.

preventing tumor cells from undergoing the process of apoptosis. In this study, we have shown a significant association between ERCC1 RNA expression levels in serum of patients with locally advanced cancer of the esophagus and minor histopathological response to CDDP-based neoadjuvant radiochemotherapy. In fact, quantitation of ERCC1 RNA expression in peripheral blood by real-time reverse transcription-PCR unequivocally identified 13 of 29 patients whose tumors did not exhibit (specificity, 100%) a major histopathological response to the applied neoadjuvant radiochemotherapy. This result adds another piece to the puzzle of molecular response prediction by ERCC1. Associations with clinical response and ERCC1 mRNA expression have been demonstrated for adjuvant and neoadjuvant chemotherapy in various solid cancers, for example, gastric or colon cancer.[14,15] Recently, we have demonstrated that high ERCC1 mRNA expression in tumor tissues of patients with locally advanced esophageal cancer is significantly associated with histopathological minor response to neoadjuvant radio-chemotherapy (5-FU, *cis*-Platin, 36 Gy) in this disease.[9] Interestingly, the results obtained in the previous study are similar to the current one. High ERCC1 RNA expression in tumor tissues was significantly (sensitivity 62.5; specificity 100%) associated with minor histopathological response to neoadjuvant

Table 1 Association of ERCC1 Expression in Blood and Clinicopathological Variables

Parameter	*n*	Median ERCC1 expression	*p*
Gender			
Male	23	0,41 (minimum 0; maximum 1.68)	n.s.
Female	6	0,39 (minimum0; maximum 2.48)	
ypT status			n.s.
pT_0	4	0.26 (minimum 0.01; maximum 0.45)	
pT_1	3	0.20 (minimum 0; maximum 0.27)	
pT_2	5	0.01 (minimum 0; maximum 1.31)	
pT_3	17	0.62(minimum 0; maximum 2.48)	
ypN status			n.s.
pN_0	15	0.33 (minimum 0; maximum 1.31)	
pN_1	14	0.47 (minimum 0; maximum 2.48)	
Histology			n.s.
Squamous cell ca	11	0.45 (minimum 0; maximum 2.48)	
Adenocarcinoma	18	0.39 (minimum 0; maximum 1.68)	
Histopathological response			0.004[a]
Minor	19	0.62 (minimum 0; maximum 2.48)	
Major	10	0.24 (minimum 0; maximum 0.452)	

n.s. Not significant, *n* number of patients
[a] Mann–Whitney test

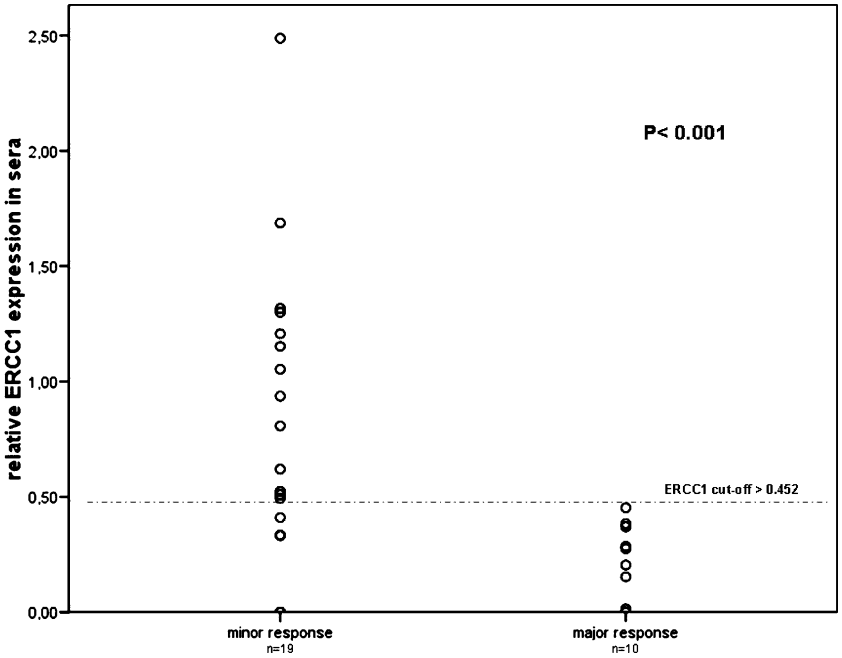

Figure 2 Scattergram showing relative ERCC1 expression levels in peripheral blood in relation to minor and major histopathological response in patients sera. ERCC1 expression levels of >0.452 are exclusively present in the group of minor histopathological response (sensitivity, 68.4%; specificity, 100%).

radio-chemotherapy in locally advanced cancer of the esophagus. In the current study, we obtained similar results by analyzing ERCC1 RNA expression in peripheral blood of patients with locally advanced cancer of the esophagus that undergo neoadjuvant therapy. In concordance, high ERCC1 RNA expression in peripheral blood was significantly associated with minor histopathological response with a sensitivity of 68.4 and specificity of 100%. These results fit with intuition. The patients in the two studies were treated with exactly the same neoadjuvant radio-chemotherapy protocol. Furthermore, the methods for quantitative ERCC1 RNA expression analysis were identical, i.e., primers and probes, TaqMan, cycling conditions, etc. The only difference was the collection of samples for expression analysis. While the previous study used tumor tissues obtained during endoscopy, this study used peripheral blood samples for molecular analysis. These results suggest that free circulating ERCC1 RNA in peripheral blood reflects the molecular situation in the primary cancer of the esophagus, which has also been suggested by results from other studies.[21,22]

To the best of our knowledge, this is the first study to successfully report a non-invasive molecular marker of response to neoadjuvant therapy in locally advanced cancer of the esophagus. These results have several important applications. First of all, a subset of patients could be unequivocally identified as minor responders to neoadjuvant radio-chemotherapy by a simple peripheral blood test with a high sensitivity (68.4%) but more important with a specificity of 100%. Furthermore, changes in gene expression could be easily followed longitudinally during therapy or during follow-up by a simple blood draw from each patient, as has been shown by other studies.[13,21,23] Hoffmann et al.[13] demonstrated that complete surgical resection of gastrointestinal malignancies was associated with a significantly decreased Survivin RNA expression in peripheral blood, and Fiegl et al.[23] showed an association of blood DNA methylation with response to adjuvant tamox-

Table 2 ERCC1 RNA Expression in Blood and Response to Therapy: Prediction of Minor Histopathological Response (ERCC1>0.452): Sensitivity 68.4%; Specificity 100%; χ^2 analysis (Fisher's exact test), $p<0.001$

ERCC1	Regression grading		
	MiHR	MaHR	Total
≤0.452	6 (21)	10 (34)	16 (55)
>0.452	13 (45)	0 (0)	13 (45)
Total	19 (65)	10 (35)	29 (100)

Values represent *n* (%) throughout the table.
ERCC1 Dichotomized ERCC1 RNA levels, MiHR minor histopathological response, *MaHR* major histopathological response

ifen therapy to breast cancer. However, these promising results for the development of blood-based molecular markers for different therapies of solid tumors have to be investigated in further studies.

We can expect, however, that the measured cutoff value in this pilot study might change with increasing numbers of patients analyzed in large prospective trials. At this point, the median follow-up is too short to allow a meaningful evaluation between the association of ERCC1 expression levels in peripheral blood and survival in our protocol. Since this is an ongoing trial, we might be able to identify a prognostic cutoff value with increasing time of follow-up and numbers of patients analyzed. However, it has been demonstrated in the past that only patients with major histopathological responses benefit from this type of treatment independent of the applied protocol.[1,3,4]

In the current study, both adenocarcinoma and squamous cancer were included because the treatment of both cancers is identical.[1–3] In addition, several studies have revealed similarities between these two tissue types.[24] Furthermore, in our study, the response to treatment did not differ, irrespective of tissue type. Although the patient cohort in this study was relatively moderate in size, the demographics showed a homogeneous cohort, and the protocol for the applied neoadjuvant radiochemotherapy was absolutely uniform in all patients.

Conclusion

In conclusion, the present results of this ongoing study are promising, and it appears that we unequivocally identify approximately 40% of patients by a simple peripheral blood test that fulfills the criteria for neoadjuvant treatment for locally advanced esophageal cancer but will not benefit from our treatment protocol. Our results suggest quantification of ERCC1 RNA expression in peripheral blood as a potential non-invasive marker for response prediction to neoadjuvant radio-chemotherapy in locally advanced cancer of the esophagus. This might prevent our patients from expensive, noneffective, and potentially harmful therapies and lead to a more individualized type of multimodal treatment in the near future based on a non-invasive molecular test. Future studies are warranted to determine the value of quantitative ERCC1 RNA expression analysis in peripheral blood for prediction of response to neoadjuvant therapy in esophageal cancer.

References

1. Walsh TN, et al. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med 1996;335(7):462–467. doi:10.1056/NEJM199608153350702.
2. Sherman CA, et al. Locally advanced esophageal cancer. Curr Treat Options Oncol 2002;3(6):475–485. doi:10.1007/s11864-002-0067-3.
3. Urba SG, et al. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol 2001;19(2):305–313.
4. Schneider PM, et al. Histomorphologic tumor regression and lymph node metastases determine prognosis following neoadjuvant radiochemotherapy for esophageal cancer: implications for response classification. Ann Surg 2005;242(5):684–692. doi:10.1097/01.sla.0000186170.38348.7b.
5. Wang KK, Wongkeesong M, Buttar NS. American Gastroenterological Association medical position statement: role of the gastroenterologist in the management of esophageal carcinoma. Gastroenterology 2005;128(5):1468–1470. doi:10.1053/j.gastro.2005.03.076.
6. Higashi H, et al. Down-regulation of Gadd45 expression is associated with tumor differentiation in non-small cell lung cancer. Anticancer Res 2006;26(3A):2143–2147.
7. Ling FC, et al. HIF-1alpha mRNA is not associated with histopathological regression following neoadjuvant chemoradiation in esophageal cancer. Anticancer Res 2006;26(6B):4505–4509.
8. Xi H, et al. High cyclooxygenase-2 expression following neoadjuvant radiochemotherapy is associated with minor histopathologic response and poor prognosis in esophageal cancer. Clin Cancer Res 2005;11(23):8341–8347. doi:10.1158/1078-0432.CCR-04-2373.
9. Warnecke-Eberz U, et al. High specificity of quantitative excision repair cross-complementing 1 messenger RNA expression for prediction of minor histopathological response to neoadjuvant radiochemotherapy in esophageal cancer. Clin Cancer Res 2004;10(11):3794–3799. doi:10.1158/1078-0432.CCR-03-0079.
10. Warnecke-Eberz U, et al. Overexpression of survivin mRNA is associated with a favorable prognosis following neoadjuvant radiochemotherapy in esophageal cancer. Oncol Rep 2005;13(6):1241–1246.
11. Miyazono F, et al. Quantitative c-erbB-2 but not c-erbB-1 mRNA expression is a promising marker to predict minor histopathologic response to neoadjuvant radiochemotherapy in oesophageal cancer. Br J Cancer 2004;91(4):666–672.
12. Hamilton JP, et al. Reprimo methylation is a potential biomarker of Barrett's-associated esophageal neoplastic progression. Clin Cancer Res 2006;12(22):6637–6642. doi:10.1158/1078-0432.CCR-06-1781.
13. Hoffmann AC, et al. Survivin mRNA in peripheral blood is frequently detected and significantly decreased following resection of gastrointestinal cancers. J Surg Oncol 2007;95(1):51–54. doi:10.1002/jso.20630.
14. Shirota Y, et al. ERCC1 and thymidylate synthase mRNA levels predict survival for colorectal cancer patients receiving combination oxaliplatin and fluorouracil chemotherapy. J Clin Oncol 2001;19(23):4298–4304.
15. Metzger R, et al. ERCC1 mRNA levels complement thymidylate synthase mRNA levels in predicting response and survival for gastric cancer patients receiving combination cisplatin and fluorouracil chemotherapy. J Clin Oncol 1998;16(1):309–316.
16. Lord RV, et al. Low ERCC1 expression correlates with prolonged survival after cisplatin plus gemcitabine chemotherapy in non-small cell lung cancer. Clin Cancer Res 2002;8(7):2286–2291.
17. Schroder W, et al. Frequency of nodal metastases to the upper mediastinum in Barrett's cancer. Ann Surg Oncol 2002;9(8):807–811.
18. Gibson UE, Heid CA, Williams PM. A novel method for real time quantitative RT-PCR. Genome Res 1996;6(10):995–1001. doi:10.1101/gr.6.10.995.

19. Heid CA, et al. Real time quantitative PCR. Genome Res 1996;6 (10):986–994. doi:10.1101/gr.6.10.986.
20. Metz CE, Goodenough DJ, Rossmann K. Evaluation of receiver operating characteristic curve data in terms of information theory, with applications in radiography. Radiology 1973;109(2):297–303.
21. Kawakami K, et al. Hypermethylated APC DNA in plasma and prognosis of patients with esophageal adenocarcinoma. J Natl Cancer Inst 2000;92(22):1805–1811. doi:10.1093/jnci/92.22.1805.
22. Usadel H, et al. Quantitative adenomatous polyposis coli promoter methylation analysis in tumor tissue, serum, and plasma DNA of patients with lung cancer. Cancer Res 2002;62(2):371–375.
23. Fiegl H, et al. Circulating tumor-specific DNA: a marker for monitoring efficacy of adjuvant therapy in cancer patients. Cancer Res 2005;65(4):1141–1145. doi:10.1158/0008-5472.CAN-04-2438.
24. McCabe ML, Dlamini Z. The molecular mechanisms of oesophageal cancer. Int Immunopharmacol 2005;5(7–8):1113–1130. doi:10.1016/j.intimp.2004.11.017.

J Gastrointest Surg (2008) 12:1822–1829
DOI 10.1007/s11605-008-0680-y

Preoperative Liver Function Tests and Hemoglobin will Predict Complications Following Pancreaticoduodenectomy

Christopher Hughes · Michael G. Hurtuk · Karen Rychlik · Margo Shoup · Gerard V. Aranha

Received: 19 May 2008 / Accepted: 20 August 2008 / Published online: 12 September 2008

Abstract
Introduction Previous studies identified an association between dilated pancreatic and biliary ducts and lower rates of pancreatic leak after pancreaticoduodenectomy, but it remains unclear whether elevated liver function tests are also associated with lower rates of complications. The purpose of this study was to determine if preoperative liver function tests are associated with postoperative complications.
Materials and Methods We identified 452 patients who received a pancreaticoduodenectomy from 1990–2007. Clinicopathological data was collected for each patient, and regression analyses were performed to identify predictors of postoperative complications.
Results Of the patients studied, 289(64%) experienced no postoperative complications. In univariate analysis, patients with a low or normal preoperative aspartate aminotransferase ($p=0.03$) or alkaline phosphatase($p=0.03$), had higher rates of complications. Multivariate analysis confirmed an elevated alkaline phosphatase was associated with a lower incidence of complications (OR=0.56, $p=0.02$), while preoperative anemia was found to be a predictor of complications following pancreaticoduodenectomy(OR=2.01, $p=0.02$).
Conclusion Anemic patients and those with normal liver function tests were more likely to experience complications after pancreaticoduodenectomy. This may represent extent of disease and tumors not causing biliary or pancreatic dilatation, respectively. Precautions, such as intraoperative ductal stents, should be considered when operating on this group of patients to minimize complications.

Keywords Pancreaticoduodenectomy · Preoperative laboratory values · Postoperative complications

Presented at the 49th Annual Meeting of the Society for Surgery of the Alimentary Tract, May 17–21, 2008. San Diego Convention Center, San Diego, California.

C. Hughes
Stritch School of Medicine, Loyola University Chicago, Maywood, IL 60153, USA

M. G. Hurtuk · M. Shoup · G. V. Aranha (✉)
Division of Surgical Oncology, Department of Surgery, Loyola University Medical Center, 2160 S. First Ave, Maywood, IL 60153, USA
e-mail: garanha@lumc.edu

K. Rychlik
Department of Biostatistics, Loyola University Medical Center, Maywood, IL 60153, USA

Introduction

Pancreaticoduodenectomy (PD) remains the standard surgical treatment for various pathologies of the pancreas and the periampullary area. In the period immediately following its inception, the procedure was associated with significantly high rates of intraoperative and postoperative complications, including a mortality rate of nearly 20%.[1,2] However, advances in surgical techniques and postoperative critical care have dramatically improved surgical outcomes after PD.[3–8] Several studies have demonstrated significant reductions in both morbidity and mortality associated with PD, especially in high-volume centers.[9–13]

Nonetheless, PD remains a complicated surgical procedure that can significantly impact a patient's subsequent quality of life. Despite improvements in perioperative care, certain complications such as pancreatic leak, delayed

gastric emptying, intra-abdominal abscess, and hemorrhage are relatively common after surgery and can adversely affect patients' health and recovery.[14–16]

A few studies have investigated preoperative factors that might predict postoperative complications following PD in order to better anticipate and address postoperative morbidity. These studies have addressed anatomic factors, duct size, and texture of the pancreatic remnant as potential predictors of postoperative complications.[15,17,18] Recently, a few studies have addressed the issue of preoperative biochemical markers in predicting complications after PD.[19–21]

As PD continues to gain acceptance as an effective treatment for various pathologies of the pancreatic head and periampullary region, there is a need for further evaluation of potential risk factors for postoperative morbidity and mortality following PD. With an enhanced understanding of the etiology of PD-associated morbidity, we may be able to address preoperative factors before they contribute to perioperative morbidity.

In the present study, we performed a retrospective analysis from a prospective database to determine which preoperative lab values were significant in predicting postoperative morbidity and mortality following PD.

Material and Methods

Patients

We conducted a retrospective review of data from our prospectively collected database of 452 patients undergoing PD at our institution from 1990 to 2007. Patients included in the analysis had surgery for both malignant and benign disease and they each received standard PD with either of two anastomotic variants: pancreaticogastrostomy (PG) or pancreaticojejeunostomy (PJ).

Definitions

Preoperative laboratory values were obtained from the medical record, and, in most cases, were obtained within 1 week of surgery. The primary outcome variables were complications following PD, including pancreatic leak (previously defined at our institution as drainage of amylase-rich fluid three times the upper normal limit of serum amylase 1 day after the patients began general diet and at least 50 cc/d[16]), intra-abdominal abscess (fluid from an intraoperative drain with positive cultures or a new fluid collection requiring drain placement), wound infection (purulent drainage requiring wound reopening), bile leak (any bilious drainage from the right drain placed in the subhepatic area without regard to duration and volume of bile), gastric leak (CT or upper gastrointestinal contrast extravasation from the gastrojejeunostomy), and hemorrhage (angiographic, laboratory, or CT evidence of postoperative intra-abdominal bleeding). Mortality was defined as death occurring within the first 30 days after operation or during hospitalization.

Statistics

Preoperative lab values were analyzed as continuous variables for frequency analyses within the study population. Categorical variables were then created for each test based on the statistical range of normal laboratory values for our institution's laboratory, and chi-square tests were performed to assess for differences between PG and PJ patients. The categorical laboratory test variables were then each entered into a univariate analysis with the chi-square statistic. Variables determined to be approaching significance in the univariate analysis ($p \leq 0.20$) were subsequently entered into a multivariate model using binary logistic regression with forward stepwise elimination. Evaluation of continuous variables was conducted with the *t*-test and evaluation of all categorical variables was conducted using the chi-square test where appropriate. All statistical analysis was performed using SPSS (v. 15.0, Chicago, IL, USA).

Results

Table 1 displays the preoperative patient characteristics of our study population. We evaluated a total of 452 patients over a 17-year period. The mean age at surgery for the entire patient cohort was 64.5 (±12.6) years and 56.4% of the patients were male. According to the data, most patients

Table 1 Patient Demographics

	All patients
N	452
Male gender (%)	255 (56.4)
Mean age, years (SD)	64.5 (12.6)
Pathologies	
Pancreatic cancer	195
Duodenal cancer	27
Ampullary cancer	65
CBD	31
NET	19
Pancreatitis	34
Cystic neoplasms	36
IPMN	14
Other	31

CBD Common bile duct (cholangiocarcinoma), *NET* neuroendocrine tumor, *Cystic neoplasms* mucinous and serous cystadenomas and cystadenocarcinomas, *IPMN* intraductal papillary mucinous neoplasm

underwent PD for pancreatic cancer. The postoperative outcomes and complications are presented in Table 2. Of the patient cohort, 63.9% experienced no significant postoperative complications following PD. All patients were evaluated and assessed for each of seven different potential postoperative complications. For the entire cohort, pancreatic leak was the most commonly observed complication in 71 (15.7%) patients. Four (5.6%) of the pancreatic fistulas were due to drain erosion into the pancreaticoenteric anastomosis. If we were to relate our data to the International Study Group of Pancreatic Fistula (ISGPF) definition, 44 (66%) had a grade B fistula, while 23 (44%) had a grade C fistula that were controlled with new drains and TPN.[22]

There were no statistically significant differences between patients receiving PG or PJ with respect to any of the outcome variables (data not shown). Mortality within 30 days of PD was 1.8% for the entire study population. Among the eight patient deaths, one was due to acute respiratory distress syndrome, one was subsequent to an anoxic brain injury after cardiac arrest, one was due to massive intraoperative blood loss, two were secondary to postoperative bleeding following pancreatic leak, one was secondary to uncontrolled sepsis following pancreatic leak, one was due to hemorrhage from a gastric ulcer, and one was a death from suicide. Three of the eight deaths reported involved pancreatic leak.

Table 3 illustrates the univariate analyses of potential risk factors for postoperative morbidity and mortality for the study population. According to the data, an elevated preoperative aspartate aminotransferase (AST) was associated with a lower incidence of postoperative complications when compared to those patients with normal AST levels (p=0.03). Additionally, a higher proportion of postoperative complications was demonstrated in those patients with a normal alkaline phosphatase when compared to patients with elevated preoperative levels of alkaline phosphatase (p=0.03). We performed a subset analysis of those patients experiencing a postoperative complication to evaluate whether primary pathology differed between normal and elevated alkaline phosphatase groups. Patients experiencing a complication who had normal alkaline phosphatase levels were more likely than those with elevated alkaline phosphatase levels to have primary tumors other than pancreatic adenocarcinoma (p=0.002) (data not shown). Intraoperative blood loss >1,000 cc was also found to be significantly associated with increased rates of complications following PD (p=0.04). Similar trends were observed with respect to total bilirubin and ALT, but the results were not statistically significant (p=0.09 and p=0.10, respectively). Interestingly, low preoperative albumin was not associated with increased rates of complications (p=0.74). None of the studied variables was significantly associated with mortality following PD.

Each of the variables considered to be approaching statistical significance in the univariate analyses ($p \leq 0.20$) was then entered into a multivariate binary logistic regression. The results are depicted in Table 4. Of the variables entered into the regression model, an elevated alkaline phosphatase was found to be associated with lower rates of postoperative complications following PD (OR=0.5, p=0.01). Additionally, preoperative anemia (OR=2.1, p=0.01) and significant intraoperative blood loss >1,000 cc (OR=1.9, p=0.01) were each independently associated with increased postoperative morbidity. In an effort to evaluate potential

Table 2 Postoperative Outcomes and Complications

	All patients
Zero complications (%)	289 (63.9)
Postoperative complications (%)	
Death	8 (1.8)
Pancreatic leak	71 (15.7)
IAA	28 (6.2)
Wound infection	21 (4.6)
Hemorrhage	9 (2.0)
Bile leak	9 (2.0)
Gastric leak	3 (0.7)
Other	21 (4.6)

Some patients had multiple complications
IAA Intra-abdominal abscess, *Other* small bowel obstruction, DVT, and pulmonary complications

Table 3 Markers for Morbidity and Mortality following PD: Univariate Analysis

	Number	Morbidity OR	p value	Mortality OR	p value
Hgb (<14)	323		0.16	1.6	NS
Hct (<40)	267	1.3	NS	2.3	NS
Plt (<150)	29	1.1	NS	2.7	NS
Wbc(>10)	68	0.9	NS	2.4	NS
BUN(>22)	41	1.0	NS	2.3	NS
Cr(>1.5)	17	1.3	NS	–	NS
ALT(>40)	218	0.7	0.10	–	NS
AST(>40)	213	0.6	0.03	0.2	NS
Alk Phos (>110)	267	0.6	0.03	0.7	NS
Total Bili (≥1.5)	212	0.7	0.09	0.2	NS
Alb (<3.6)	177	0.9	NS	0.2	NS
Blood loss (>1,000 cc)	153	1.5	0.04	2.6	NS
Stent	290	0.7	NS	1.6	NS

Hgb Hemoglobin, *Hct* hematocrit, *Plt* platelets, *Wbc* white blood cell count, *BUN* blood urea nitrogen, *Cr* creatinine, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *Alk Phos* alkaline phosphatase, *Total Bili* total bilirubin, *Alb* albumin, *Blood Loss* intraoperative blood loss, *Stent* preoperative biliary stent

Table 4 Markers for Morbidity following PD: Multivariate Analysis

	Morbidity OR	*p* value
Hgb (<14)	2.1	0.01
ALT (>40)	1.2	NS
AST (>40)	0.7	NS
Alk Phos (>110)	0.5	0.01
Total Bili (≥1.5)	0.8	NS
Blood loss (>1,000 cc)	1.9	0.01

Hgb Hemoglobin, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *Alk Phos* alkaline phosphatase, *Total Bili* total bilirubin, *Blood loss* intraoperative blood loss

predictors of mortality following PD, we performed an additional regression with mortality as the outcome variable, but none of the variables reached statistical significance in the analysis (data not shown).

Discussion

As recent studies have shown over the last three decades, morbidity and mortality after PD has dramatically decreased since the procedure's inception.[3–13] Several reports have illustrated this decrease in high volume centers, and in our present study we experienced a postoperative morbidity and mortality rate of 36.1% and 1.8%, respectively. As PD continues to be the only definitive operation available for various pathologies of the pancreatic head and periampullary area, it becomes more important for surgeons to be able to recognize preoperative etiologies of post-PD complications.

A few previous studies have evaluated the role of abnormal preoperative biochemical markers in postoperative complications following PD. In a recent analysis, Winter et al.[20] found that a preoperative BUN ≥18 mg/dL and a preoperative albumin ≤3.5 g/dL were each independently significant predictors of postoperative complications. The authors previously found that a preoperative hypoalbuminemia was independently associated with postoperative mortality as well.[14] Preoperative serum albumin levels as a predictor of operative mortality and morbidity has also been shown by others.[23–25] Other studies have found evidence linking elevated preoperative creatinine with an increased risk for post-PD complications.[19]

In the present study, we found no such relationship between preoperative hypoalbuminemia or elevated BUN and increased rates of postoperative complications following PD, but we did find that elevated preoperative alkaline phosphatase was significantly associated with decreased rates of complications in a multivariate analysis. An intrinsic, albeit non-specific, marker for inflammation within the biliary tree, an elevated alkaline phosphatase reflects a disease process that more acutely involves damaged or inflamed biliary anatomy. Tumors located in this area might be more likely to cause obstructive symptoms, and thus patients with this type of pathology might be detected at an earlier stage of disease and may consequently have improved post-surgical outcomes.

However, elevated alkaline phosphatase could also serve as a proxy for a double duct sign which would be associated with a firm to hard pancreatic texture that would hold sutures better. Based on our subset analysis of those patients with a post-PD complication, fewer patients with normal alkaline phosphatases had pathologies consistent with pancreatic primary tumors when compared to those patients with elevated alkaline phosphatases. Accordingly, those patients with a complication and a normal alkaline phosphatase most likely had a soft pancreatic remnant. Conversely, those patients with a complication and an elevated alkaline phosphatase most likely had a hard pancreatic remnant because, as a group, they had a higher percentage of pancreatic primary tumors. A hard pancreas may lead to a larger duct which would provide a mechanical advantage for reanastomosis during PD and this advantage could be contributing to the lower incidence of postoperative complications seen in patients with elevated alkaline phosphatase in our population. This larger duct phenomenon could also be applied to the biliary system, in that larger ducts, allow for easier anastomosis. Several previous studies have found that a soft pancreatic remnant with non-dilated pancreatic ducts (<3 mm in diameter) is independently associated with increased rates of pancreatic leak following PD.[17,25,26]

The management of the soft pancreatic remnant after PD remains a subject of considerable debate.[27] Lillemoe et al.[28] studied the effect of fibrin glue in cases with small ducts and a soft pancreatic remnant. They found that while fibrin glue did not prevent a leak, the leak rate was reduced from 30% in controls to 26% in the fibrin glue group. Wada and Traverso[25] studied whether better vision with the operating microscope when compared to surgical loupes would reduce the leak rate in internally stented duct to mucosa PJ after PD. They found that in the soft gland with small ducts, the 23% leak rate using surgical loupes was reduced to 4% with the microscope. Poon et al.[26] studied the external drainage of the pancreatic duct with a stent to reduce the leak rate of PJ after PD. In this prospective randomized study, a subset analysis of the soft pancreatic remnant found a leak rate of 12% in the stented group versus 30% in the non-stented group. Billingsley et al.[21] reported a 0% leak rate in 227 consecutive patients with PJ following PD, irrespective of the texture of the pancreatic remnant. Strasberg et al.[29] found that optimizing the blood supply of the edge of the pancreatic remnant was a key to

decreasing the leak rate. A randomized controlled trial comparing each of the above surgical techniques to each other would be one way to resolve this debate surrounding the management of the soft pancreatic remnant.

Our findings with respect to the association between preoperative anemia, intraoperative blood loss, and increased complications is in accordance with much of the surgical literature. Carson et al.[30] reported on the effect of anemia and cardiovascular surgical mortality and morbidity in 1,958 patients who, for religious reasons, refused all blood transfusions. They found that low preoperative hemoglobin was associated with an increased risk of death or serious morbidity. This was seen more often in those patients with cardiovascular risk. Wu et al.[31] studied preoperative hematocrit levels and postoperative outcomes in older patients undergoing non-cardiac surgery. They found that even mild degrees of preoperative anemia were associated with increased 30-day postoperative mortality and cardiac events in mostly older male veterans. Neither of the two above studies had any patients having PD. Healthy adults have been shown to adapt to anemia by an increase in cardiac output and oxygen extraction and decrease in vascular resistance.[31] In the elderly patient, however, cardiac reserve is diminished and subclinical coronary disease may exist that would blunt the physiologic response to anemia.[31] Because they are more often elderly, it would therefore make sense to optimize preoperative hemoglobin and hematocrit levels and to minimize intraoperative blood loss in those patients undergoing PD.

Spence et al.[32] studied 107 consecutive Jehovah's Witness patients who underwent major elective surgery. They found that mortality was 3.2% in patients whose preoperative hemoglobin levels were greater than 10 g/dL and 5% in patients whose hemoglobin was 6–10 g/dL. Mortality was significantly increased with an estimated blood loss of greater than 500 mL regardless of the preoperative hemoglobin level. In our PD population, we found that patients with intraoperative blood loss greater than 1,000 cc had increased rates of postoperative complications when compared to those patients with less blood loss.

The strengths of the present study are the large number of patients in the database giving support to our conclusions that preoperative anemia, normal liver function tests, and significant intraoperative blood loss are associated with increased postoperative morbidity following PD. There are, however, some limitations to our study. Although the data was collected prospectively, the study is retrospective in nature. We included only the most recent preoperative lab data from each patient, but it is possible that there are varying amounts of time between lab collection and surgery for each patient. In addition, patients with elevated alkaline phosphatases may represent earlier stages of disease at detection and at treatment, and thus our findings may represent an element of selection bias as well.

Conclusion

The results from the present study of 452 patients demonstrate that low preoperative hemoglobin, a normal preoperative alkaline phosphatase, and significant intraoperative blood loss are independent predictors of postoperative complications following PD. Despite the existing evidence, it remains important for future studies to continue to evaluate the etiologies of post-PD complications. As PD continues to be the accepted method for resection of both benign and malignant disease of the pancreatic head and periampullary area, it is crucial for surgeons to be able to anticipate and, eventually, prevent increased postoperative morbidity. As more and more patients undergo PD, a better understanding of the role of preoperative laboratory markers is essential to prevent or to be more vigilant of postoperative complications.

This study brings awareness of the complications that patients undergoing PD may face in relation to their preoperative laboratory values. Obviously, abnormal liver function tests (LFTs) cannot be induced in patients to achieve better outcomes after PD. We feel that abnormal LFTs may be a sign of local fibrosis and pancreatic hardening, which may be induced primarily by the patient's pathology and possibly by preoperative stenting in these patients. In patients with normal LFTs and a soft pancreatic remnant a randomized study comparing stenting of the pancreatic duct to no stenting following PD is needed.

In patients who have extensive cardiac histories, hemoglobin should be optimized, or liberal use of intraoperative blood transfusions may be used to decrease rates of complications. Our study showed patients with hemoglobin levels above 14 had decreased incidence of complications. This value would be difficult to achieve in patients with chronic diseases, such as cancer. We plan on further studying both of the above ideas.

References

1. Shapiro TM. Adenocarcinoma of the pancreas: a statistical analysis of biliary bypass vs. Whipple resection in good risk patients. Ann Surg 1975;182(6):715–721. doi:10.1097/00000658-197512000-00010.
2. Crile G. The advantages of bypass operations over radical pancreaticoduodenectomy in the treatment of pancreatic carcinoma. Surg Gynecol Obstet 1970;130(6):1049–1053.
3. Grace PA, Pitt HA, Tompkins RK, DenBesten L, Longmire WP Jr. Decreased morbidity and mortality after pancreaticoduodenectomy. Am J Surg 1986;151(1):141–149. doi:10.1016/0002-9610(86)90024-3.

4. Crist DW, Sitzmann JV, Cameron JL. Improved hospital morbidity, mortality and survival after the Whipple procedure. Ann Surg 1987;206(3):358–365. doi:10.1097/00000658-198709000-00014.
5. Pellegrini CA, Heck CF, Raper S, Way LW. An analysis of the reduced morbidity and mortality rates after pancreaticoduodenectomy. Arch Surg 1989;124(7):778–781.
6. Trede M, Schwall G, Saeger HD. Survival after pancreaticoduodenectomy: 118 consecutive resections without an operative mortality. Ann Surg 1990;211(4):447–458. doi:10.1097/00000658-199004000-00011.
7. Cameron JL, Pitt HA, Yeo CJ et al. One hundred and forty-five consecutive pancreaticoduodenectomies without mortality. Ann Surg 1993;217(5):430–435. doi:10.1097/00000658-199305010-00002.
8. Aranha GV, Hodul PJ, Creech S, Jacobs W. Zero mortality after 152 consecutive pancreaticoduodenectomies with pancreaticogastrostomy. J Am Coll Surg 2003;197(2):223–232. doi:10.1016/S1072-7515(03)00331-4.
9. Gouma DJ, van Geenen R, van Gulik TM, de Haan RJ, de Wit LT, Busch OR et al. Rates of complications and death after pancreaticoduodenectomy: risk factors and the impact of hospital volume. Ann Surg 2000;232(6):786–795. doi:10.1097/00000658-200012000-00007.
10. Ho V, Heslin MJ. Effect of hospital volume and experience on in-hospital mortality for pancreaticoduodenectomy. Ann Surg 2003;237(4):509–514. doi:10.1097/00000658-200304000-00012.
11. Lieberman MD, Kilburn H, Lindsey M, Brennan MF. Relation of perioperative deaths to hospital volume among patients undergoing pancreatic resection for malignancy. Ann Surg 1995;222(5):638–645. doi:10.1097/00000658-199511000-00006.
12. Sosa JA, Bowman HM, Gordon TA et al. Importance of hospital volume in the overall management of pancreatic cancer. Ann Surg 1998;228(3):429–438. doi:10.1097/00000658-199809000-00016.
13. Kotwall CA, Maxwell G, Brinker CC, Koch GG, Covington DL. National estimates of mortality rates for radical pancreaticoduodenectomy in 25,000 patients. Ann Surg Oncol 2002;9(9):847–854. doi:10.1007/BF02557520.
14. Sohn TA, Yeo CJ, Cameron JL et al. Resected adenocarcinoma of the pancreas—616 patients: results, outcomes, and prognostic indicators. J Gastrointest Surg 2000;4(6):567–579. doi:10.1016/S1091-255X(00)80105-5.
15. Cullen JJ, Starr MG, Ilstrup DM. Pancreatic anastomotic leak after pancreaticoduodenectomy: incidence, significance, and management. Am J Surg 1994;168(4):295–298. doi:10.1016/S0002-9610(05)80151-5.
16. Aranha GV, Aaron JM, Shoup M, Pickleman J. Current management of pancreatic fistula after pancreaticoduodenectomy. Surgery 2006;140(4):561–569. doi:10.1016/j.surg.2006.07.009.
17. Yang YM, Tian XD, Zhuang Y, Wang WM, Wan YL, Huang YT. Risk factors of pancreatic leakage after pancreaticoduodenetomy. World J Gastroenterol 2005;11(16):2456–2461.
18. van Berge Henegouwen MI, De Wit LT, van Gulik TM, Obertop H, Gouma DJ. Incidence, risk factors, and treatment of pancreatic leakage after pancreaticoduodenectomy: drainage versus resection of the pancreatic remnant. J Am Coll Surg 1997;185(1):18–24.
19. Adam U, Makowiec F, Riediger H, Schareck WD, Benz S, Hopt UT. Risk factors for complications after pancreatic head resection. Am J Surg 2004;187(2):201–208. doi:10.1016/j.amjsurg.2003.11.004.
20. Winter JM, Camerol JL, Yeo CJ, Alao B, Lillemoe KD, Campbell KA et al. Biochemical markers predict morbidity and mortality after pancreaticoduodenectomy. J Am Coll Surg 2007;204(5):1029–1038. doi:10.1016/j.jamcollsurg.2007.01.026.
21. Billingsley KG, Hur K, Henderson WG, Daley J, Khuri SF, Bell RH Jr. Outcome after pancreaticoduodenectomy for periampullary cancer: an analysis from the Veterans Affairs National Quality Improvement Program. J Gastrointest Surg 2003;7(4):484–491. doi:10.1016/S1091-255X(03)00067-2.
22. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. J Surg 2005;138(1):8–13. doi:10.1016/j.surg.2005.05.001.
23. Gibbs J, Cull W, Henderson W, Daley J, Hur K, Khuri SF. Preoperative serum albumin level as a predictor of operative mortality and morbidity: results from the National VA Surgical Risk Study. Arch Surg 1999;134(1):36–42. doi:10.1001/archsurg.134.1.36.
24. Goldwasser P, Feldman J. Association of serum albumin and mortality risk. J Clin Epidemiol 1997;50(6):693–703. doi:10.1016/S0895-4356(97)00015-2.
25. Wada K, William Traverso L. Pancreatic anastomotic leak after the Whipple procedure is reduced using the surgical microscope. Surgery 2006;139(6):735–742. doi:10.1016/j.surg.2005.11.001.
26. Poon RT, Fan ST, Lo CM, Ng KK, Yuen WK, Yeung C et al. External drainage of pancreatic duct with a stent to reduce leakage rate of pancreaticojejeunostomy after pancreaticoduodenectomy: a prospective randomized trial. Ann Surg 2007;246(3):425–435. doi:10.1097/SLA.0b013e3181492c28.
27. Marcus SG, Cohen H, Ranson JH. Optimal management of the pancreatic remnant after pancreaticoduodenectomy. Ann Surg 1995;221(6):635–648. doi:10.1097/00000658-199506000-00003.
28. Lillemoe K, Cameron JL, Kim MP, Campbell KA, Sauter PK, Coleman JA et al. Does fibrin glue sealant decrease the rate of pancreatic fistula after pancreaticoduodenectomy? Results of a prospective randomized trial. J Gastrointest Surg 2004;8(7):766–774. doi:10.1016/j.gassur.2004.06.011.
29. Strasberg SM, Drebin JA, Mokadam NA, Green DW, Jones KL, Ehlers JP et al. Prospective trial of a blood supply-based technique of pancreaticojejeunostomy: effect on anastomotic failure in the Whipple procedure. J Am Coll Surg 2002;194(6):746–758. doi:10.1016/S1072-7515(02)01202-4.
30. Carson JL, Duff A, Poses RM, Berlin JA, Spence RK, Trout R et al. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. Lancet 1996;348(9034):1055–1060. doi:10.1016/S0140-6736(96)04330-9.
31. Wu WC, Schifftner TL, Henderson WG, Eaton CB, Poses RM, Uttley G et al. Preoperative hematocrit levels and postoperative outcomes in older patients undergoing noncardiac surgery. JAMA 2007;297(22):2481–2488. doi:10.1001/jama.297.22.2481.
32. Spence RK, Carson JA, Poses R, McCoy S, Pello M, Alexander J et al. Elective surgery without transfusion: influence of preoperative hemoglobin level and blood loss on mortality. Am J Surg 1990;159(3):320–324. doi:10.1016/S0002-9610(05)81227-9.

Discussion

Preoperative Liver Function Tests and Hemoglobin will Predict Complications Following Pancreaticoduodenectomy

L. William Traverso, M.D. (Seattle, Washington): You presented 452 Whipple operations which at Loyola is a respectable 1.8% mortality rate in a high-volume center as defined at Loyola as 27 cases per year. You did not tell us how many surgeons performed these operations so we do not know if this is a high-volume single surgeon at a high-volume hospital. Your Whipple specific outcomes were a 16% pancreatic anastomotic leak rate and a 6% intra-

abdominal abscess rate. Using univariate analysis you then showed that an increased AST and on both univariate and multivariate analysis an increased alkaline phosphatase were associated with complications, so they were inversely proportional. Normal LFTs meant higher complications, which is difficult to initially get your hands around, but after reading the manuscript I have an idea why that was. Then you showed that increased blood loss of over a liter was associated with increased complications—now that makes sense. Then you did a subset analysis in the manuscript that showed that cases with increased alkaline phosphatase and therefore lower complications were those patients that were more likely to have pancreatic cancer and therefore have larger ducts and therefore the anastomotic leak rate would be less.

What was missing from the manuscript and would be really helpful to critique it was that you took a continuous variable like alkaline phosphatase, converted it to a categorical variable and then used Chi square analysis. With this method you lose a lot of sensitivity. It may be that the elevation of alkaline phosphatase, whether it was minimal or very high, would help to make this very confusing finding of normal LFTs being associated with increased complications—I do not really think we can say a whole lot about that at the moment, other than go along with your speculation that increased incidence of pancreatic cancer, meaning increased fibrosis and big ducts meant lesser complications and associated with higher LFTs. What would be helpful is if you stated what the incidence of a soft gland or a small main pancreatic duct of less 3 mm.I would like to quibble a little bit about your leak definition. Why didn't you use the International Study Group leak definition? That has been published and could have been used. Your definition was an elevated amylase in the drain of over three times normal at a day when the patient was eating solid food, so that would miss a lot of the increased amylase levels that you see after day 3, 4 and 5 that the International Study Group picks up. This makes more distribution of your cases and therefore you can analyze it better and may have shown why the alkaline phosphatase might have been associated with complications, yes or no.

Let's get beyond that. How about an operative blood loss of greater than 1,000? Why did you choose that number? At Hopkins 750 ml is associated with lower survivorship and in Seoul, Korea, it is about 500 ml. Why did you choose a liter? Why not also do continuous variable analysis rather than categorical analysis there?

There are some patient-based issues that we can deal with: anemia, and you suggested taking care of those preoperatively; higher blood loss, that's a surgeon-based thing. Let's improve operative technique so that we never can have a blood loss over a value which as yet you have not told me what it should be to minimize complications.

As you can imagine what is missing from the current manuscript is the *mean* estimated blood loss. What was it? Were just a few cases over a liter per operation?

This potpourri of outcomes and preoperative lab values after a Whipple operation is a very important thing to do because, as Dr. Low at the podium last year described, with esophagectomy, it is not about mortality any more—your mortality is very low. It is hard to see any association with mortality when you only have a couple cases, but when you have a lot of morbidity then you can see the associations if you drill down enough.

Very nice job on your presentation.

Christopher D. Hughes, M.D. (Maywood, IL, USA): Thank you for your review, Dr. Traverso.

As you mentioned, we did divide the patients with complication between those with normal alkaline phosphatase and those with elevated alkaline phosphatase. We found that significantly more patients with elevated alkaline phosphatase had pancreatic carcinomas, and we postulated that the elevated enzyme could thus be serving as a proxy for a hard and fibrotic pancreatic remnant and that might explain some of the lower leak rates that we observed in that patient population. Because this was a retrospective analysis, we unfortunately do not have the data on intraoperative remnant texture or duct size for each of our patients.

However, we also speculated that the increase in preoperative alkaline phosphatase might be acting as a marker for damaged or inflamed biliary anatomy. We could therefore be seeing an effect of early detection bias, as patients with tumors in this location could be presenting earlier with symptomatic obstruction and could be benefiting from earlier treatment of their cancers.

With respect to your point about the classification of the pancreatic leak, we used the same endpoints that we have used in previous publications with data from our institution. The International Study Group Classifications were published in 2005, and our study encompasses data from as far back as 1990.

With respect to mean intraoperative blood loss, I do not have that data for you today. We did perform a subset analysis with varying cutpoints, both 500 and 750 cc. We did not find the lower blood loss values to be significant, but we did find significance with the 1,000 cc. Furthermore, we did an analysis to see if there was any significant difference based on pathology between patients and the amount of blood that they lost intraoperatively, but we did not find any associated difference.

Lygia Stewart, M.D. (San Francisco, CA, USA): One quick question. You did not find any correlation with albumin. Can you comment? Did you give your patients preoperative or postoperative nutrition with tube feeds or any kind of enteral-based formulas?

Dr. Hughes: We did not give any supplemental nutrition.

Colin D. Johnson, M.D. (Southampton, England): There are two explanations for why someone has a normal alkaline phosphatase. It may be normal all the time or there may have been biliary obstruction which has been relieved. Can you tell us whether any of these patients with a normal alkaline phosphatase had preoperative biliary drainage?

Dr. Hughes: We did look at preoperative biliary drainage as a yes/no variable and whether or not that was associated with increased rates of complication. We did not find any association in that respect.

Gerard V. Aranha, M.D. (Maywood, IL, USA): Just to clear things up if I might, Dr. Traverso. When the alkaline phosphatase is normal the pancreatic remnant is usually soft and the primary pathology is not pancreatic cancer. Since it is a retrospective study, we cannot tell you about the texture of the remnant or the size of the pancreatic duct. We are looking at both these parameters now as part of the international study you are conducting.

As far as the definition goes, that is the one that we have used since 1990. The International Study Group definition was released in 2005. Our future publications will list our pancreatic fistulae following pancreaticoduodenectomy according to the International Study Group definition.

J Gastrointest Surg (2008) 12:1830–1838
DOI 10.1007/s11605-008-0683-8

Nodal Microinvolvement in Patients with Carcinoma of the Papilla of Vater Receiving No Adjuvant Chemotherapy

Dean Bogoevski · Hassan Chayeb · Guell Cataldegirmen · Paulus G. Schurr · Jussuf T. Kaifi · Oliver Mann · Emre F. Yekebas · Jakob R. Izbicki

Received: 21 May 2008 / Accepted: 20 August 2008 / Published online: 13 September 2008

Abstract
Background To assess the prognostic significance of nodal microinvolvement in patients with carcinoma of the papilla of Vater.
Methods From 1993 to 2003 at the University Clinic Hamburg, 777 patients were operated upon pancreatic and periampullary carcinomas. The vast majority of patients were operated upon pancreatic ductal adenocarcinoma (n=566, 73%), followed by carcinomas of the papilla of Vater (n=112, 14%), pancreatic neuroendocrine carcinomas (n=39, 5%), intraductal papillary mucinous neoplasms (n=33, 4%), and distal bile duct carcinomas (n=27, 3%). Fresh-frozen tissue sections from 169 lymph nodes (LNs) classified as tumor free by routine histopathology from 57 patients with R0 resected carcinoma of the papilla of Vater who had been spared from adjuvant chemotherapy were immunohistochemically (IHC) examined, using a sensitive IHC assay with the anti-epithelial monoclonal antibody Ber-EP4 for tumor cell detection. With regard to histopathology, 39 (63%) of the patients were staged as pT1/pT2, 21 (37%) as pT3/pT4, 30 (53%) as pN0, while 38 (67%) as G1/G2.
Results Of the 169 "tumor-free" LNs, 91 LNs (53.8%) contained Ber-EP4-positive tumor cells. These 91 LNs were from 40 (70%) patients. The mean overall survival in patients without nodal microinvolvement of 35.8 months (median—not yet reached) was significantly longer than that in patients with nodal microinvolvement (mean 16.6; median 13; p=0.019). Multivariate Cox regression analysis for overall survival revealed that grading was the most significant independent prognostic factor (p=0.001), followed by nodal microinvolvement (p=0.013).
Conclusions The influence of occult tumor cell dissemination in LNs of patients with histologically proven carcinoma of the papilla of Vater supports the need for further tumor staging through immunohistochemistry.

Keywords Carcinoma of the papilla of Vater · Nodal microinvolvement · BEr-EP4

Introduction

The term periampullary carcinoma is a common term used for description of carcinomas originating from the papilla of Vater, the periampullary region of the pancreatic head as well as the distal common bile duct carcinomas. The incidence of the carcinoma of the papilla of Vater is four new cases per 100,000 persons per year and is almost fivefold lower than the incidence of the pancreatic cancer. However, on autopsy, the detection of carcinoma of the papilla of Vater is almost 0.2%. Although these tumors predominantly develop sporadically, the risk of carcinoma of the papilla of Vater development is extremely high in patients with familial adenomatous polyposis (FAP)[1,2] and the Gardner syndrome[3] where the lifetime risk is almost 100%. The adenoma to carcinoma sequence in the development of the carcinoma of the papilla of Vater, similarly to the colorectal carcinoma, is already proved and goes over several steps. In patients with FAP, the region of the papilla of Vater is the second most frequent place for

D. Bogoevski (✉) · H. Chayeb · G. Cataldegirmen · P. G. Schurr · J. T. Kaifi · O. Mann · E. F. Yekebas · J. R. Izbicki
University Clinic Eppendorf,
Hamburg, Germany
e-mail: dbogoevski@uke.uni-hamburg.de

tumor development,[4] after colorectum, so the patients who already had protective proctocolectomy has to be under close follow-up for early detection of tumor of the papilla of Vater.

The carcinoma of the papilla of Vater is often mismatched with the pancreatic ductal adenocarcinoma, since sometimes even histologically, it is not possible clearly to distinguish whether the primary tumor originates from the papilla of Vater or from the pancreatic head. However, one has to discriminate these two types of tumors since the carcinoma of the papilla of Vater has considerably better overall prognosis than the pancreatic ductal adenocarcinoma.

The detection of cholestasis and painless jaundice is often an early symptom in these patients, unlike in the patients with pancreatic ductal adenocarcinoma, where the jaundice is a late sign. Gastric outlet obstruction is frequently a late symptom and regularly a sign of inoperability.

The prognosis for patients with carcinoma of the papilla of Vater who undergo resection has been shown to be determined by both the pathologic and molecular characteristics of the resected tumor. Stage, grade, and resection margin status are currently accepted as the most accurate pathologic variables predicting survival.[5–7] Pathologic staging only insufficiently reflects the individual risk to develop tumor recurrence which is even higher in early tumor stages.

Early metastatic relapse after complete resection of an apparently localized primary lesion indicates that disseminated tumor cells, undetectable by current methods, may already have been present at the time of surgery. Occult residual tumor disease is suggested when either bone marrow or lymph nodes from which tumor relapse may originate are affected by micrometastatic lesions undetectable by conventional histopathology.[8] The clinical significance of antibodies against tumor associated targets both in lymph nodes[9–12] and in bone marrow[11,13] is still controversially discussed.[11,13–24] Various monoclonal antibodies are in use for micrometastatic detection, thus contributing to the incongruity of data and validity of results. These assays have been rarely used in patients with carcinoma of the papilla of Vater.[25] Recently, our group showed that immunohistochemical staining with the monoclonal antibody Ber-EP4 is a sensitive and specific method for detecting isolated or clusters of tumor cells in lymph nodes from patients with lung,[10] esophageal,[22] or pancreatic carcinomas.[21,26] Ber-EP4 is an antibody against two glycopolypeptides of 34 and 49 kD on the surface and in the cytoplasm of all epithelial cells (except parietal cells, hepatocytes, and the superficial layers of squamous epithelium).

The present study was intended to increase our knowledge gained in the previous studies on lymph node micrometastasis. In patients with carcinoma of the papilla of Vater, the risk to develop tumor relapse in pN1 patients is overall greater than in pN0 patients. However, we have shown that further risk stratification for patients with histopathological involvement may be performed according to their immunohistochemical status. The primary aim of this study was to assess the role of immunohistochemically detectable micrometastases in lymph nodes of an unselected group of patients with "curatively" resected carcinoma of the papilla of Vater.

Materials and Methods

The local ethical committee of Hamburg approved this study. Informed consent was obtained from all patients before inclusion in the study. From1993 to 2003 at the University Clinic Hamburg, 777 patients were operated upon pancreatic and periampullary carcinomas. The vast majority of patients were operated upon pancreatic ductal adenocarcinoma (n=566, 73%), followed by carcinoma of the papilla of Vater (n=112, 14%), neuroendocrine carcinoma (n=39, 5%), intraductal papillary mucinous neoplasms (n=33, 4%), and distal bile duct carcinoma (n=27, 3%).

The most frequent surgical procedure in the treatment of patients with carcinomas of the papilla of Vater was pancreatoduodenectomy (n=110), followed by pancreatic preserving duodenectomy (n=2, for pTis). Lymph node dissection was performed as previously described by Pedrazzoli et al.[27] A total of 2,039 lymph nodes were removed with a median number of 18 (range five to 39) lymph nodes per patient. Tumor stage and grade were classified according to the sixth edition of the tumor–node–metastasis classification of the International Union against Cancer[28] by investigators unaware of the immunohistochemical findings.

Fresh-frozen tissue sections from 57 patients with R0 resected carcinoma of the papilla of Vater who had been spared from adjuvant chemotherapy were immunohistochemically (IHC) examined, using a sensitive IHC assay with the anti-epithelial monoclonal antibody Ber-EP4 for tumor cell detection. Among all histopathologically negative lymph nodes, 169 were selected in a representative fashion as described most recently for subsequent immunohistochemical screening.[21]

Follow-up evaluations at 3-month intervals in the first 12 months and afterwards every 6 months in the first 5 years included a physical examination, abdominal ultrasonography, and computed tomography of the abdomen. Out of all 57 patients studied, the vital status in 54 patients could be determined at the end of the study.

With regard to histopathology, 39 (63%) of the patients were staged as pT1/pT2, 21 (37%) as pT3/pT4, 30 (53%) as pN0, while 38 (67%) as G1/G2. One patient was excluded from the survival analysis because he died

within 90 days after surgery. From nine patients, only information about the date of death but not of recurrence was available.

Tissue Preparation and Immunohistochemical Analysis

Lymph nodes were divided into two parts: one for conventional histopathology and the other was snap-frozen in liquid nitrogen within 3 h after their removal and stored at −80°C until use. Only histopathologically "tumor-free" lymph nodes were screened by immunohistochemistry with the anti-epithelial cell monoclonal antibody Ber-EP4 (IgG1; Dako, Hamburg, Germany) as described previously.[21] Ber-EP4 is an antibody against two glycopolypeptides of 34 and 49 kD on the surface and in the cytoplasm of all epithelial cells (except parietal cells, hepatocytes, and the superficial layers of squamous epithelium). The antibody does not react with mesenchymal tissue, including lymphoid tissue.[11,19] Cryostat sections (5 to 6 μm thick) were cut at three different levels in each node and transferred onto glass slides treated with 3-triethoxysilylpropylamin (Merck, Darmstadt, Germany). One section of the sample obtained at each level was stained by the alkaline phosphataseantialkaline phosphatase technique combined with the new fuchsine stain (Sena, Heidelberg, Germany) for the visualization reaction.[20] In 16 control patients with nonepithelial tumors or inflammatory diseases, lymph nodes were consistently stained negative. Sections of normal colon served as positive staining controls and isotype-matched irrelevant murine monoclonal antibodies served as negative controls (purified immunoglobulin mouse myeloma protein for IgG1; Sigma, Deisenhofen, Germany). The slides were evaluated in a blinded fashion by two observers working independently (D.B., H.C.). Minimal tumor cell involvement in a lymph node that was considered as tumor free by conventional histopathological staining was defined as the presence of one to ten positive cells in the body of the node (Fig. 1). If more than ten cells were detected (four lymph nodes in two patients), a hematoxylin–eosin restaining was conducted. Under routine histology, all lymph nodes were judged as negative.

Statistical Analysis

All statistical calculations concerning survival (overall and recurrence-free survival) were based on the group of 57 patients who were available for follow-up. The primary outcome measure was the 5-year survival probability. Secondary outcomes were the incidence of local recurrence and distant metastases of the disease. Survival was calculated from the date of resection until the date of death from any cause. For patients lost to follow-up, data were censored on the date the patient was last seen alive. Associations between categorical variables were assessed using Fisher's exact test. Survival estimates were derived using the method proposed by Kaplan and Meier[29] and the log-rank test was used to assess differences in survival estimates among the groups. Point and interval estimates of the survival probabilities at 60 months were calculated. For comparison purposes, log-rank test and exact stratified log-rank test were performed. Cox proportional hazards modelling[30] was used to investigate and adjust the major prognostic and stratification factors. $p<0.05$ was considered statistically significant. Since this analysis was intended to be explorative, no adjustment for multiple testing was carried out.

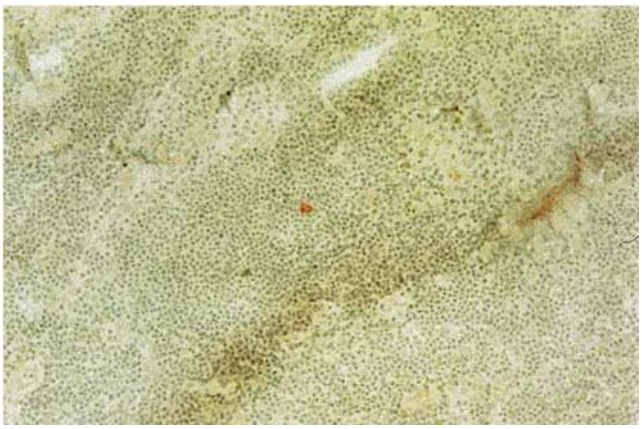

Figure 1 Immunohistochemically detected cell in the lymph node of patient with carcinoma of the papilla of Vater.

Results

Characteristics of Patients

Fifty-seven patients [21 (37%) women and 36 (63%) men] with carcinoma of the papilla of Vater were included in the study. The median age was 63 years (range 39 to 83 years, mean 62.5 years). Table 1 shows the characteristics of patients and tumors. A total of 169 lymph nodes classified as "tumor free" by conventional histopathology were analyzed. Positive cells in the sinuses, the lymphoid interstitium or in both locations were found in 91 lymph nodes (53.8%). These 91 positive lymph nodes were found in 40 (70.2%) of the 57 patients. Whereas the presence of Ber-EP4 cells was significantly associated with nodal metastases (pN1) identified through conventional histopathology ($p=0.019$), no correlation between tumor stage and tumor grade was found.

Survival

After an average observation period of 62 months (range 3 to 144 months, median 39 months), the

Table 1 Characteristics of Patients and Tumors

Variable	Number of patients	Nodal microdissemination	Significance *p*
Total patients	57	40 (70.2%)	
Total lymph nodes	169	91 (53.8%)	
Sex			0.064
Male	36 (63%)	29 (77.8%)	
Female	21 (21%)	11 (57.1%)	
Primary tumor			0.172
pTis	2 (3.5%)	0 (0%)	
pT1	7 (12.3%)	6 (85.7%)	
pT2	27 (47.4%)	20 (74%)	
pT3	20 (35.1%)	13 (65%)	
pT4	1 (1.8%)	1 (100%)	
Lymph nodes			0.019
pN0	30 (52.6%)	17 (56.7%)	
pN1	27 (47.4%)	23 (85.1%)	
Histological grading			0.304
G1	4 (7%)	1 (25%)	
G2	43 (75.4%)	31 (72.1%)	
G3	10 (17.5%)	8 (80%)	

presence of nodal microinvolvement was associated with significantly reduced overall survival probabilities. The Kaplan–Meyer overall survival curve for all patients who were stratified according to the presence or absence of occult tumor cells in lymph nodes showed a significant survival benefit for patients negative by immunohistochemical methods (mean overall survival 71.5 vs. 28.6 months; median overall survival 144 vs. 23 months, 5-year survival 73.2% vs. 27.6%; 10-year survival 62.7% vs. 0%) irrespective of the histopathological classification (pN0/pN1) of the lymph nodes (log-rank test; $p<0.008$; Fig. 2).

The analysis of the subset of patients who were staged as pN0 in conventional histopathology revealed significantly better survival rates in patients without occult tumor cells as compared with those with nodal microinvolvement (mean 126.4 vs. 44.1 months; median 144 vs. 28 months; 5-year survival 92.3% vs. 26.8%; 10-year survival 79.1% vs. 0%; log-rank test; $p=0.008$; Fig. 3). Patients without any nodal involvement, as excluded by both conventional histopathology and immunohistochemistry, had an excellent 5-year overall survival probability of 92% (standard error—11.4%). In contrast, the 5-year survival probability of pN0 patients with nodal microinvolvement (26.8%) resembled that of pN1 patients (24.9%; log-rank test; $p=0.198$) and in both groups, no patient was still alive 10 years after surgery. The additional detection of nodal microinvolvement in other lymph nodes classified as tumor free by routine histopathology in patients already staged as pN1 had no influence on overall survival probabilities (median survival 22 vs.

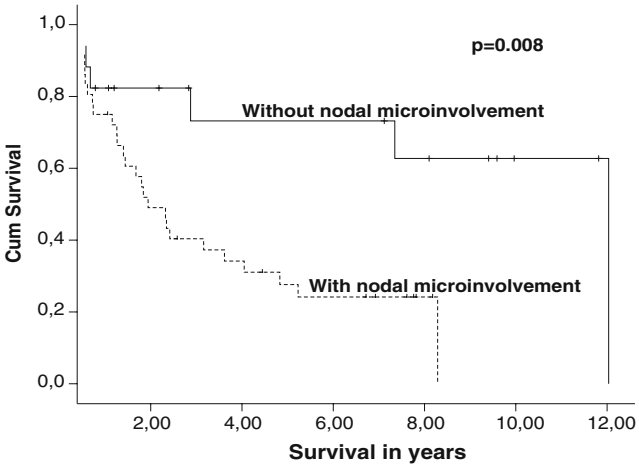

Figure 2 Overall survival according to the presence or absence of nodal microinvolvement in immunohistochemistry. Median—144 vs. 23 months; mean—71.5 vs. 28.6 months; 5-year overall survival 73.2% vs. 27.6%; 10-year survival 62.7% vs. 0%; log-rank test; $p=0.008$.

8 months; 5-year survival 28.4% vs. 0%; 10-year survival 0% vs. 0%; log-rank test; $p=0.434$, data not shown).

The crucial importance of the disseminated tumor cells in patients with carcinomas of the papilla of Vater was even more evident in respect to the disease-free survival. Only one of the patients negative in both routine histology and IHC had recurrence of the disease (either local or distant), namely 9 years after the primary surgery (5-year disease-free survival (DFS) 100%, 10-year DFS 80%), whereas the 5-year DFS rate in pN0 but with nodal microinvolvement was 55.6% (10-year DFS 55.6%; $p=0.023$; Fig. 4) and it was not statistically different than

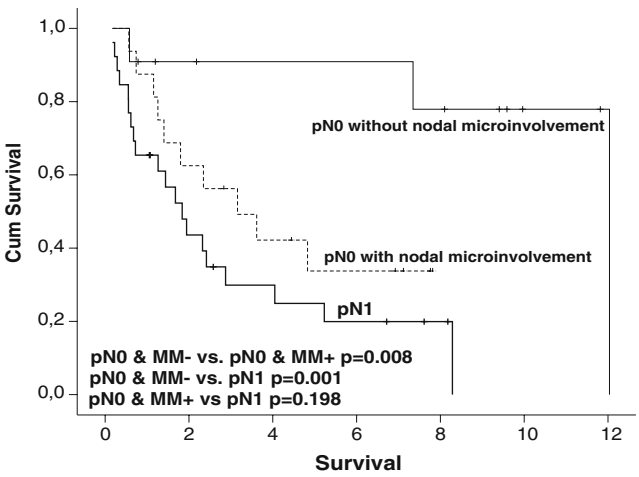

Figure 3 Overall survival according to the presence or absence of nodal metastases in conventional histology and immunohistochemistry. Mean 126.4 vs. 44.1 vs. 35.7 months; median 144 vs. 28 vs. 22 months; 5-year survival 92.3% vs. 26.8% vs. 24.9%; 10-year survival 79.1% vs. 0% vs. 0%.

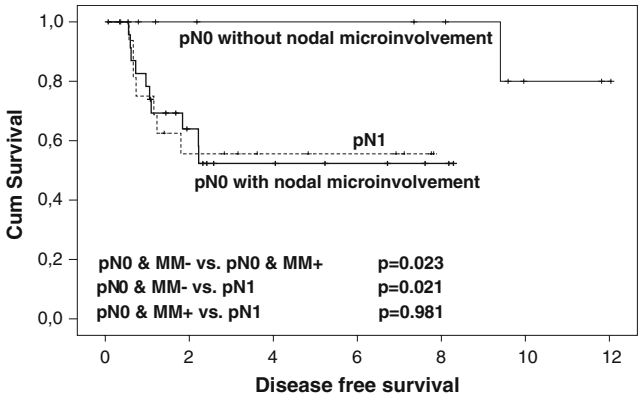

Figure 4 Disease-free survival according to the presence or absence of nodal metastases in conventional histology and immunohistochemistry. Mean 138.1 vs. 57.4 vs. 59.3 months; 5-year disease-free survival 100% vs. 52.3% vs. 55.6%; 10-year disease-free survival 80% vs. 52.3% vs. 55.6%.

in patients already staged as positive in routine histology (5-year DFS 52.3%; 10-year DFS 52.3; $p=0.981$).

Apart from nodal involvement assessed either by histopathology or immunohistochemistry, the comparison of survival curves revealed also significant differences with respect to grading when G1,2 tumors were compared to G3 tumors (median survival time—49 vs. 8 months; log-rank test; $p=0.001$).

Multivariate Analysis

Multivariate Cox regression analysis for overall survival revealed that nodal microinvolvement together with histological grading were the most significant independent prognostic factors analyzed (Table 2). With respect to 5-year overall survival, nodal microinvolvement had a relative risk of 5.677 (95% confidence interval—1.157 to 27.857; $p=0.032$), as compared with negative findings in immunohistochemistry. G3 tumors had a relative risk of 2.883 as compared with G1/2 tumors (95% confidence interval—1.068 to 7.777; $p=0.037$). Age, sex, nodal involvement, and tumor stage had no independent prognostic influence on overall survival. The analysis of the interaction between pN status, nodal microinvolvement, and grading did not reveal that the proportional assumption was violated. Hence, the Cox model appeared appropriate and grading followed by nodal microinvolvement remained the two most important prognostic variables also in the subset of pN0 patients.

Discussion

Since most of the patients with carcinoma of the papilla of Vater develop jaundice early in their course, almost 80% to 90% of all patients are still operable at the time of presentation. The 5-year survival rates, independent from the tumor stage, are between 21% and 61%.[31,32] Not surprisingly, together with the resection margin status, the nodal infiltration defined by routine histology has a significant influence on overall prognosis, and, almost always, the patients burdened with residual disease develop a recurrence (local or distant). Sometimes, even patients staged as free of residual disease (R0 and N0) develop recurrence. The question that arises is: can we enhance the staging system and identify the patients under higher risk for recurrence?

The key finding of this study is that isolated tumor cells, detectable in lymph nodes by immunohistochemical analysis, are strong independent prognosticators in patients with carcinomas of the papilla of Vater. We have analyzed patients with carcinomas of the papilla of Vater who did not receive any adjuvant radio-, chemo-, or radiochemotherapy. In the group of patients staged as node negative by routine histology, two subsets could be identified: one subset with a poor 5-year survival probability of 27% (10 year 0%) which was close to that of patients with overt nodal involvement (pN1; 5 year 25%, 10 year 0%), the other subset without nodal microinvolvement had a much better prognosis with a five-year survival probability of over 92% (10 year 79%), suggesting that immunohistochemistry can confirm the cardinal importance of occult tumor cells for the separation of the respective survival curves in pN0 patients. In patients who were already staged as node positive (pN1), the detection of occult tumor cells in the rest of the "tumor-free" lymph nodes had no prognostic significance. This finding was in contrast with previous observations of our group showing that survival is significantly worsened in esophageal,[22] pancreatic,[21,26] and nonsmall cell lung carcinoma[10] when histopathological pN1 status is accompanied with nodal microinvolvement. Basically, pN1 status in solid tumors is considered as a local disease which can be potentially cured with surgery, although it generally carries a higher risk of systemic dissemination than pN0 status.

Table 2 Multivariate Analysis

	Significance	Exp(B)	95.0% CI for Exp(B)	
			Lower	Upper
Histological grading	0.037	2.883	1.068	7.777
Nodal microinvolvement	0.032	5.677	1.157	27.857
Nodal involvement (pN)	0.136	4.678	0.615	35.614

The contemporary studies of the influence of the adjuvant therapy in patients operated upon carcinomas of the papilla of Vater have mostly showed no significant advantage in relation to patients submitted only to surgical resection. Nakano et al. have studied the influence of preoperative radiotherapy vs. surgery alone and no significant benefit was found.[33] Also the combined radiochemotherapy (local radiation combined with systemic 5-Fu) showed no benefit,[34] as was the case with the intensified radiochemotherapy (5-FU + Leucovorin + EBRT).[5] Although chemoradiation and/or chemotherapy for adjuvant treatment of carcinoma of the papilla of Vater may have severe side effects,[5] in common clinical practice, it is in most instances applied irrespective of tumor stage. This reflects the distrust in the value of conventional tumor staging nomenclature in terms of reliably predicting the risk of tumor relapse even in patients with early pancreatic cancer (T1, N0). Our data indicate that immunohistochemical assessment of lymph nodes can be used to refine the staging system for carcinoma of the papilla of Vater and might help us to identify patients who could not be cured by surgery alone and need adjuvant therapy. In turn, patients who are true node negative both in histopathology and in immunohistochemistry have an excellent 5-year survival probability of nearly 93%, even without chemotherapy. Whether this prognosis can be further improved by adjuvant therapy needs to be discussed.

The percent of the detected tumor cells in lymph nodes with IHC methods in our cohort was surprisingly high, higher than in other tumor collectives (esophageal, pancreatic, and lung carcinoma—17%, 42%, 53%, respectively). A similar percent of affected lymph nodes with nodal microinvolvement was reported by Hosch et al.[35] in esophageal carcinoma (71%).

The detection of nodal microinvolvement even in the early tumor stage (pT1—85%) doubt the validity of local therapeutic regimens (like ampullectomy or local excision) already proposed by some.[36] Demetriades et al.[37] assume the local excision in early tumor stage (pT1) as adequate, not paying attention to lymph node involvement. On this line are also the findings from Beger et al.[38] who showed that even the patients staged as pTis or pT1 without nodal involvement will benefit from the lymphadenectomy. Yoon et al.[39] already described the ampullectomy as unacceptable in the treatment of early carcinomas of the papilla of Vater, since the recurrence rate of 18.2% was too high. Furthermore, without formal lymphadenectomy, the patients cannot be scrutinized according to the nodal involvement (conventional or IHC) and, thus, the patients at need for adjuvant chemotherapy will not receive the adequate therapy.

The local growth of the tumor and the potential for developing distant metastasis are completely independent processes.[40] Therefore, the detection of nodal microinvolvement by IHC in patients within early tumor stage can be an early prognostic sign of tumor dissemination, and, therefore, an important prognosticator in patients with carcinomas of the papilla of Vater. Muhlhofer et al.[41] have examined the immunohistochemically detected cells in patients with R0-resected esophageal carcinoma and have found out that the detection of disseminated cells is not correlated with lymphovascular tumor infiltration. It is therefore obvious that not all disseminated tumor cells have the potential to grow into an overt metastasis. This is also an indicator that not only the absolute number of disseminated tumor cells but also the biological attributes of the homing organ have an important if not the crucial role in the process of homing the tumor cells and development of overt metastasis. Evidence exists that disseminated tumor cells can remain in a dormant state in the local environment and then develop into overt metastases when the environmental conditions are right.[35,42–45]

At the end as a conclusion, one can draw several points:

- Patients operated upon carcinomas of the papilla of Vater have much better prognosis than patients operated upon pancreatic ductal adenocarcinoma
- The detection of nodal microinvolvement has a significant influence on overall survival in patients operated upon carcinomas of the papilla of Vater
- Local types of therapy (ampullectomy, duodenectomy) in patients operated upon carcinomas of the papilla of Vater is insufficient in the treatment of patients operated upon carcinomas of the papilla of Vater

References

1. Iwama T, Mishima Y, Utsunomiya J. The impact of familial adenomatous polyposis on the tumorigenesis and mortality at the several organs. Its rational treatment. Ann Surg 1993;217(2):101–108. doi:10.1097/00000658-199302000-00002.
2. Galle TS, Juel K, Bulow S. Causes of death in familial adenomatous polyposis. Scand J Gastroenterol 1999;34(8):808–812. doi:10.1080/003655299750025741.
3. Tonelli F, Nardi F, Bechi P, et al. Extracolonic polyps in familial polyposis coli and Gardner's syndrome. Dis Colon Rectum 1985;28(9):664–668. doi:10.1007/BF02553447.
4. Fischer HP, Zhou H. Pathogenesis and histomorphology of ampullary carcinomas and their precursor lesions review and individual findings. Pathologe 2003;24(3):196–203.
5. Abrams RA, Grochow LB, Chakravarthy A, et al. Intensified adjuvant therapy for pancreatic and periampullary adenocarcinoma: survival results and observations regarding patterns of failure, radiotherapy dose and CA19-9 levels. Int J Radiat Oncol Biol Phys 1999;44(5):1039–1046. doi:10.1016/S0360-3016(99)00107-8.
6. Albores-Saavedra J, Henson DE, Sobin LH. The WHO histological classification of tumors of the gallbladder and extrahepatic bile ducts. A commentary on the second edition. Cancer 1992;70

(2):410–414. doi:10.1002/1097-0142(19920715)70:2<410::AID-CNCR2820700207>3.0.CO;2-R.
7. Alstrup N, Burcharth F, Hauge C, Horn T. Transduodenal excision of tumours of the ampulla of Vater. Eur J Surg 1996;162(12):961–967.
8. Pantel K, Brakenhoff RH. Dissecting the metastatic cascade. Nat Rev Cancer 2004;4(6):448–456. doi:10.1038/nrc1370.
9. Byrne J, Waldron R, McAvinchey D, Dervan P. The use of monoclonal antibodies for the histopathological detection of mammary axillary micrometastases. Eur J Surg Oncol 1987;13 (5):409–411.
10. Passlick B, Izbicki JR, Kubuschok B, et al. Immunohistochemical assessment of individual tumor cells in lymph nodes of patients with non-small-cell lung cancer. J Clin Oncol 1994;12(9):1827–1832.
11. Latza U, Niedobitek G, Schwarting R, et al. Ber-EP4: new monoclonal antibody which distinguishes epithelia from mesothelial. J Clin Pathol 1990;43(3):213–219. doi:10.1136/jcp.43.3.213.
12. Raymond WA, Leong AS. Immunoperoxidase staining in the detection of lymph node metastases in stage I breast cancer. Pathology 1989;21(1):11–15. doi:10.3109/00313028909059522.
13. Pantel K, Izbicki JR, Angstwurm M, et al. Immunocytological detection of bone marrow micrometastasis in operable non-small cell lung cancer. Cancer Res 1993;53(5):1027–1031.
14. Bussolati G, Gugliotta P, Morra I, et al. The immunohistochemical detection of lymph node metastases from infiltrating lobular carcinoma of the breast. Br J Cancer. 1986;54(4):631–636.
15. Chen ZL, Perez S, Holmes EC, et al. Frequency and distribution of occult micrometastases in lymph nodes of patients with non-small-cell lung carcinoma. J Natl Cancer Inst 1993;85(6):493–498. doi:10.1093/jnci/85.6.493.
16. Casson AG, Rusch VW, Ginsberg RJ, et al. Lymph node mapping of esophageal cancer. Ann Thorac Surg 1994;58(5):1569–1570.
17. de Mascarel I, Bonichon F, Coindre JM, Trojani M. Prognostic significance of breast cancer axillary lymph node micrometastases assessed by two special techniques: reevaluation with longer follow-up. Br J Cancer 1992;66(3):523–527.
18. Martini N, Flehinger BJ, Zaman MB, Beattie EJ Jr. Results of resection in non-oat cell carcinoma of the lung with mediastinal lymph node metastases. Ann Surg 1983;198(3):386–397. doi:10.1097/00000658-198309000-00015.
19. Momburg F, Moldenhauer G, Hammerling GJ, Moller P. Immunohistochemical study of the expression of a Mr 34,000 human epithelium-specific surface glycoprotein in normal and malignant tissues. Cancer Res 1987;47(11):2883–2891.
20. Pantel K, Schlimok G, Angstwurm M, et al. Methodological analysis of immunocytochemical screening for disseminated epithelial tumor cells in bone marrow. J Hematother 1994;3(3):165–173.
21. Bogoevski D, Yekebas EF, Schurr P, et al. Mode of spread in the early phase of lymphatic metastasis in pancreatic ductal adenocarcinoma: prognostic significance of nodal microinvolvement. Ann Surg 2004;240(6):993–1000. discussion 1000–1. doi:10.1097/01.sla.0000145922.25106.e3.
22. Izbicki JR, Hosch SB, Pichlmeier U, et al. Prognostic value of immunohistochemically identifiable tumor cells in lymph nodes of patients with completely resected esophageal cancer. N Engl J Med 1997;337(17):1188–1194. doi:10.1056/NEJM199710233371702.
23. Kasper M, Stosiek P, Typlt H, Karsten U. Histological evaluation of three new monoclonal anti-cytokeratin antibodies. 1. Normal tissues. Eur J Cancer Clin Oncol 1987;23(2):137–147. doi:10.1016/0277-5379(87)90007-1.
24. Z'Graggen K, Centeno BA, Fernandez-del Castillo C, et al. Biological implications of tumor cells in blood and bone marrow of pancreatic cancer patients. Surgery 2001;129(5):537–546. doi:10.1067/msy.2001.113819.
25. Scheunemann P, Stoecklein NH, Rehders A, et al. Frequency and prognostic significance of occult tumor cells in lymph nodes in patients with adenocarcinoma of the papilla of Vater. HPB Oxf 2007;9(2):135–139. doi:10.1080/13651820601090646.
26. Yekebas EF, Bogoevski D, Bubenheim M, et al. Strong prognostic value of nodal and bone marrow micro-involvement in patients with pancreatic ductal carcinoma receiving no adjuvant chemotherapy. World J Gastroenterol 2006;12(40):6515–6221.
27. Pedrazzoli S, DiCarlo V, Dionigi R, et al. Standard versus extended lymphadenectomy associated with pancreatoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas: a multicenter, prospective, randomized study. Lymphadenectomy Study Group. Ann Surg 1998;228(4):508–517. doi:10.1097/00000658-199810000-00007.
28. UICC. TNM classification of malignant tumors. 4th ed. New York: Springer, 1987.
29. Moeschberger ML, Klein JP. Statistical methods for dependent competing risks. Lifetime Data Anal 1995;1(2):195–204. doi:10.1007/BF00985770.
30. Cox D. Regression models and life tables with discussion. J R Stat Soc [Ser A] 1972;34:187–220.
31. Ouaissi M, Sielezneff I, Alves A, et al. Long term outcome following 26 surgical ampullectomies. Ann Chir 2006;131 (5):322–327. doi:10.1016/j.anchir.2006.03.004.
32. Group ILBCS. Prognostic importance of occult axillary lymph node micrometastases from breast cancers. Lancet 1990;335 (8705):1565–1568.
33. Nakano K, Chijiiwa K, Toyonaga T, et al. Combination therapy of resection and intraoperative radiation for patients with carcinomas of extrahepatic bile duct and ampulla of Vater: prognostic advantage over resection alone? Hepatogastroenterology 2003;50 (52):928–933.
34. Lee JH, Whittington R, Williams NN, et al. Outcome of pancreaticoduodenectomy and impact of adjuvant therapy for ampullary carcinomas. Int J Radiat Oncol Biol Phys 2000;47 (4):945–953. doi:10.1016/S0360-3016(00)00537-X.
35. Hosch S, Kraus J, Scheunemann P, et al. Malignant potential and cytogenetic characteristics of occult disseminated tumor cells in esophageal cancer. Cancer Res 2000;60(24):6836–6840.
36. Witzigmann H, Mobius C, Uhlmann D, et al. Treatment concept of adenomas of Vater's ampulla. Chirurg 2000;71(2):196–201.
37. Demetriades H, Zacharakis E, Kirou I, et al. Local excision as a treatment for tumors of ampulla of Vater. World J Surg Oncol 2006;4:14. doi:10.1186/1477-7819-4-14.
38. Beger HG, Treitschke F, Gansauge F, et al. Tumor of the ampulla of Vater: experience with local or radical resection in 171 consecutively treated patients. Arch Surg 1999;134(5):526–532. doi:10.1001/archsurg.134.5.526.
39. Yoon YS, Kim SW, Park SJ, et al. Clinicopathologic analysis of early ampullary cancers with a focus on the feasibility of ampullectomy. Ann Surg 2005;242(1):92–100. doi:10.1097/01.sla.0000167853.04171.bb.
40. Fidler IJ, Kripke ML. Metastasis results from preexisting variant cells within a malignant tumor. Science 1977;197(4306):893–895. doi:10.1126/science.887927.
41. Muhlhofer A, Kronawitter U, Zoller WG. Prognostic value of immunohistochemically identifiable tumor cells in lymph nodes of patients with RO-resected esophageal carcinoma. Z Gastroenterol 1998;36(5):479–481.
42. Garrido F, Ruiz-Cabello F, Cabrera T, et al. Implications for immunosurveillance of altered HLA class I phenotypes in human tumours. Immunol Today 1997;18(2):89–95. doi:10.1016/S0167-5699(96)10075-X.
43. Delcore R, Rodriguez FJ, Forster J, et al. Significance of lymph node metastases in patients with pancreatic cancer undergoing

curative resection. Am J Surg 1996;172(5):463–468. discussion 468–9. doi:10.1016/S0002-9610(96)00237-1.
44. Bodmer WF, Browning MJ, Krausa P, et al. Tumor escape from immune response by variation in HLA expression and other mechanisms. Ann N Y Acad Sci 1993;690:42–49. doi:10.1111/j.1749-6632.1993.tb43994.x.
45. Fleming KA, McMichael A, Morton JA, et al. Distribution of HLA class 1 antigens in normal human tissue and in mammary cancer. J Clin Pathol. 1981;34(7):779–784. doi:10.1136/jcp.34.7.779.

Discussion

Nodal Microinvolvement in Patients with Carcinoma of the Papilla of Vater Receiving No Adjuvant Chemotherapy

A. James Moser, M.D. (Pittsburgh, PA): It was really a pleasure to read your manuscript, Dr. Bogoevski. It was as clear and concise as the rest of your presentation. In looking at the manuscript, I was struck by a few observations, particularly by the observation that patients with pathologic T1 lesions had a significant incidence of nodal disease that wasn't detected by standard methods. I was hoping you could comment on three relatively brief questions that came to mind as I reviewed your manuscript.

The first is that you suggest in the discussion section of your manuscript that nodal involvement reflects localized disease. If that is the case, are you suggesting that radical nodal dissection is the treatment for nodal micrometastases and, if so, should we be evaluating lymph nodes by rapid molecular techniques intraoperatively, as has been proposed for the treatment of melanoma?

Dean Bogoevski, M.D. (Hamburg, Germany): Thank you for your remarks and thoughtful comments. I would like to point out two different things. First of all, in previous studies published by our group concerning patients with pancreatic ductal adenocarcinoma, we were able to show that even patients staged as node positive (pN1) on routine histology but who were additionally burdened with nodal microinvolvement had significantly worse overall survival probabilities than the patients who were staged as node negative without nodal microinvolvement. This means that probably the detection of nodal microdissemination is a sign of generalization of the disease. On contrary, in the group of patients with carcinoma of the papilla of Vater the patients staged as node positive and additionally burdened with nodal microinvolvement, no significant worsening of the survival was recorded in comparison to pN1 but without nodal microinvolvement.

On the other hand, as you already mentioned, in the group of patients histologically staged as pT1, the detection of nodal microinvolvement was far higher than in patients with pancreatic ductal adenocarcinoma, even higher than 85%. It might be that in patients with carcinoma of the papilla of Vater, the dissemination of the cells starts early, but they probably stay dormant and do not have that capacity to develop themselves into a nodal metastasis. One can only speculate that that is the reason why these patients have better overall survival probabilities of 12 years' median survival vs. 2–1/2 in pancreatic ductal adenocarcinoma.

Concerning your second comment, I have noting to add and I agree that we need to concern different molecular markers for detection of nodal microinvolvement.

Dr. Moser: You started to touch on my second question. Can you share some data on the patterns of first sites of recurrence in patients with nodal micrometastases? The question that comes to mind is whether micrometastasis is really a marker of rapid distant progression, as I think you just suggested, or are nodal micrometastases evidence for persistent local disease?

Dr. Bogoevski: As you can realize, we have examined only three lymph nodes per patient. Actually, we have conducted this study in a manner that we have divided the lymph nodes in three different compartments: The superior–anterior compartment concerning here the lymph nodes at the celiac trunk, the common hepatic artery, and the prepancreatic lymph nodes, the lymph nodes at the hepatoduodeal ligament, and then the posterior–inferior compartment with the lymph nodes from interaortocaval compartment and the lymph nodes around the superior mesenteric artery.

We were able to show, as well as in patients with pancreatic ductal adenocarcinoma, that there is no typical mode of dissemination of the cells. I mean, sometimes nodal microdissemination was detected even in the interaortocaval lymph nodes. So there is no pattern for dissemination of these tumor cells.

Dr. Moser: My last question concerns your statement that the group is homogeneous because no patients received adjuvant treatment. In fact, the rate of node positivity was somewhere between 85–100% for every pathologic T stage. In light of your data, do you believe that all patients with ampullary cancer should receive adjuvant treatment when immunohistochemistry is not available given the likelihood that all negative nodes are actually positive? And how do you reconcile that statement with prior trials, for example, EORTC, among others, that did not show a benefit of adjuvant treatment for patients with ampullary cancer? Do you have any ideas on that subject?

Dr. Bogoevski: Unlike in pancreatic ductal adenocarcinoma, the pointed EORTC study did not show any benefit for patients with carcinomas of the papilla of Vater. I am not quite sure, but my personal opinion is that the additional chemotherapy in this group of patients, the chemotherapy that is now available, is fully questionable.

Dr. Moser: The best outcome would be for everybody in the room who treats these diseases to agree to do a study.

Your study of 112 patients is a large series, but accrual took 10 years. An SSAT-wide effort would be very revealing. It really is amazing that the five-year survival rate of node positive patients, meaning the vast majority, is really only 27%. So although ampullary cancer is better than pancreatic cancer, I don't think any of us in the room would want it.

Dr. Bogoevski: It will be much better.

Frank Makowiec, M.D. (Frieburg, Germany): Do you know the costs of the additional examinations (i.e. immunohistochemistry) for each lymph node?

Dr. Bogoevski: No. I'm sorry about that. That's out of my range. Sorry.

J Gastrointest Surg (2008) 12:1839–1846
DOI 10.1007/s11605-008-0679-4

Recent Trends of Hepatic Resection in Canada: 1995–2004

Ryan J. McColl · Xiaoqing You · William A. Ghali · Gilaad Kaplan · Robert Myers · Elijah Dixon

Received: 13 May 2008 / Accepted: 20 August 2008 / Published online: 11 September 2008

Abstract
Introduction Recently, many surgical procedures have become regionalized in the United States, likely owing to research demonstrating a relationship between volume and outcome. We sought to describe patient characteristics and outcomes according to hospital volume along with patterns of regionalization for hepatic resection in Canada from 1995 to 2004.
Methods Discharge data from all hospitals across Canada except Quebec were obtained from the Canadian Institute for Health Information for 1995–2004. All patients undergoing a hepatic resection were identified using ICD-9 and ICD-10 codes. High-volume hospitals were defined as those performing ten or more procedures per year.
Results A total of 9,912 patients (mean age 59 years) underwent hepatic resection. The proportion of procedures performed at high-volume hospitals increased from 42% in 1995 to 84% in 2004. Overall mortality rate for the study period was 5.0% which decreased over time. Mortality rates were higher at low-volume (6.1%) compared to high-volume centers (4.6%), but this finding was not statistically significant (p=0.7451). Those factors predictive of mortality in a multivariate analysis included age, gender, year of operation, operative indication, comorbidity score, and admission status.
Discussion Mortality rates have significantly improved. Hospital volume is not a significant predictor of mortality following liver resection in Canada.

Presented in oral format at a Surgical Society of the Alimentary Tract Plenary Session of Digestive Disease Week, May 19, 2008, San Diego Convention Center, San Diego, CA, USA.

R. J. McColl
Department of Surgery, University of Calgary,
Calgary, AB, Canada

X. You
University of Calgary,
Calgary, AB, Canada

W. A. Ghali · G. Kaplan · R. Myers
Department of Medicine and Community Health Sciences,
University of Calgary,
Calgary, AB, Canada

E. Dixon (✉)
Department of Surgery, Oncology,
and Community Health Sciences, University of Calgary,
1331—29th Street NW,
Calgary, AB, Canada T3Z 3M9
e-mail: Elijah.dixon@calgaryhealthregion.ca

Keywords Hepatic resection · Canada · Mortality · Hospital volume · Outcome

Introduction

Liver resection (LR) is now considered the mainstay of therapy for selected patients with primary and secondary hepatobiliary malignancy and the only effective treatment for a variety of benign hepatic diseases.[1–7] As a result of the attendant risks and the complexity of the procedure, LR has been the focus of much recent study with respect to health care delivery.[8–15]

There have been calls for the regionalization of certain complex procedures; this has been driven by evidence showing that there is a strong correlation between hospital volume and outcome for complex surgical procedures.[8–13,16–22] Further work has gone on to estimate the potential lives that could be saved from the selective referral of

several types of elective surgeries to high-volume centers.[16,17,23] Despite such evidence from the United States (US), it remains controversial; some arguing it would save a minimal number of lives in a Canadian setting.[24] This study describes recent trends of hepatic resection in Canada based on information from a national database. Volume–outcome relationships are explored as well as patterns of regionalization over the period 1995–2004. Comparisons with recent American data are undertaken.

Methods

Data Source

All patients ≥18 years of age who underwent hepatic resection in the years 1995–2004 were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification 9 and 10 codes (ICD-9 and ICD-10) from the Canadian Institute for Health Information (CIHI) database. This is a national database containing patient discharge information for all hospitals in Canada excluding those in the province of Quebec (Quebec does not report data to the Canadian Institute for Health Information).

Patient Variables

Data about age, gender, comorbid disease, admission status, indication for operation, province LR was performed in, in-hospital mortality, and length of stay (LOS) were derived directly from the database. Admission status was defined as elective, urgent, and emergent. The Charlson comorbidity score was calculated for each patient using the original weights described.[25] Indications for LR were determined using the ICD-9/10 code and were divided into three categories: primary hepatic malignancy, secondary hepatic malignancy, and others (trauma, primary biliary malignancy, benign disease).

Liver Resection Rates

The national age- and sex-adjusted LR rate per 100,000 persons aged ≥18 years was calculated by the direct method of standardization for each year in the study period. The year 2001 was used as a reference population for the calculations. Population size for each year as the denominator in our calculations was obtained from Statistics Canada.

Outcomes

Measured outcome variables include in-hospital mortality and LOS in days.

Hospital Volume

We divided hospitals into two groups a priori; this definition has been used previously in the US (high volume [≥10/year] versus low volume [1–9/year]).[10] The proportion of procedures performed at high-volume centers was calculated across the study period in order to describe regionalization trends. Both in-hospital mortality and LOS were calculated according to hospital volume status. We performed a sensitivity analysis across a broad range of hospital volume definitions to ensure that our definition of "volume" did not lead to a type II error (see Table 6).

Comparison to the United States

US LR data was obtained from a population-based study by Dimick et al. for the period 1988–2000.[10] Dimick's data was derived from the Nationwide Inpatient Sample (NIS) which is a 20% stratified random sample of all hospital discharges in the US. The NIS is the largest all-payer health care database in the US and is thought to be representative of US health care statistics making our comparison of national trends valid.

Statistical Analysis

Descriptive statistics are used to illustrate the data, including the means, median, and 95% confidence intervals. A two-sided p value of <0.05 was considered statistically significant. Univariate comparisons of baseline characteristics and crude in-hospital mortality were performed using chi-square tests for categorical data and simple logistic regression analysis for continuous data. Predictors of in-hospital mortality that were found to be statistically significant on univariate analysis were entered into a multivariate logistic regression analysis. Analysis was performed using SAS Software Version 9.1 (Cary, NC, USA).

Results

Patient Characteristics

Over the study period, 9,912 patients underwent LR (Table 1). There was a relatively even distribution across genders. The majority of cases were done on an elective basis on patients with a Charlson score of 0 or 1.

Liver Resection Rates

The national rate of LR increased by 80% from 3.2 per 100,000 adults in 1995 to 5.9 per 100,000 adults in 2004 (McColl et al., submitted for publication; Table 2).

Table 1 Patient Characteristics

Characteristics	
Patients, *n*	9,912
Age (years; mean±SD)	59±14
Male gender, *n* (%)	5,258 (53)
Urgent type, *n* (%)	3,515 (35)
Emergent type, *n* (%)	362 (4)
Elective type, *n* (%)	6,035 (61)
Number of comorbid diseases, *n* (%)	
None	4,354 (44)
One	3,864 (39)
Two	1,341 (14)
Three or more	353 (3)

Hospital Characteristics

A total of 247 hospitals performed at least one LR over the study period in question. Of these, 23 hospitals (9%) were considered high-volume. Of the 9,912 LR cases, 7,459 (75%) took place at a high-volume center. Across the study period, an increasing number of LRs were performed at high-volume centers with 42% in 1995 and 84% in 2004, demonstrating a 100% increase in LR regionalization to high-volume centers over the study period in question.

Operative Indications

Benign and traumatic diseases were consistently the commonest indications for LR (Table 3). To assess temporal trends in operative indications a priori, we divided the study period into three time segments: segment 1 (1995–1998), segment 2 (1999–2001), and segment 3 (2002–2004). The proportion of LRs for secondary metastases increased from 35% in time segment 1 to 40% in segment 3 (Table 3).

Operative Mortality

The overall in-hospital mortality rate was 5.0%. An improvement in perioperative mortality was demonstrated across the study: the mortality rate in 1995–1996 was 5.8% compared to 4.2% in 2003–2004 ($p<0.0001$; Fig. 1). Furthermore, the odds of mortality in the first half of the study (1995–1999) compared to the second half (2000–2004) was 1.4 (95% confidence interval [95%CI]=1.2–1.7, $p=0.0002$).

The mortality rate varied dramatically according to operative indication. For secondary malignancy, mortality was 2.7% compared to 8.2% for primary malignancy ($p<0.0001$). This is not an unexpected finding and has been described previously,[8,10,12] relating to the association of hepatocellular cancer with underlying liver disease/cirrhosis which increases the risks of liver failure and death for patients undergoing surgery. There were measurable differences in mortality based on which province the LR was performed in (Table 4).

Hospital volume was significant only on univariate testing: the mortality rate at high-volume centers was 4.6% compared to 6.1% at low-volume centers ($p=0.0046$ versus $p=0.7451$ on multivariate testing; Table 5). Those factors predictive of mortality in the multivariate analysis included age, gender, year, operative indication, Charlson score, and admission status (Table 5). When run in the model simultaneously, some have lost their significance (volume). Possible explanations for this include differences in case mix between high- and low-volume hospitals, i.e., younger patients, lower Charlson score, and less primary malignancy. These differences may in fact partially account for the lower mortality rates seen at high-volume hospitals.

In repeating the multivariate analysis across a broad range of hospital volume definitions, our post hoc exploratory analysis proved that the insignificance of volume was not based on how we categorized hospitals into high- and low-volume a priori (Table 6). This analysis was performed with multiple definitions after our a priori definition of volume was found to be not significant. As this was done after out initial analysis, it was exploratory in nature and designed to be hypothesis-generating, as opposed to an analysis upon which we could draw conclusions.

Length of Stay

The mean LOS for high-volume hospitals (12.1, range 1–267) was slightly lower than for low-volume hospitals (13.2, range 1–188).

Table 2 Rates of LR in Canada for 1995–2004

Year	1995	1998	2001	2004
Population ≥18 years	16,289,370	16,289,370	17,368,200	17,368,200
LR Cases	524	566	984	1,018
Age- and sex- adjusted rate	3.2	3.5	5.7	5.9

Values are LR cases per 100 000 aged ≥18 years (McColl et al., submitted for publication)

Table 3 Indications for Hepatic Resection over Three Time Segments

Indication for operation	Segment 1 (1995–1998)		Segment 2 (1999–2001)		Segment 3 (2002–2004)	
	n	%	N	%	*n*	%
Secondary malignancy	772	35	895	38	2,101	40
Primary malignancy	297	13	283	12	585	11
Others[a]	1,161	52	1,186	50	2,632	49

[a] Others includes liver resection for benign liver disease, primary biliary malignancy, and trauma

Canada–US Comparison

The proportion of LRs performed for secondary malignancy increased in a similar fashion in the two countries. In the US, metastases comprised 51% of all LRs in 1988 compared to 56% in 2000. Overall mortality rates were lower in Canada (5.0% compared to 7.4%). Hospital volume was not a statistically significant predictor of mortality in Canada as it was in the US.

Discussion

This study based on a comprehensive national database provides information on the recent trends of hepatic resection in Canada. From 1995 to 2004, increases in the use of LR were observed for all indications, especially those for metastatic disease or secondary malignancy. Improving mortality rates are also demonstrated along with strong patterns of regionalization.

The advantages of using large administrative databases such as CIHI to evaluate national trends in the use of procedures has been cited previously in the literature.[10] Dimick et al. commented on the failure of single-center studies to convey national temporal trends in the rates of use of procedures due to the effect of regional referral patterns. He also noted that outcome data from single-center studies, typically from high-profile institutions, may not be replicable across a broad range of hospitals.[10] We agree with the above highlighted shortcomings of regional studies and, therefore, describe true national trends of the use of LR in Canada.

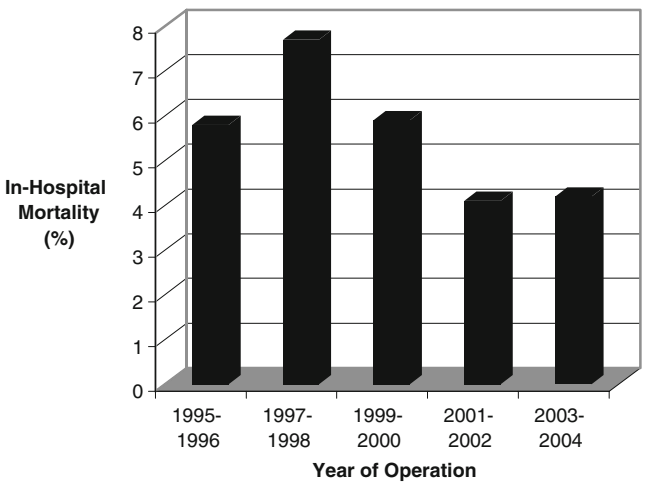

Figure 1 Operative mortality rates from 1995 to 2004.

Over the study period, the rate of LR increased by 80%. Similar increases have also been noted in the US.[10] This is likely a result of improving perioperative mortality rates, now documented to be less than 6% at high-volume centers,[1–5,8,10,26] that have made more patients candidates for LR. Reasons for improving outcomes have been attributed to an increasing use of parenchyma-sparing segmental resections, improvements in anesthetic technique, better postoperative care, and the development of hepatobiliary surgery as a defined area of surgical subspecialization.[26,27] Increasing comfort among specialists with complex hepatic procedures and improvements in the adjuvant care of patients with metastatic colorectal cancer which has resulted in many more patients benefiting from downstaging of their hepatic disease and becoming surgical candidates has probably also contributed to the observed rise in LR rates.[28,29]

Resection for metastases represented the largest proportionate increase amongst operative indications. The overwhelming data demonstrating 5-year survival in over one third of patients following LR for colorectal metastases[3,5,30–32] has likely spurred this change.

Table 4 Mortality Rate by Province

Province	Mortality rate (%)
Prince Edward Island	4.0
British Columbia	4.4
Alberta	4.8
Manitoba	4.9
Ontario	4.9
Nova Scotia	5.4
Saskatchewan	5.9
New Brunswick	6.8
Newfoundland	9.4

Province refers to the location of the performing hospital

Table 5 Multivariate Analysis of Mortality in Canada: Independent Predictors of Operative Mortality for Liver Resection

Independent variable	Odds ratio of mortality (95%CI)	*p* value
High-volume hospital[a]	1.04 (0.83–1.31)	0.7451
Time period 1[b]	1.44 (1.18–1.76)	0.0003
Age[c]	1.02 (1.01–1.02)	<0.0001
Female gender[d]	0.59 (0.48–0.71)	<0.0001
Primary malignancy[e]	2.93 (2.19–3.92)	<0.0001
Charlson score	1.04 (1.01–1.08)	0.009
Elective admission[f]	0.66 (0.55–0.79)	<0.0001

[a] High-volume (≥10 LRs per year) compared to low-volume hospital (<10 LRs per year)
[b] Time period 1 (1995–1999) compared to time period 2 (2000–2004)
[c] Odds of mortality for (X+[1 year]) compared to X
[d] Compared to male gender
[e] Compared to secondary malignancy
[f] Compared to urgent admission

A decrease in LR mortality was observed from 5.8% (1995–1996) to 4.2% (2003–2004) yielding an overall rate of 5.0%. These results are excellent for a country as a whole and are comparable to outcomes from high-profile institutions in the US and Europe that have documented mortality rates of 3.1% and 4.4%, respectively.[26,27]

Why was hospital volume not a significant predictor of LR mortality as it is in the US?[8–12] An attenuated volume–

Table 6 Sensitivity Analysis of In-Hospital Mortality for Liver Resection According to Definition of Hospital Volume

Hospital volume categories	Adjusted odds ratio (95%CI)[a]	*p* value[b]
Volume as dichotomous variable		0.1037
Low (n<40)	1.00	
High (n≥40)	1.23 (0.96–1.58)	
Volume as dichotomous variable		0.9824
Low (n<100)	1.00 (0.81–1.25)	
High (n≥100)	1.00	
Volume divided into three groups		0.2151
Low (n<50)		
Medium (n=50–99)	1.00	
High (n≥100)	0.76 (0.52–1.10)	
Volume in quartiles		0.3768
Low (n=1–3)	0.44 (0.14–1.40)	
Medium (n=4–6)		
High (n=7–20)		
Very high (n>20)	1.00	
Volume in quintiles		0.1220
Very low (n=1–2)	0.44 (0.14–1.43)	
Low (n=3–4)		
Medium (n=5–9)		
High (n=10–26)		
Very high (n>26)	1.00	
Volume in tertiles defined on a yearly basis		0.2291
Low (n=1–2)	0.80 (0.56–1.14)	
Medium (n=3–4)		
High (n>4)	1.00	
Volume in quartiles defined on a yearly basis		0.4547
Low (n=1)	0.86 (0.54–1.38)	
Medium (n=2)		
High (n=3–6)		
Very high (n>7)	1.00	
Volume as dichotomous variable defined on a yearly basis		0.7451
Low (n<10)	1.00	
High (n≥10)	1.04 (0.83–1.31)	

n number of liver resections
[a] Adjusted for same factors as for multivariate logistic regression analysis
[b] p value for multivariate logistic regression analysis that includes year of operation, patient age, gender, operative indication, admission status, and Charlson score

outcome association in Canada has been described in the literature for a variety of surgical treatments.[33] Urbach et al., in a systematic review of 142 volume–outcome articles in Canada and the US, was able to show that the odds of finding a statistically significant volume–outcome association was substantially lower in Canada (odds ratio=0.24, 95%CI=0.08–0.74, p=0.01). He argued that the different models of health care delivery and financing between the two countries might affect patterns of volume–outcome associations. In the US, where the medical profession is more entrepreneurial than elsewhere,[34] there is likely greater competition between hospitals and providers which may exacerbate variations in outcomes between hospitals.[33] Urbach et al. also pointed out the relative lack of super high-volume "centers of excellence" in Canada which likely reduces the heterogeneity between high- and low-volume hospitals.[33] A recent outcome analysis from the Memorial Sloan-Kettering Cancer Center in New York demonstrated a case volume of 1,803 patients over a 10-year period.[26]

Beyond processes of care, perhaps there exist differences in case mix between high- and low-volume Canadian hospitals that weaken the relationship between volume and outcome. It is possible that low-volume hospitals perform, in general, less complex hepatic resections when compared to high-volume centers; unfortunately, administrative data does not allow a detailed assessment of case complexity. Furthermore, it is also likely that low-volume centers selectively refer to high-volume centers patients with primary hepatic malignancy or those with a heavy comorbid disease burden. The higher LR mortality for patients with primary malignancy who have low physiologic reserve and impaired coagulation has been demonstrated previously.[8,10,12]

We have demonstrated a remarkable trend of regionalization in Canada where 84% of LRs are now performed at high-volume hospitals. Similar patterns have also been documented for esophageal, lung, and pancreatic surgery in Canada.[15,35] It has been put forth in the literature that Canada is more regionalized compared to the US due to reduced competition among providers and to single-payer funding of health care.[24] It is also likely that US data depicting superior LR outcomes at high-volume centers[8–12] has contributed to a change in referral patterns in Canada. Such regionalization is also reflective of the recent pattern of subspecialization in general surgery. In a national survey of 250 Canadian general surgeons, 65% had undergone subspecialty training. Furthermore, 93% of respondents felt that major hepatectomy was a subspecialty procedure and most did not consider themselves to be adequately trained to perform complex hepatopancreaticobiliary procedures.[36] Such discomfort with the procedure may cause low-volume general surgeons to selectively refer patients for LR.

It is useful to compare Canadian trends of LR to those in the US to contrast health care delivery between the two countries. In comparing our data to Dimick's,[10] we have shown that the mortality rate in Canada following LR is lower than that reported in the US, although our study was conducted several years later. In the US private sector, purchasers try to sign on with managed care plans that contract selectively with efficient providers.[34] It is, therefore, plausible that patients in this system are withheld certain aspects of their perioperative care in the aim to increase hospital efficiency. Indeed, postoperative care has been shown to affect outcomes following LR.[26] Access to care issues may also be reflected in this data. Canadian patients may have easier access to diagnostic services allowing for an earlier diagnosis of their disease resulting in improved postoperative outcomes.

There are several limitations to this study. First, our data does not include the province of Quebec which may raise questions regarding the external validity of the national trends conveyed in this study. Despite this, there is no evidence to suggest that Quebec care significantly differs from the rest of Canada. Our study's second limitation is that we could not assess the differences in case mix between high- and low-volume hospitals to see if this may have contributed to our finding of a weak relationship between hospital volume and outcome. There could be better outcomes at high-versus low-volume centers in Canada and that our findings can be partially explained by confounding due to differences in case mix. These differences in case mix cannot be measured using administrative data. There may be other measures that we have not studied which are useful to evaluate the advantages of procedure regionalization. Long-term survival, cancer-free survival, or health-related quality of life outcomes such as postoperative renal dysfunction may be better indicators of the quality of surgical care.[24]

Conclusion

We have shown that outcomes following hepatic resectional surgery are improving and that hospital volume may not be related to outcome as it is in the US.

Acknowledgements Dr. E. Dixon is supported through a Population Health Investigator award from the Alberta Heritage Foundation for Medical Research (AHFMR) and a New Investigator award from the Canadian Institute of Health Research. This study was funded through an Establishment Grant from the AHFMR. Dr. W.A. Ghali is funded by a Government of Canada Research Chair in Health Services Research and by a Senior Health Scholar Award from AHFMR.

References

1. Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK, Yeung C, Wong J. Hepatectomy for hepatocellular carcinoma: toward zero hospital

deaths. Ann Surg 1999;229(3):322–330. doi:10.1097/00000658-199903000-00004.
2. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 1999;230(3):309–318. (discussion 318–321). doi:10.1097/00000658-199909000-00004.
3. Gayowski TJ, Iwatsuki S, Madariaga JR, Selby R, Todo S, Irish W, Starzl T. Experience in hepatic resection for metastatic colorectal cancer: analysis of clinical and pathologic risk factors. Surgery 1994;116(4):703–710. (discussion 710–701).
4. Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P, Jaeck D. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. Cancer 1996;77(7):1254–1262. doi:10.1002/(SICI)1097-0142(19960401)77:7<1254::AID-CNCR5>3.0.CO;2-I.
5. Scheele J, Stang R, Altendorf-Hofmann A, Paul M. Resection of colorectal liver metastases. World J Surg 1995;19(1):59–71. doi:10.1007/BF00316981.
6. Jarnagin WR, Fong Y, DeMatteo RP, Gonen M, Burke EC, Bodniewicz BJ, Youssef BAM, Klimstra D, Blumgart LH. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg 2001;234(4):507–517. (discussion 517–509). doi:10.1097/00000658-200110000-00010.
7. Charny CK, Jarnagin WR, Schwartz LH, Frommeyer HS, DeMatteo RP, Fong Y, Blumgart LH. Management of 155 patients with benign liver tumours. Br J Surg 2001;88(6):808–813. doi:10.1046/j.0007-1323.2001.01771.x.
8. Dimick JB, Cowan JA Jr, Knol JA, Upchurch GR Jr. Hepatic resection in the United States: indications, outcomes, and hospital procedural volumes from a nationally representative database. Arch Surg 2003;138(2):185–191. doi:10.1001/archsurg.138.2.185.
9. Choti MA, Bowman HM, Pitt HA, Sosa JA, Sitzmann JV, Cameron JL, Gordon TA. Should hepatic resections be performed at high-volume referral centers? J Gastrointest Surg 1998;2(1):11–20. doi:10.1016/S1091-255X(98)80098-X.
10. Dimick JB, Wainess RM, Cowan JA, Upchurch GR Jr, Knol JA, Colletti LM. National trends in the use and outcomes of hepatic resection. J Am Coll Surg 2004;199(1):31–38. doi:10.1016/j.jamcollsurg.2004.03.005.
11. Begg CB, Cramer LD, Hoskins WJ, Brennan MF. Impact of hospital volume on operative mortality for major cancer surgery. JAMA 1998;280(20):1747–1751. doi:10.1001/jama.280.20.1747.
12. Glasgow RE, Showstack JA, Katz PP, Corvera CU, Warren RS, Mulvihill SJ. The relationship between hospital volume and outcomes of hepatic resection for hepatocellular carcinoma. Arch Surg 1999;134(1):30–35. doi:10.1001/archsurg.134.1.30.
13. Gordon TA, Bowman HM, Bass EB, Lillemoe KD, Yeo CJ, Heitmiller RF, Choti MA, Burleyson GP, Hsieh G, Cameron JL. Complex gastrointestinal surgery: impact of provider experience on clinical and economic outcomes. J Am Coll Surg 1999;189(1):46–56. doi:10.1016/S1072-7515(99)00072-1.
14. Shah SA, Bromberg R, Coates A, Rempel E, Simunovic M, Gallinger S. Survival after liver resection for metastatic colorectal carcinoma in a large population. J Am Coll Surg 2007;205(5):676–683. doi:10.1016/j.jamcollsurg.2007.06.283.
15. Simunovic M, Rempel E, Theriault ME, Coates A, Whelan T, Holowaty E, Langer B, Levine M. Influence of hospital characteristics on operative death and survival of patients after major cancer surgery in Ontario. Can J Surg 2006;49(4):251–258.
16. Dudley RA, Johansen KL, Brand R, Rennie DJ, Milstein A. Selective referral to high-volume hospitals: estimating potentially avoidable deaths. JAMA 2000;283(9):1159–1166. doi:10.1001/jama.283.9.1159.
17. Birkmeyer JD, Finlayson EV, Birkmeyer CM. Volume standards for high-risk surgical procedures: potential benefits of the Leapfrog initiative. Surgery 2001;130(3):415–422. doi:10.1067/msy.2001.117139.
18. Birkmeyer JD. Should we regionalize major surgery? Potential benefits and policy considerations. J Am Coll Surg 2000;190(3):341–349. doi:10.1016/S1072-7515(99)00270-7.
19. Birkmeyer JD, Siewers AE, Finlayson EV, Stukel TA, Lucas FL, Batista I, Welch HG, Wennberg DE. Hospital volume and surgical mortality in the United States. N Engl J Med 2002;346(15):1128–1137. doi:10.1056/NEJMsa012337.
20. Dimick JB, Stanley JC, Axelrod DA, Kazmers A, Henke PK, Jacobs LA, Wakefield TW, Greenfield LJ, Upchurch GR Jr. Variation in death rate after abdominal aortic aneurysmectomy in the United States: impact of hospital volume, gender, and age. Ann Surg 2002;235(4):579–585. doi:10.1097/00000658-200204000-00017.
21. Luft HS, Bunker JP, Enthoven AC. Should operations be regionalized? The empirical relation between surgical volume and mortality. N Engl J Med 1979;301(25):1364–1369.
22. Milstein A, Galvin RS, Delbanco SF, Salber P, Buck CR Jr. Improving the safety of health care: the leapfrog initiative. Eff Clin Pract 2000;3(6):313–316.
23. Birkmeyer JD, Lucas FL, Wennberg DE. Potential benefits of regionalizing major surgery in Medicare patients. Eff Clin Pract 1999;2(6):277–283.
24. Urbach DR, Bell CM, Austin PC. Differences in operative mortality between high- and low-volume hospitals in Ontario for 5 major surgical procedures: estimating the number of lives potentially saved through regionalization. CMAJ 2003;168(11):1409–1414.
25. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373–383. doi:10.1016/0021-9681(87)90171-8.
26. Jarnagin WR, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S, Corvera C, Weber S, Blumgart LH. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. Ann Surg 2002;236(4):397–406. (discussion 406–397). doi:10.1097/00000658-200210000-00001.
27. Belghiti J, Hiramatsu K, Benoist S, Massault P, Sauvanet A, Farges O. Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. J Am Coll Surg 2000;191(1):38–46. doi:10.1016/S1072-7515(00)00261-1.
28. Masi G, Cupini S, Marcucci L, Cerri E, Loupakis F, Allegrini G, Brunetti IM, Pfanner E, Viti M, Goletti O, Filipponi F, Falcone A. Treatment with 5-fluorouracil/folinic acid, oxaliplatin, and irinotecan enables surgical resection of metastases in patients with initially unresectable metastatic colorectal cancer. Ann Surg Oncol 2006;13(1):58–65. doi:10.1245/ASO.2006.03.094.
29. Adam R, Avisar E, Ariche A, Giachetti S, Azoulay D, Castaing D, Kunstlinger F, Levi F, Bismuth F. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal. Ann Surg Oncol 2001;8(4):347–353. doi:10.1007/s10434-001-0347-3.
30. Rosen CB, Nagorney DM, Taswell HF, Helgeson SL, Ilstrup DM, van Heerden JA, Adson MA. Perioperative blood transfusion and determinants of survival after liver resection for metastatic colorectal carcinoma. Ann Surg 1992;216(4):493–504. (discussion 504–495). doi:10.1097/00000658-199210000-00012.
31. Nordlinger B, Quilichini MA, Parc R, Hannoun L, Delva E, Huguet C. Hepatic resection for colorectal liver metastases. Influence on survival of preoperative factors and surgery for recurrences in 80 patients. Ann Surg 1987;205(3):256–263. doi:10.1097/00000658-198703000-00007.

32. Fong Y, Cohen AM, Fortner JG, Enker WE, Turnbull AD, Coit DG, et al. Liver resection for colorectal metastases. J Clin Oncol 1997;15(3):938–946.
33. Urbach DR, Croxford R, MacCallum NL, Stukel TA. How are volume-outcome associations related to models of health care funding and delivery? A comparison of the United States and Canada. World J Surg 2005;29(10):1230–1233. doi:10.1007/s00268-005-7994-7.
34. Brown LD. Comparing health systems in four countries: lessons for the United States. Am J Public Health 2003;93(1):52–56.
35. Simunovic M, To T, Theriault M, Langer B. Relation between hospital surgical volume and outcome for pancreatic resection for neoplasm in a publicly funded health care system. CMAJ 1999;160(5):643–648.
36. Dixon E, Vollmer CM Jr, Bathe O, Sutherland F. Training, practice, and referral patterns in hepatobiliary and pancreatic surgery: survey of general surgeons. J Gastrointest Surg 2005;9(1):109–114. doi:10.1016/j.gassur.2004.03.008.

Discussion

Recent Trends of Hepatic Resection in Canada: 1995–2004

Craig P. Fischer, M.D. (Houston, TX, USA): Ryan, thanks very much for the manuscript in advance. It is well-written and your arguments are clearly stated. Your group has examined patterns of regionalization of hepatic resection in Canada, from 1995 to 2004. You showed that rates of hepatic resection have increased, mortality rates have improved, and a larger percentage of procedures are now performed at high-volume centers.

We saw a paper earlier today on the same subject about high-volume versus low-volume surgical centers in HPB surgery, and the summary of that paper was this—the devil is in the details. Reasonable outcomes were noted at low-volume centers in this study from University of Massachusetts and are also seen in your study. But are similar operations being performed at low- and high-volume centers? Do low-volume centers do wedge resections and high-volume trisegmentectomies in sick patients? Tell us about the database you examined—what is the level of detail about comorbidities and case mix and did you analyze it?

Secondly, we need to know more about the surgeons. You mentioned a paper from Elijah Dixon and Chuck Vollmer in 2005, which was a survey of 250 Canadian surgeons—65% of the respondents were fellowship-trained. The majority of respondents in that study believed that major HPB cases should be referred to a specialty center. It seems likely, then, that surgeons who performed liver resection at low-volume centers in your study would likely be fellowship-trained. We need to know the training status of surgeons in this study, particularly at low- and high-volume hospitals. Do you think this information is important, and how might you obtain that information in a future study?

Canada and the United States have vastly different health care delivery models. I do think we need detailed information that may not be generally available in administrative data sets—prior to making public policy decisions in either country.

I enjoyed the manuscript. I enjoyed the presentation. I know you are a second-year resident. A very good job.

Ryan McColl, M.D. (Calgary, AB, Canada): Thank you, Dr. Fischer. In regards to your first question, I believe there are two ways that we could answer this. One way would be to modify the database in the future so that it would include information on the types of resections that are occurring at high- versus low-volume centers.

The second way would be to perform a survey study. There were 247 hospitals that were included in this paper. We could send a survey to each of these hospitals. I think the weakness of that approach is that we may not gain the type of detailed information on exactly what type of resections are occurring at low-volume centers, but we may gain information on other factors that have shown to be predictive of mortality including the quality of the intensive care unit at each hospital.

In regards to your second question, I think that a survey study would be an excellent methodology to use. We could gain the information that we wish in regards to the surgeons' fellowship or lack of fellowship training that they have and we could easily compare the low- and high-volume centers in that regard.

Bruce D. Schirmer, M.D. (Charlottesville, VA, USA): I thought I heard you say that only 60% of the cases were elective. How do you explain such a high nonelective emergent rate? Is that correct?

Dr. McColl: Absolutely.

Dr. Schirmer: It seems awfully high.

Dr. McColl: I do not have a very satisfactory answer for your question.

Roger G. Keith, M.D. (Saskatoon, SK, Canada): I enjoyed this paper very much, and I have one question that is related to our country. You spoke of regionalization. In our country, that is a form of practice regulation by government. You talked about regionalization based on reference patterns. From a single-payer health care system, and for clarification for our colleagues in the United States, could you talk about regulation as a means to change major hepatic resections in our country and how that might have implied a change in your outcome?

Dr. McColl: I'm not sure I understand what you are asking as far as regulation is concerned. Do you mind just clarifying?

Dr. Keith: Is there a tendency for governments in our country to control the centers that will perform resections?

Dr. McColl: To my knowledge, I am not aware of any efforts on the part of the Canadian government to regulate what types of resections are occurring at different centers.

J Gastrointest Surg (2008) 12:1847–1853
DOI 10.1007/s11605-008-0681-x

Role of Prophylactic Antibiotics in Laparoscopic Cholecystectomy: A Meta-Analysis

Abhishek Choudhary · Matthew L. Bechtold · Srinivas R. Puli · Mohamed O. Othman · Praveen K. Roy

Received: 22 May 2008 / Accepted: 20 August 2008 / Published online: 9 September 2008

Abstract
Background The role of prophylactic antibiotics in laparoscopic cholecystectomy in low-risk patients is controversial. We conducted a meta-analysis to evaluate the efficacy of prophylactic antibiotics in low-risk patients (those without cholelithiasis or cholangitis) undergoing laparoscopic cholecystectomy.
Methods Multiple databases and abstracts were searched. Randomized controlled trials (RCTs) comparing prophylactic antibiotics to placebo or no antibiotics in low-risk laparoscopic cholecystectomy were included. The effects of prophylactic antibiotics were analyzed by calculating pooled estimates of overall infections, superficial wound infections, major infections, distant infections, and length of hospital stay. Separate analyses were performed for each outcome by using odds ratio or weighted mean difference. Both random and fixed effects models were used. Publication bias was assessed by funnel plot. Heterogeneity among studies was assessed by calculating I^2 measure of inconsistency.
Results Nine RCTs (N=1,437) met the inclusion criteria. No statistically significant reduction was noted for those receiving prophylactic antibiotics and those who did not for overall infectious complications (p=0.20), superficial wound infections (p=0.36), major infections (p=0.97), distant infections (p=0.28), or length of hospital stay (p=0.77). No statistically significant publication bias or heterogeneity were noted.
Conclusions Prophylactic antibiotics do not prevent infections in low-risk patients undergoing laparoscopic cholecystectomy.

Keywords Laparoscopic cholecystectomy · Prophylactic antibiotics · Superficial infection · Meta-analysis

Scientific Meeting: Data presented at Digestive Disease Week on 19 May 2008 at San Diego, CA.

A. Choudhary · M. L. Bechtold · S. R. Puli · P. K. Roy
Division of Gastroenterology,
University of Missouri School of Medicine,
Columbia, MO, USA

M. O. Othman
University of New Mexico,
Albuquerque, NM, USA

P. K. Roy (✉)
ABQ Health Partners,
2nd Floor, Gastroenterology, 5400 Gibson Blvd SE,
Albuquerque, NM 87108, USA
e-mail: pk2949@yahoo.com

Introduction

Laparoscopic cholecystectomy has become the first-line treatment modality for symptomatic cholelithiasis over open cholecystectomy. The laparoscopic approach has an extremely low rate of postoperative infection (0.4–1.1%) in comparison to open cholecystectomy, consisting mostly of superficial site infections at the umbilical trocar site.[1–4] The infection complications of open cholecystectomy are well known and prevalent; therefore, prophylactic antibiotics are routinely indicated. However, the use of prophylactic antibiotics in laparoscopic cholecystectomy remains unclear despite its popularity. Few studies have shown that prophylactic antibiotics in laparoscopic cholecystectomy decrease the incidence of postoperative complications in laparoscopic cholecystectomy.[5–7] Other randomized controlled trials (RCTs) have demonstrated no obvious role of prophylactic antibiotics in laparoscopic cholecystectomy.[8–16] However, these RCTs

were small or terminated early due to paucity of major infections.[8–16] Due to the small sample sizes of the RCTs, an adequate power to detect a difference for antibiotic use for the rare event of infections may not have been achieved. We conducted a meta-analysis of randomized controlled trials to evaluate the role of prophylactic antibiotics in laparoscopic cholecystectomy.

Materials and Methods

Study Selection Articles and abstracts that evaluated the use of antibiotic administration for the prevention of infection in laparoscopic cholecystectomy were searched. All articles were searched irrespective of language, publication status (articles or abstracts), or results. A search was conducted in MEDLINE, EMBASE, Cochran Central Register of Controlled Trials, and Pubmed (1966–October 2007). The search terms used were prophylactic administration of antibiotics and laparoscopic cholecystectomy. Additionally, references lists of retrieved articles, reviews, and meta-analyses were scanned for potential articles. Lastly, a manual search of abstracts submitted to the Digestive Disease Week, American College of Gastroenterology, and United European Gastroenterology Week (2000–2007) was performed. Inclusion criteria were randomized controlled trials that used prophylactic antibiotic(s) versus no antibiotics or placebo for laparoscopic cholecystectomy with overall infection as an end point. Exclusion criteria consisted of studies that were uncontrolled, not involving overall infection as an end point, or comparing two different antibiotics rather than placebo or control.

Data Extraction Data extraction was independently performed by two authors (Choudhary and Bechtold) and reviewed by a third for agreement. Disagreements were discussed by all three and resolved by consensus. The two authors (AC and MLB) extracted data from each study using a common data extraction form. Details of study design (randomization/blinding), number of subjects and dropouts, as well as type, dose, and schedule of antibiotic administration were recorded. Outcomes of overall, superficial, and distant infections as well as length of hospital stay were recorded. All studies were assigned a quality score on the based upon the Jadad scale, with 5 representing a high-quality study and 0 representing a poor quality.[17]

Data Analysis The effects of prophylactic antibiotics on laparoscopic cholecystectomy were analyzed by calculating pooled estimates of total, superficial, and distant infections. Separate analyses were performed for each outcome using odds ratio (OR) or weighted mean difference (WMD). Both fixed and random effects models were used. A statistically significant result was indicated by a p value <0.05 or 95% confidence interval (CI) not including 1. If statistical significance was detected, the number needed-to-treat was calculated. RevMan 4.2 software was utilized for statistical analysis of the data. Publication bias was assessed by funnel plot. Heterogeneity among studies was assessed by calculating I^2 measure of inconsistency.[18,19]

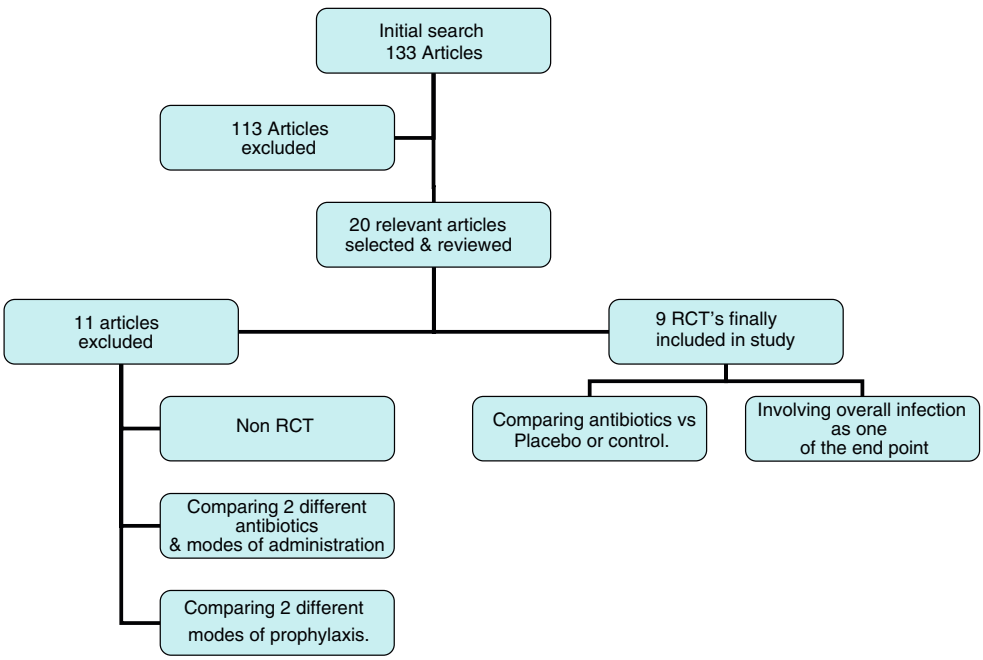

Figure 1 Article identification and selection algorithm.

Table 1 Description of Studies Included in the Meta-Analysis, Including Jadad Scores

Author	Year	Location	Centers	Type of study	Jadad score
Chang et al.	2006	Taiwan	Single	Single-blinded	4
Higgins et al.	1999	United States	Single	Double-blinded	5
Illig et al.	1997	United States	Single	RCT	2
Tocchi et al.	2000	United States	Single	Single-blinded	4
Koc et al.	2003	Turkey	Single	Double-blinded	3
Kuthe et al.	2006	India	Single	Single-blinded	4
Mahatharadol et al.	2001	Thailand	Single	RCT	3
Dobay et al.	1999	USA	Single	Double-blinded	4
Harling et al.	2000	UK	Single	RCT	3

Results

The initial search identified 133 articles using the search terms "laparoscopic cholecystectomy" and "antibiotics". Of these, 20 relevant articles were selected and reviewed by two independent authors (AC and MLB). One hundred thirteen studies did not meet the inclusion criteria and were excluded, including case reports, case series, reviews, and retrospective studies. Subsequently, 11 additional studies did not meet the inclusion criteria and were excluded, including non-randomized prospective studies[6,20] and RCTs using two different antibiotics[21] or comparing two modes and doses of antibiotics.[22,23] Nine RCTs (N=1,437), published as full-length publications in journals, met the inclusion criteria and were selected for final review and analysis (Fig. 1). Of the included nine RCTs, three trials were double-blinded. Table 1 shows the details and Jadad scores for the selected studies (5 = excellent quality, 0 = poor quality). The studies were of adequate quality (Jadad scores of 2 or more). All RCTs were published from 1997 to 2006. Trials were done worldwide, including four trials performed in the USA, three trials in Asia, and two trials in Europe. All trials were single-center studies. No significant heterogeneity was present among the studies for any of the outcomes.

Different antibiotics were evaluated in the selected trials. Three RCTs used cefazolin, two used cefotaxime and cefuroxime, one used cefotetan, and one used cefotetan and cefazolin. Antibiotics were administered preoperatively in all studies. Three RCTs used multiple doses with the first dose preoperatively and other doses postoperatively. Publication bias was evaluated by funnel plot with no significant publication bias identified (Fig. 2).

Overall Infectious Complications Nine trials provided information about overall infectious complications.[8–16]

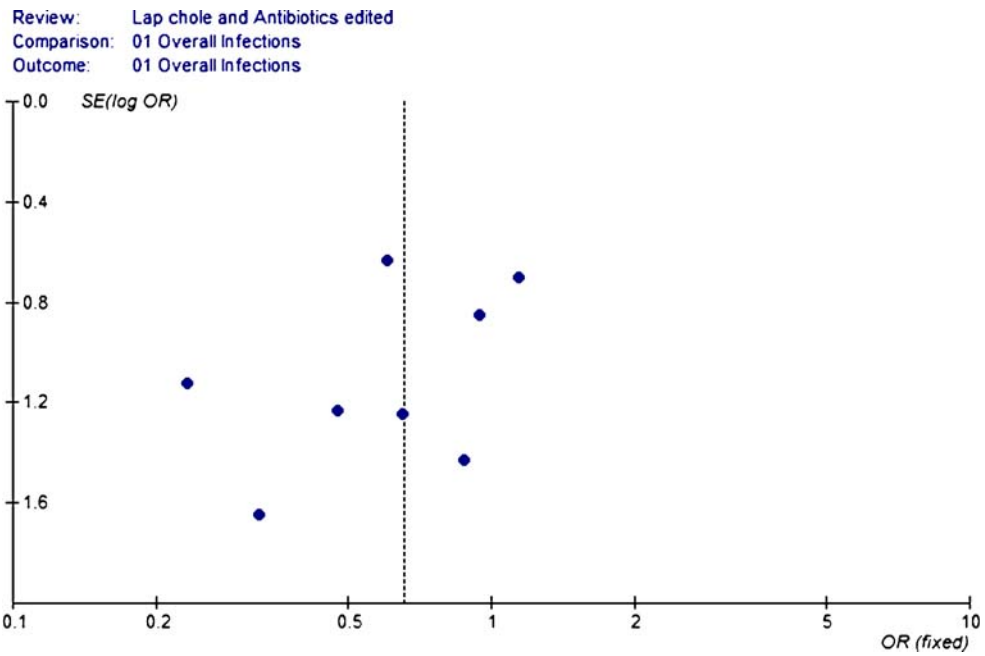

Figure 2 Funnel plot for overall infections suggesting no publication bias by showing multiple studies on both sides of the *dotted line* in an approximately equal distribution.

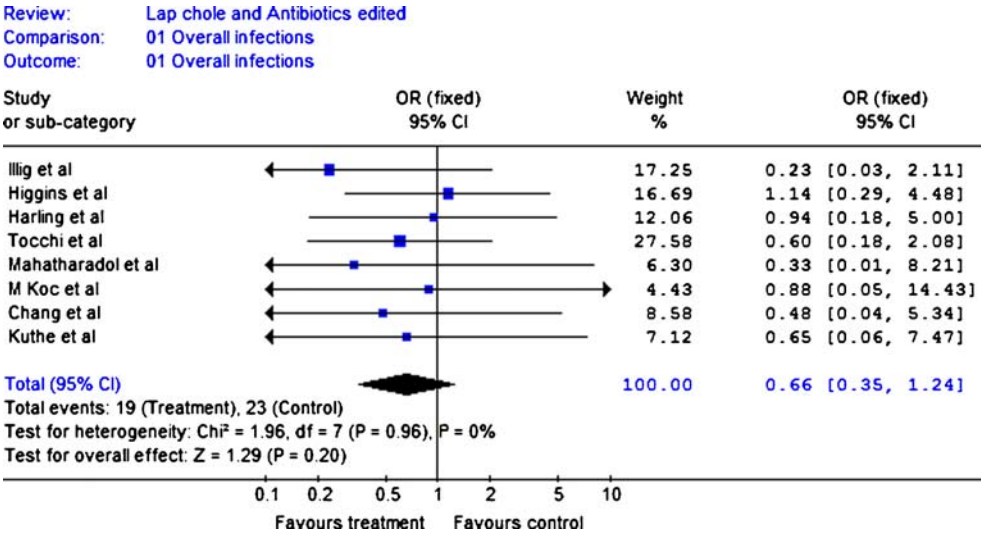

Figure 3 Forrest plot demonstrating overall infectious complications with prophylactic antibiotic(s) compared to no antibiotic(s) or placebo for laparoscopic cholecystectomy.

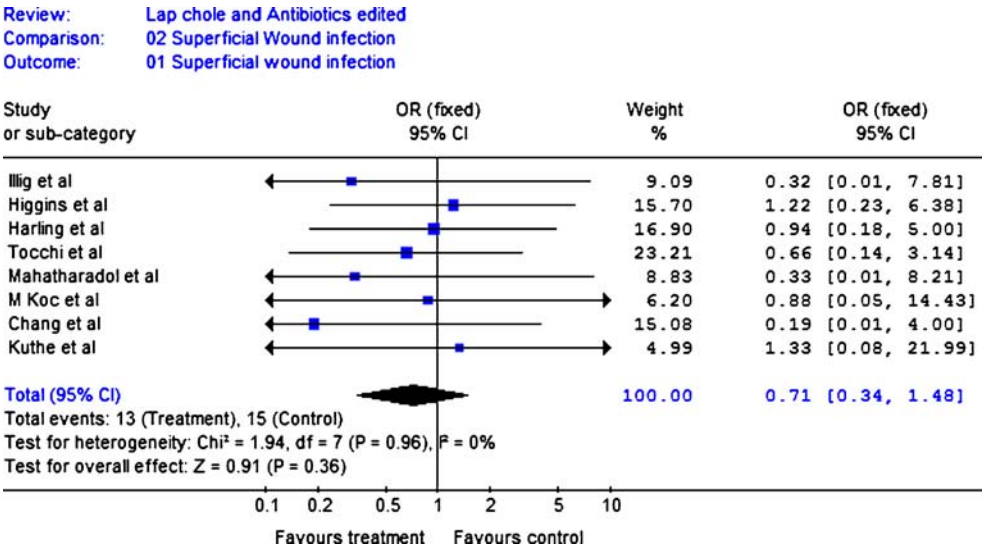

Figure 4 Forrest plot demonstrating superficial infection with prophylactic antibiotic(s) compared to no antibiotic(s) or placebo for laparoscopic cholecystectomy.

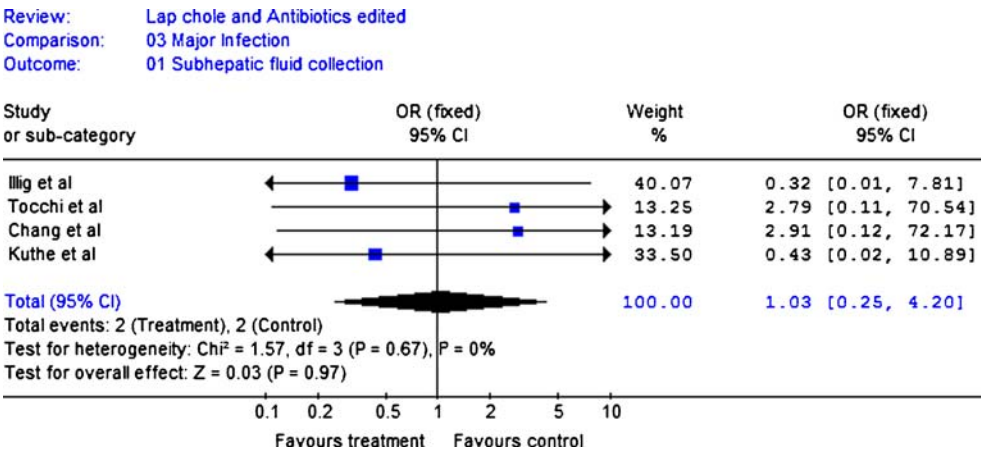

Figure 5 Forrest plot demonstrating major infection with prophylactic antibiotic(s) compared to no antibiotic(s) or placebo for laparoscopic cholecystectomy.

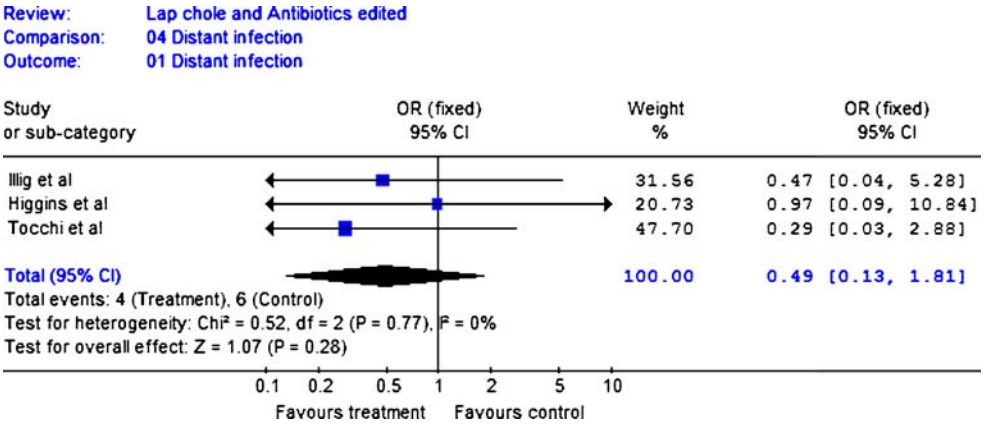

Figure 6 Forrest plot demonstrating distant infection with prophylactic antibiotic(s) compared to no antibiotic(s) or placebo for laparoscopic cholecystectomy.

The study by Dobay et al.[13] demonstrated no infections for either the group, resulting in the inability to analyze the data. Therefore, the Dobay et al. study is not included in the Forrest plot. Overall infectious complications were documented in 19 of 797 patients (2.4%) treated with prophylactic antibiotics prior to laparoscopic cholecystectomy versus 23 of 640 patients (3.6%) not treated with prophylactic antibiotics. Pooled analysis revealed no statistically significant odds reduction with prophylactic antibiotics prior to laparoscopic cholecystectomy for overall infectious complications (OR 0.66; 95% CI 0.35–1.24; p=0.20; Fig. 3). There was no significant heterogeneity among the studies (I^2=0%, p=0.96). Further subgroup analyses were performed according to types of infection.

Superficial Wound Infections Eight trials provided information regarding superficial infections.[8–12,14–16] Superficial wound infections were present in 13 of 797 patients (1.6%) who received prophylactic antibiotics prior to laparoscopic cholecystectomy and 15 of 640 patients (2.3%) who did not receive prophylactic antibiotics. Pooled analysis showed no statistically significant odds reduction with prophylactic antibiotics prior to laparoscopic cholecystectomy for superficial wound infections (OR 0.71; 95% CI 0.34–1.48; p=0.36; Fig. 4). Heterogeneity was not statistically significant (I^2=0%, p=0.96).

Major Infections Only four trials offered information regarding major infections.[10,11,15,16] Major infections, in the form of intraabdominal collections or abscesses, were present in two of 630 patients (0.3%) who received prophylactic antibiotics prior to laparoscopic cholecystectomy versus two of 486 patients (0.4%) who received no prophylactic antibiotics. Pooled analysis demonstrated no statistically significant odds reduction with prophylactic antibiotics prior to laparoscopic cholecystectomy for major infections (OR 1.03; 95% CI 0.25–4.20; p=0.97; Fig. 5). Heterogeneity was not statistically significant (I^2=0%, p=0.67).

Distant Infections Only three trials provided information regarding distant infections.[9–11] Distant infections were defined as any infection away from the wound, including urinary tract or respiratory tract infections. Distant infections were present in four of 499 patients (0.8%) who received prophylactic antibiotics prior to laparoscopic cholecystectomy versus six of 297 patients (2.0%) who received no prophylactic antibiotics. Pooled analysis showed no statistically significant odds reduction with prophylactic antibiotics prior to laparoscopic cholecystectomy for distant infections (OR 0.49; 95% CI 0.13–1.81; p=0.28; Fig. 6), with no heterogeneity identified (I^2=0%, p=0.77).

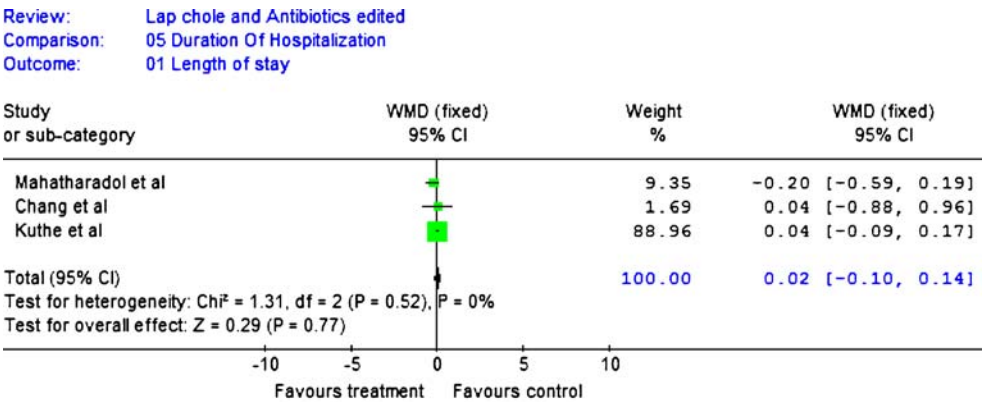

Figure 7 Forrest plot demonstrating hospital stay with prophylactic antibiotic(s) compared to no antibiotic(s) or placebo for laparoscopic cholecystectomy.

Hospital Stay Only three trials offered evaluation regarding hospital stay.[12,15,16] Prophylactic antibiotics prior to laparoscopic cholecystectomy did not lead to shorter hospital stays (WMD 0.02; 95% CI −0.10–0.14; $p=0.77$), with no heterogeneity identified ($I^2=0\%$, $p=0.52$; Fig. 7).

Discussion

Despite controversy surrounding the use of prophylactic antibiotics in laparoscopic cholecystectomy, 79% of patients undergoing laparoscopic cholecystectomy have received prophylactic antibiotics preoperatively and 63% received antibiotics postoperatively.[3] Many studies have evaluated this issue further with controversial results.

A prospective non-randomized trial by Frantzides and Sykes[20] found no beneficial effect of prophylactic cefotetan over chlorhexidine gluconate scrub alone. Chang et al.[15] demonstrated that no prophylactic antibiotics (cefotetan) are necessary after wound closure in an effort to decrease incidence of superficial wound infections in elective laparoscopic cholecystectomies. Furthermore, Kuthe et al.[16] also demonstrated a similar result with cefuroxime.

Tocchi et al.[11] concluded that antibiotics prophylaxis should be given only in those patients with episodes of colic within 30 days of surgery or diabetes. Koc et al.[14] concluded no role of prophylactic antibiotics in laparoscopic cholecystectomy in 92 patients. Higgins et al.[9] also concluded that prophylactic cefotetan and cefazolin have no beneficial effects in laparoscopic cholecystectomy. Furthermore, if no antibiotics were used, savings of ~$30,000 were calculated at the investigator's institute (USA).[9]

In our meta-analysis, prophylactic antibiotics prior to laparoscopic cholecystectomy resulted in no statistically significant benefit for total infections, superficial infections, major infections, distant infections, and reduction of hospital stay.

The strengths of this meta-analysis include use of only randomized controlled trials, varying populations (Europe, USA, Asia), and similar outcomes in all studies even though various antibiotics were utilized. Also, no heterogeneity was noted for any of the major outcomes and no publication bias was noted. Limitations of this meta-analysis include uncertainty about the use of prophylactic antibiotics in high-risk patients undergoing laparoscopic cholecystectomy, which is controversial at this time. High-risk patients have been defined by some investigators as age >60 years or the presence of diabetes mellitus, acute colic within 30 days before laparoscopic cholecystectomy, jaundice, acute cholecystitis, or cholangitis. Tocchi et al.[11] and Koc et al.[14] found that the presence of diabetes mellitus, episodes of biliary colic in preceding 30 days of surgery, and age >60 years were independent risk factors for the development of infectious complications; however, Kuthe et al.[16] and Chang et al.[15] failed to show similar results. Despite the controversy, none of the RCTs provided separate data about the effect of prophylactic antibiotics in laparoscopic cholecystectomy in this particular subgroup of high-risk patients for comparison. In addition, all trials excluded those patients with choledocholithiasis and cholangitis and all trials, except one[15], excluded patients with acute cholecystitis. Therefore, since this high-risk population was not evaluated in the RCTs, this population cannot be fully evaluated in this meta-analysis.

In conclusion, the current meta-analysis of RCTs on the use of prophylactic antibiotics in laparoscopic cholecystectomy reveals no beneficial effects in low-risk individuals. Future multicenter RCTs with adequate statistical power and involving a higher number of patients with subgroups, particularly those at high-risk for infections, are needed to complete the evaluation of prophylactic antibiotics prior to laparoscopic cholecystectomy for high-risk patients.

Acknowledgments No additional acknowledgments. No grant support or external funding were utilized.

References

1. Shea JA, Berlin JA, Bachwich DR, Staroscik RN, Malet PF, McGuckin M, Schwartz JS, Escarce JJ. Indications for and outcomes of cholecystectomy: a comparison of the pre and post laparoscopic eras. Ann Surg 1998;227:343–350.
2. Chuang SC, Lee KT, Chang WT, Wang SN, Kuo KK, Chen JS, Sheen PC. Risk factors for wound infection after cholecystectomy. J Formos Med Assoc 2004;103:607–612.
3. McGuckin M, Shea JA, Schwartz JS. Infection and antimicrobial use in laparoscopic cholecystectomy. Infect Control Hosp Epidemiol 1999;20:624–626.
4. The Southern Surgeon's club. A prospective analysis of 1518 laparoscopic cholecystectomies. N Engl J Med 1991;324:1073–1078.
5. Shindholimath VV, Seenu V, Parshad R, Chaudhry R, Kumar A. Factors influencing wound infection following laparoscopic cholecystectomy. Trop Gastroenterol 2003;24:90–92.
6. Uchiyama K, Kawai M, Onishi H, Tasni M, Kinoshita H, Ueno M, Yamaue H. Preoperative antimicrobial administration for prevention of postoperative infection in patients with laparoscopic cholecystectomy. Dig Dis Sci 2003;48:1955–1959.
7. Al-Abassi AA, Farghaly MM, Ahmed HL, Mobasher LL, Al-Manee MS. Infection after laparoscopic cholecystectomy: effect of infected bile and infected gallbladder wall. Eur J Surg 2001;167:268–273.
8. Harling R, Moorjani N, Perry C, MacGowan AP, Thompson MH. A prospective, randomized trial of prophylactic antibiotics versus bag extraction in the prophylaxis of wound infection in laparoscopic cholecystectomy. Ann R Coll Surg Engl 2000;82:408–410.
9. Higgins A, London J, Charland S, Ratzer E, Clark J, Haun W, Maher DP. Prophylactic antibiotics for elective laparoscopic cholecystectomy: are they necessary? Arch Surg 1999;134:611–613.

10. Illig KA, Schmidt E, Cavanaugh J, Krusch D, Sax HC. Are prophylactic antibiotics required for elective laparoscopic cholecystectomy? J Am Coll Surg 1997;184:353–356.
11. Tocchi A, Lepre L, Costa G, Liotta G, Mazzoni G, Maggiolini F. The need for antibiotic prophylaxis in elective laparoscopic cholecystectomy: a prospective randomized study. Arch Surg 2000;135:67–70.
12. Mahatharadol V. A reevaluation of antibiotic prophylaxis in laparoscopic cholecystectomy: a randomized controlled trial. J Med Assoc Thai 2001;84:105–108.
13. Dobay KJ, Freier DT, Albear P. The absent role of prophylactic antibiotics in low-risk patients undergoing laparoscopic cholecystectomy. Am Surg 1999;65:226–228.
14. Koc M, Zulfikaroglu B, Kece C, Ozalp N. A prospective randomized study of prophylactic antibiotics in elective laparoscopic cholecystectomy. Surg Endosc 2003;17:1716–1718.
15. Chang WT, Lee KT, Chuang SC, Wang SN, Kuo KK, Chen JS, Sheen PC. The impact of prophylactic antibiotics on postoperative infection complication in elective laparoscopic cholecystectomy: a prospective randomized study. Am J Surg 2006;191:721–725.
16. Kuthe SA, Kaman L, Verma GR, Singh R. Evaluation of the role of prophylactic antibiotics in elective laparoscopic cholecystectomy: a prospective randomized trial. Trop Gastroenterol 2006;27:54–57.
17. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12.
18. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–1558.
19. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Br Med J 2003;327:557–560.
20. Frantzides CT, Sykes A. A reevaluation of antibiotic prophylaxis in laparoscopic cholecystectomy. J Laparoendosc Surg 1994;4:375–378.
21. Orozco H, Sifuentes-Osorio J, Chan C, Medina-Franco H, Vargas- Vorackova F, Prado E, Arch J. Comparison of ceftibuten vs. amoxicillin/clavulanic acid as antibiotic prophylaxis in cholecystectomy and/or biliary tract surgery. J Gastrointest Surg 2000;4:606–610.
22. Pourriat JL, The French Multicentric Group. Antibiotic prophylaxis of laparoscopic cholecystectomies with 1 versus 2 grams of cefotetan. Rec Adv Chemother 1995;19:554–556.
23. Zurbuchen U, Ritz JP, Lehmann KS, Groene J, Heidari M, Buhr HJ, Germer CT. Oral vs intravenous antibiotic prophylaxis in elective laparoscopic cholecystectomy-an exploratory trial. Langenbecks Arch Surg 2008;393(4):479–85. (Jul).

Discussion

John B. Marshall, M.D. (Columbia, MO): This is a practical paper that has the potential to change practice habits. A majority of surgeons presently give prophylactic antibiotics before laparoscopic cholecystectomy. While randomized controlled trials have not shown a benefit, a number of the trials have been underpowered and not included enough subjects to exclude a benefit. Meta-analysis is a statistical technique that permits the results of different studies to be combined. The results of this well-conducted meta-analysis found no benefit from prophylactic antibiotics given before laparoscopic cholecystectomy. This is an important finding given the cost implications and various other potential deleterious effects of prescribing unwarranted antibiotics. Most of the trials in this study excluded so-called high-risk patients, though the various studies tended to define high risk in various ways. Additional investigation is needed in the high-risk subset. However, the verdict seems clear in most patients undergoing laparoscopic cholecystectomy, prophylactic antibiotics are not needed.

J Gastrointest Surg (2008) 12:1854–1865
DOI 10.1007/s11605-008-0666-9

Mechanisms of Ileal Adaptation for Glucose Absorption after Proximal-Based Small Bowel Resection

C. W. Iqbal · H. G. Qandeel · Y. Zheng · J. A. Duenes · M. G. Sarr

Received: 16 May 2008 / Accepted: 8 August 2008 / Published online: 3 September 2008

Abstract
Introduction The hexose transmembrane transporters SGLT1 and GLUT2 are present in low quantities in ileum where little glucose absorption occurs normally; however, glucose uptake in ileum is highly adaptable after small bowel resection.
Hypothesis Ileal adaptability for glucose absorption after jejunal resection is mediated predominately by upregulation of GLUT2.
Methods Rats underwent 70% proximal-based jejunoileal resection. Transporter-mediated glucose uptake was measured in proximal and distal remnant ileum 1 and 4 wk postoperatively (n=6 rats, each) and in corresponding ileal segments in control and 1 wk sham laparotomy rats (n=6, each) without and with selective inhibitors of SGLT1 and GLUT2. In separate groups of rats (n=6, each), protein (Western blots), mRNA (reverse transcriptase polymerase chain reaction [RT-PCR]), and villus height (histomorphology) were measured.
Results After 70% proximal intestinal resection, there was no dramatic change in protein or mRNA expression per cell of either SGLT1 or GLUT2, but median glucose uptake (nmol/cm/min) increased markedly from 52 (range 28–63) in controls to 118 (range 80–171) at 1 wk, and 203 (range 93–248) at 4 wk ($p \leq 0.04$ each) correlating with change in villus height ($p \leq 0.03$).
Conclusions Ileal adaptation for glucose transport occurs through cellular proliferation (hyperplasia) and not through cellular upregulation of glucose transporters.

Keywords Absorption · Hexose transporters · Physiology · Adaptation · Intestinal resection

C. W. Iqbal and H. G. Qandeel have contributed sufficiently to warrant co-first authors.

Presented in part at the Society for Surgery of the Alimentary Tract 49th Annual Meeting, May 17–22, 2008, San Diego, CA and published in abstract form in *Gastroenterology*
Research supported by NIH grant DK39337 (MGS)

C. W. Iqbal · H. G. Qandeel · Y. Zheng · J. A. Duenes · M. G. Sarr
Gastrointestinal Research Unit and Department of Surgery,
Mayo Clinic,
Rochester, MN, USA

M. G. Sarr (✉)
J. C. Mason Professor of Surgery, Mayo Clinic,
200 1st Street SW,
Rochester, MN 55905, USA
e-mail: Sarr.michael@mayo.edu

Introduction

Short bowel syndrome is a devastating clinical problem that usually results from operative resection of diseased intestine resulting in an inadequate length of residual bowel.[1] The treatment options for these patients are limited, and outcomes with these therapies are often poor.[2–4] The ability of the ileum to adapt after massive small bowel resection has created interest in studying the cellular mechanisms responsible for ileal adaptation to uncover novel therapies for short bowel patients.[5–11] Additionally, current models of ileal adaptation have suggested a cellular upregulation of membrane expression of intestinal hexose transporters, which makes models of ileal adaptation particularly interesting in understanding cellular mechanisms responsible for the regulation of intestinal hexose transporters.[12–13]

The primary glucose transporter in the small intestine has been thought traditionally to be SGLT1, an active

sodium-glucose co-transporter.[14–17] With normal intestinal continuity, SGLT1 is expressed and functions at a very low level in the ileum where the presence of luminal glucose is also very low.[18] Glucose absorption in the ileum increases after massive small bowel resection when luminal glucose loads to the distal gut are increased.[9,12–13,19] It has been reported that the ileum adapts by increasing surface area through increased villus height and crypt depth, but most investigators believe that this adaptation is also due, in part, to upregulation of the primary intestinal glucose transporter SGLT1. Data from our laboratory and others suggested that GLUT2, a facilitated glucose transporter typically localized to the basolateral membrane, may also have a substantive role in *apical* glucose transport in the jejunum.[20–24] Whether or not upregulation of apical GLUT2 plays a role in ileal adaptation is not known, and if so, to what extent. We hypothesized that after a massive, proximal-based small bowel resection, the ileum would adapt not only by hyperplasia but also by upregulating both the gene and protein expression and function of both SGLT1 and apical GLUT2 within the enterocyte.

Design

Rats underwent a 70%, proximal-based small bowel resection (see below). These rats were then survived and studied at 1 or 4 wk (n=12, each group). An additional group of 12 rats were studied 1 wk after sham celiotomy to control for anesthesia and other postoperative changes; a group of 12 naïve control rats (NC) were studied as a negative control. All rats were housed in a 12-h light–dark cycle (6 A.M. lights on; 6 P.M. lights off) and were allowed free access to standard rat chow (5001 Rodent Diet, PMI Nutrition International LLC, Brentwood, MO) and water.

Twelve rats were designated for study in each group at each time point; six rats were used for mRNA and protein analysis of SGLT1 and GLUT2, while the remaining six rats per groups were used to measure villus height and transporter-mediated glucose uptake without and with the SGLT1 inhibitor, phlorizin, and with the GLUT2 inhibitor, phloretin.

Small Intestinal Resection

After approval from the Mayo Clinic Institutional Animal Care and Use Committee, male Lewis rats (250–300 g) were anesthetized using inhaled 2% isoflurane induction followed by intraperitoneal injection of sodium thiopental (50 mg/kg). A short-celiotomy (1 cm) was performed, and the small bowel was extra-corporealized. The proximal 70% of the small intestine starting from the ligament of Treitz was resected after ligating the mesenteric blood supply leaving about 14 cm of distal ileum. An end-to-end, single-layer anastomosis was then performed using running 7–0 polypropylene sutures. The intestine was then returned into the peritoneal cavity, and the abdominal wall was closed in two layers with running 5–0 polyglactin suture. Sham celiotomy was performed under similar anesthesia using a short celiotomy with extra-corporealization of the entire small bowel. The intestine was manipulated manually for 5 min prior to reduction back into the abdomen. Abdominal closure was performed as above. Postoperatively, all animals were maintained on water containing acetaminophen for 48 h prior to having free access to chow.

Tissue Harvest

At the time of tissue harvest, rats were anesthetized with inhaled 2% isoflurane followed by intraperitoneal injection of sodium thiopental (50 mg/kg). All tissue was harvested at 9 A.M. due to known diurnal patterns in expression and function of hexose transporters.[15,18,25–26] The duodenum was cannulated just distal to the pylorus and was flushed with cold (4°C) mammalian Ringers solution (in millimolar [mM]: 128 NaCl, 4.7 KCl, 2.5 $CaCl_2$, 1.2 KH_2PO_4, 1.2 $MgSO_4$, 20 $NaHCO_3$; pH 7.3–7.4; 290 mOsm). The remnant ileum was excised. In NC and shams, the distal 14 cm of ileum was harvested, which corresponded to the same length of ileum left in the resection animals. For each group, six rats were designated randomly for mRNA and protein analysis. In these animals, the remnant ileum was opened, and in ice-cold, phosphate-buffered saline (PBS), the mucosa was scraped with a glass slide. The samples for mRNA analysis were placed in RNA stabilization buffer (RNALater, Qiagen, Valencia, CA), snap frozen in liquid nitrogen, and then stored at −80°C. The samples for protein analysis were collected separately from both the proximal and distal portions of the remnant ileum, placed in cold RIPA containing protease inhibitors Halt (Pierce, Rockford, IL) and PMSF, snap frozen in liquid nitrogen, and stored at −80°C for later batch analysis. The other six rats in each group were designated randomly for measurements of glucose uptake using our modification of the everted sleeve technique and histologic analysis.[18,27] These animals were anesthetized in a similar fashion followed by flushing of the entire small bowel with 4°C mammalian Ringers solution. The proximal and distal portions of the remnant ileum after resection and the corresponding ileal region in the NC and sham animals were placed in 4°C mammalian Ringers solution oxygenated with 95% O_2–5% CO_2 until study. In addition, 0.5 cm of proximal and distal portions of ileal segments were pinned on a support and fixed in 10% buffered formalin for histomorphometry.

mRNA Measurement

Reverse transcription real-time polymerase chain reaction (PCR) was used to quantitate mRNA levels for SGLT1 and GLUT2.[18,26] The mucosal samples stored in RNA stabilization buffer were thawed on ice and homogenized. Samples from the proximal remnant and the distal remnant were studied as distinct groups. RNA was isolated using the RNeasy Midi kit (Qiagen, Valencia, CA). RNA was then reverse-transcribed into complementary DNA (cDNA) using the Super Script III kit (Invitrogen, Carlsbad, CA). The resultant cDNA was stored at −20°C. cDNA levels of SGLT1, GLUT2, and the stably expressed housekeeping gene, glyceraldehyde-6-phosphate dehydrogenase (GAPDH) was determined using real-time PCR. PCR was performed in a 7500 thermocycler (Applied Biosystems, San Francisco, CA) using Taqman® chemistries with primers and fluorescently labeled probes in assay mixes purchased from Applied Biosystems. Standard curves from serial dilutions of known copy numbers were used to calculate the number of copies of cDNA for each sample. 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° and 1 min at 60°C after which fluorescence measurements were made. Transporter copy numbers were normalized to copy numbers of GAPDH from each sample.

Protein Measurement

Western blotting was used to measure semi-quantitatively the protein levels of SGLT1 and GLUT2.[26] Tissue samples stored in RIPA buffer containing protease inhibitors were thawed on ice and placed in RIPA lysis buffer containing protease inhibitors to prevent protein degradation.[18] Samples from the proximal remnant ileum were studied separately from the distal samples. Samples were homogenized using a Kontes Pellet Pestle (Fischer Scientific, Pittsburg, PA). The protein-containing supernatant was then separated by centrifugation at 5000×*g* for 15 min. Protein concentrations were measured by the bicinchoninic acid method (Pierce, Rockford, IL); 200 µg of protein was resolved on a 10% SDS-PAGE gel (Bio-Rad, Hercules, CA) and transferred electrically to a PVDF membrane (Millipore, Bedford, MA). Membranes were blocked using 5% milk in tris-buffered saline with Tween (TBS-T). To quantitate protein and GAPDH in the same sample, the membranes were cut between GAPDH and the specific proteins of interest. GAPDH was used as a stably expressed "housekeeping" protein against which SGLT1 and GLUT2 were compared (see below, Data Analysis). Cut membranes were then incubated overnight at 4°C with primary antibody SGLT1 (from Abcam, Cambridge, MA) and GLUT2 antibody from Chemicon International, Temecula, CA; GAPDH antibody from US Biological, Swampscott, MA). After incubation with primary antibody, membranes were rinsed three times with TBS-T and incubated with a secondary antibody in TBS-T containing 5% milk. Horseradish peroxidase-conjugated, goat anti-rabbit IgG was used for SGLT1 and GLUT2, (Sigma, St. Louis, MO and Upstate, Lake Placid, NY, respectfully) and horseradish peroxidase-conjugated, goat anti-mouse IgG was used for GAPDH (Sigma, St. Louis, MO). Protein bands were visualized with a colorimetric reaction using Opti-4CN Substrate kits (Bio-Rad). Amplified Opti-4CN substrate kit was used to enhance SGLT1 and GLUT2 bands. Membranes were scanned, and Scion Image (Scion Corp, MA) was used for semi-quantitative measurements of protein levels based on band densitometry. All transporter protein measurements were normalized to those of GAPDH in an attempt to estimate the amount of protein per enterocyte.

Transporter-mediated Glucose Uptake

We measured transporter-mediated glucose absorption using a previously described modified, everted sleeve technique.[18,27] After tissue harvest, the targeted segment of intestine was everted so that the mucosal surface was exposed externally. Intestinal segments were then mounted on steel rods (diameter 4 mm) and secured with two 5–0 silk ties. The redundant edges of the tissue were excised leaving a 1-cm everted segment. Due to intestinal dilation in the resection groups, larger caliber steel rods were necessary—5 mm diameter in the 1-wk group and 6 mm diameter in the 4-wk group. Sleeves were kept in chilled (4°C) mammalian Ringers solution bubbled with 95% O_2/5% CO_2 until ready for absorption experiments. Prior to measurements of absorption, tissues were transferred to a 38°C bath, preincubated in 8 ml of mammalian Ringers solution bubbled with 95% O_2–5% CO_2 for 5 min, and then placed in 8 ml of 38°C mammalian Ringers solution with iso-osmotic replacement of NaCl using 20 mM D-glucose. The solution was stirred at 1,200 rpm to mix the "unstirred layer." Radiolabeled glucose probes (1 µCi of ^{14}C-D-glucose and 2 µCi of ^{3}H-L-glucose) were included in the test solution to measure the different pathways of glucose absorption. After 1 min incubation in the glucose solution, the tissues were removed, rinsed quickly in 30 ml of chilled mammalian Ringers solution stirred at 1,200 rpm for 20 s, and placed in glass scintillation vials. One milliliter of tissue solubilizer (Perkin-Elmer, Boston, MA) was added to the vials containing the tissue segments and kept in a 50°C water bath for 3 h. After complete solubilization, 15 ml of scintillation counting cocktail (Opti-Fluor, Perkin-Elmer, Shelton, CT) was added, and probe counts were determined

using techniques of dual-marker liquid scintillation counting with a standard quench curve. When quench values were too high for the resection samples due to ileal hypertrophy, solubilized samples were separated into two or three aliquots to bring the counts into the window of validated quench and counted separately with an additional 15 ml of counting cocktail in each aliquot. The counts were then totaled, and a single uptake calculation was performed for each sample.

Phlorizin was used to inhibit SGLT1 activity at a dosage (0.2 mM) used previously.[24,28–31] The phlorizin was solubilized in ethanol, and 100 µl was then added to the 8-ml incubation bath to achieve a concentration of 0.2 mM. Phloretin was used to inhibit GLUT2 activity at a dosage (1 mM) used previously[24,32–33] and was also solubilized in ethanol and added to the incubation bath in 100-µl aliquots to achieve a concentration of 1 mM. Vehicle experiments using 100 µl of ethanol in the glucose test solution had been conducted previously and shown to cause no effect on transporter-mediated glucose uptake.[24] Three separate, 1-cm sleeves were obtained from the proximal remnant ileum for study either without inhibitors, with phlorizin, or with phloretin in the 20 mM glucose test solution. Three additional sleeves were obtained from the distal remnant ileum and studied similarly.

Villus Height, Intestinal Diameter, and Intestinal Length

The formalin-fixed tissues from all groups were embedded in paraffin and sectioned along the villus axis. A total of 18 sections were taken from each tissue sample, and hematoxylin and eosin staining was performed with three sections per each slide. Maximum villus height was measured from above the crypt to the tip of the villus at ×10 magnification using an optical reticule with a micrometer. All 18 sections were reviewed per each segment with at least three measurements of villus height per slide such that at least 54 measurements were made for each segment (proximal and distal) per rat. At the time of tissue harvest, the diameter of the ileum was evaluated subjectively, and the length of the remnant ileum in the resection animals was measured from the ileocecal valve, proximally to the anastomosis prior to excision to assess for any changes in intestinal length.

Data Analysis

mRNA and Protein levels To determine relative changes in gene expression of mRNA and protein levels, the measurements of SGLT1 and GLUT2 in the proximal and distal remnant ileum were normalized to levels of GAPDH, a stably expressed "housekeeping" gene. The relative expressions of mRNA and protein for SGLT1 or GLUT2 in the proximal and distal remnant ileum were compared on the same RT-PCR and Western blot to prevent potential errors in loading; all samples were also run in duplicate. Median values of protein were calculated for each rat in each group, and a grand median with inter-quartile range (IQR) was calculated per group.

Glucose uptake To calculate transporter-mediated glucose uptake, total glucose uptake needed to be corrected for glucose adherent to the non-absorbed, extra-mucosal layer and for passive, non-carrier-mediated uptake. ^{3}H-L-glucose is not absorbed by transporter-mediated uptake and was thus used to correct for this adherent glucose and passive uptake.[18] Transporter-mediated glucose uptake is expressed as nmol/cm/min.

Statistical Analysis

Statistical analysis was performed using JMP software. Continuous variables were compared using Kruskal–Wallis analysis for non-parametric data sets when comparing more than two groups; Wilcoxon rank sums were used to compare directly the non-parametric datasets. *P* values were corrected according to the Bonferroni method, and a corrected *p* value of ≤ 0.05 was considered significant. All data are reported as the median ± IQR or range; *n* values are number of rats.

Results

Operative Outcomes

At the time of tissue harvest, all rats that underwent either sham celiotomy or intestinal resection had gained weight over the study period (data not shown). None of the surviving animals required exclusion from the study due to postoperative complications.

mRNA

SGLT1 mRNA expression was no different among the groups in the proximal remnant ileum ($p \geq 0.9$). However, in the distal ileum1 wk after the resection, the SGLT1 mRNA expression did increase ($p < 0.001$), but the magnitude of change was small (from a median of 3×10^{-3} to 6×10^{-3}), which was not present 4 wk after resection ($p = 1.0$). There was no difference in the SGLT1 mRNA expression between the proximal or distal remnant ileum ($p \geq 0.06$) (Fig. 1a).

The overall relative expression of GLUT2 mRNA was low among all four groups (range 4×10^{-5} to 3×10^{-4}). Similar to the SGLT1 mRNA expression in the distal ileum 1 wk after resection, there was a higher relative expression of GLUT2 mRNA; however, this was found in both the proximal and distal segments ($p \leq 0.02$). The magnitude of

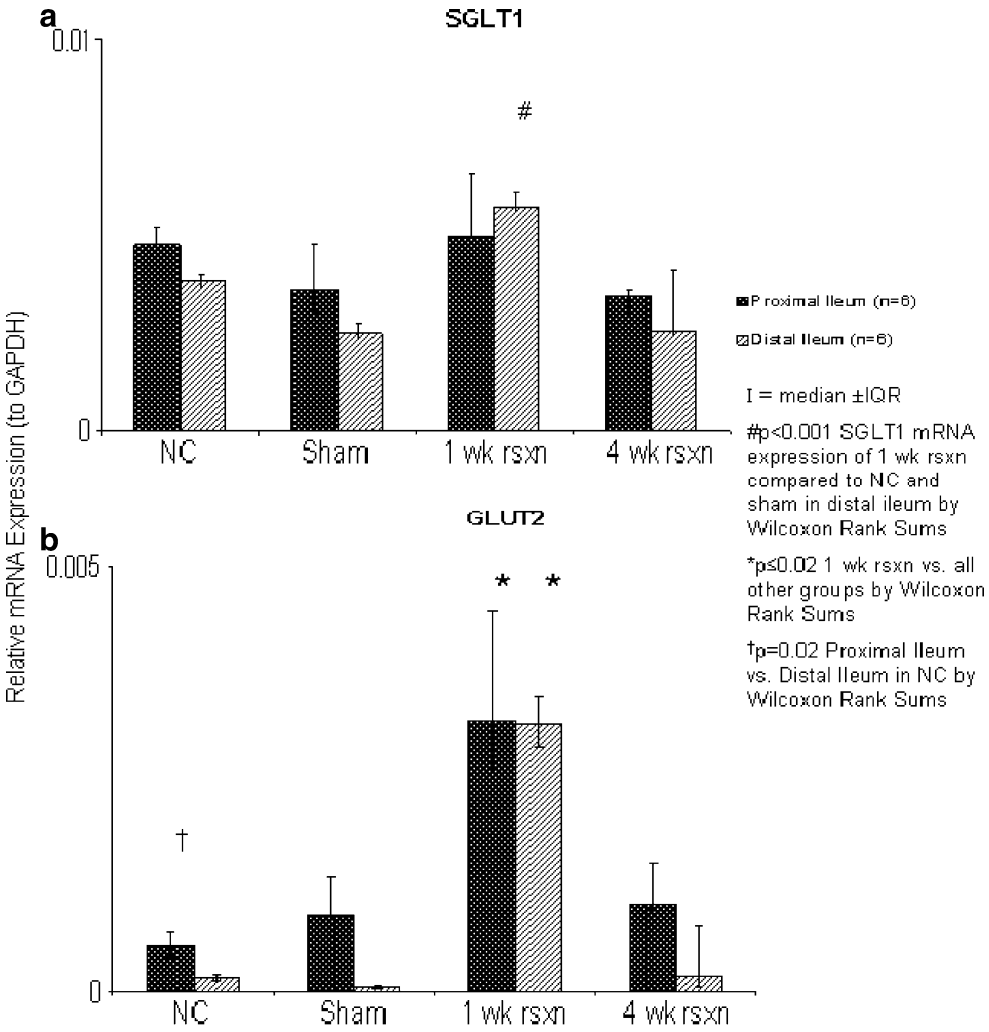

Figure 1 Relative expressions (against GAPDH) of total cellular transporter mRNA by real-time RT-PCR: (**a**) SGLT1; (**b**) GLUT2.

this increase was small (from a median of 1×10^{-4} to 7×10^{-4}) and was not present at 4 wk after resection ($p\geq0.2$). Additionally, within the control group, the relative expression of GLUT2 mRNA was greater in the proximal ileum compared to the distal ileum ($p=0.02$) (see Fig. 1b).

Protein Expression

The relative expression of SGLT1 protein by Western blotting did not demonstrate any difference among the four groups ($p\geq0.06$); specifically, after 70% proximal-based resection, there was no increase in SGLT1 expression in the remnant ileum compared to NC ileum. Additionally, there was no difference in relative expression of SGLT1 between the distal or the proximal ileal segments within any of the groups ($p\geq0.3$) (Fig. 2a). A relative expression of GLUT2 protein by Western blotting was very low among the four groups (range 0.02 to 0.24). No difference in GLUT2 protein expression was found among the four groups ($p\geq0.1$); nor was there a difference between proximal and distal segments of ileum ($p\geq0.2$) (Fig. 2b).

Transport Data

At 1 and 4 wk after small bowel resection, transporter-mediated glucose uptake within the proximal ileum increased markedly compared to the NC and sham groups ($p\leq0.04$). There was no further statistical increase in transporter-mediated glucose uptake, however, from 1 wk to 4 wk after resection ($p=0.4$). Treatment with the GLUT2 inhibitor, phloretin, had no effect on transporter-mediated glucose uptake in the proximal ileum in any group ($p\geq0.08$). In contrast, treatment with the SGLT1 inhibitor, phlorizin, led to a marked decrease in transporter-mediated glucose uptake in the proximal ileum in all four groups ($p=0.003$). At 4 wk after resection, the effect of phlorizin on the rats 4 wk after resection was marked but possibly not as profound compared to the other three groups ($p=0.02$) (Fig. 3a).

In the distal ileum, there was a similar marked increase in transporter-mediated glucose uptake at 1 and 4 wk after resection compared to the NC and sham groups ($p=0.02$). The addition of phloretin also had no effect on transporter-mediated glucose uptake in the distal ileum in any group

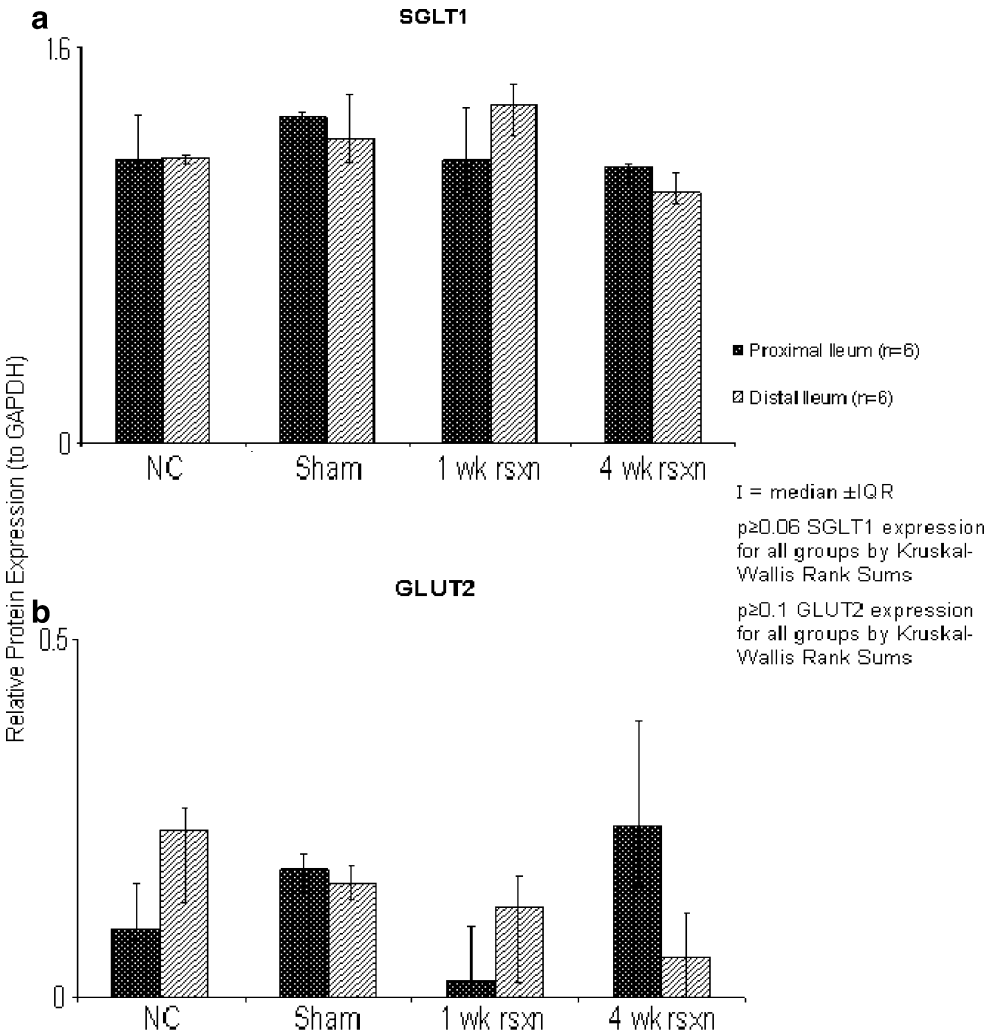

Figure 2 Relative expressions (against GAPDH) of total cellular transporter protein by Western blot: (**a**) SGLT1; (**b**) GLUT2.

($p \geq 0.6$); however, phlorizin decreased markedly transporter-mediated glucose uptake in this segment ($p \leq 0.03$). This inhibitory effect of phlorizin was also somewhat blunted at 4 wk after resection compared to the distal ileal segments in the other three groups ($p=0.01$) (Fig. 3b).

In the naïve control group, transporter-mediated glucose uptake was greater in the proximal ileum compared to the distal ileum ($p=0.02$) in the absence of any inhibitors. This difference in uptake, however, was lost in the sham controls as well as the rats both 1 and 4 wk after resection (Fig. 4). There was no difference in transporter-mediated glucose uptake between the proximal and distal segments in any of the experimental groups in the presence of either phloretin or phlorizin (Fig. 3).

Villus Height and Intestinal Length

Within the proximal segment, median villus height was greater at 1 and 4 wk after resection compared to NC rats (0.47 and 0.58 vs 0.25 mm, resp; $p \leq 0.03$; Fig. 5). Similarly, in the distal ileum, villus height was also greater at 1 and 4 wk after resection compared to NC (0.45 and 0.59 vs 0.21 mm; $p \leq 0.01$; Fig. 5). There was no difference between NC and sham in either the proximal or distal ileum ($p=0.9$). Additionally, there was no difference in villus height in rats at 1 and 4 wk after resection in either the distal or proximal remnant ileum ($p \geq 0.09$). Villus height also did not differ between the distal or proximal ileum within any of the experimental groups.

All resected animals were left with a remnant ileum of 14 cm in length at the time of resection. One week after resection, this length had shortened to a median 12 cm (range 11–13 cm; $p<0.01$); after 4 wk, the intestinal length had increased to a median of 19 cm (range 15–22 cm; $p<0.01$). In addition to intestinal length, gross luminal diameter also increased over time, and while actual measurements could not be measured reliably, the everted sleeve technique necessitated larger caliber steel rods for eversion (4 mm in NC and shams, 5 mm 1 wk after resection, and 6 mm 4 wk after resection).

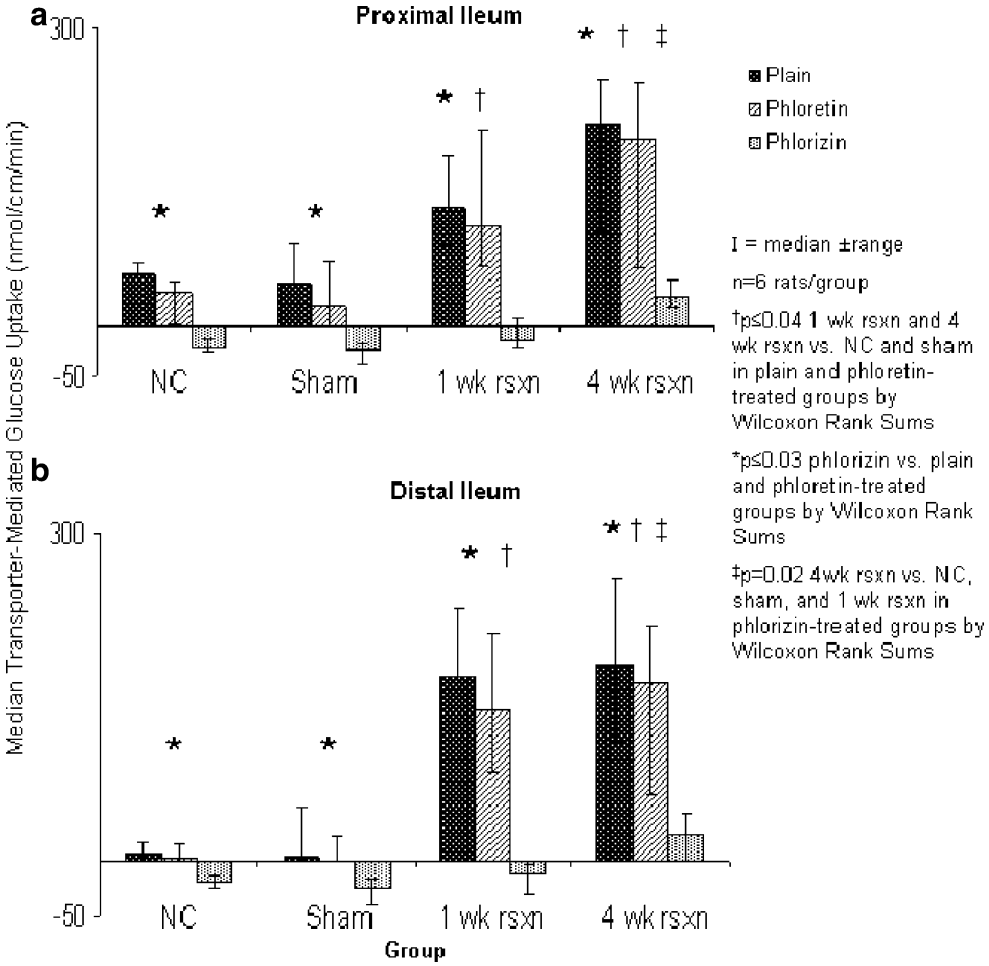

Figure 3 Transporter-mediated glucose uptake in both proximal and distal ileum in plain glucose, and with phloretin and with phlorizin.

Discussion

After proximal-based small bowel resections, the ileum is capable of adapting to the loss of absorptive surface area by effectively increasing absorption of water, electrolytes, and nutrients to maintain adequate hydration and nutrition. This inherent adaptability has made the ileum an area of interest, especially as it pertains to intestinal hexose transporters. Currently, the cellular mechanisms responsible for regulating the expression of the three primary hexose transporters (SGLT1, GLUT2, and GLUT5) are poorly understood. Because these transporters are expressed normally in such low levels in the ileum, we hoped that using a model of ileal adaptation would help us examine patterns in expression and function of these transporters before and after adaptation.

Our data confirm that the ileum, which, in the normal, intact gut is not involved in much of the glucose absorption from the gut, is highly adaptable and can increase its glucose transport after a 70% proximal-based, small bowel resection in the rat. Both of our resection groups demonstrated a marked increase in transporter-mediated glucose uptake. This adaptation appears to occur quickly because the effect was present at 1 wk after small bowel resection, and there was no difference in transporter-mediated glucose uptake at 1 wk compared to 4 wk after resection. When we examined the relative expressions of mRNA, we found very subtle changes at 1 wk after resection in SGLT1 mRNA expression in the distal remnant ileum and GLUT2 mRNA expression in both proximal and distal segments. These very small changes may reflect adaptive changes; however, we did not find any significant changes in comparing NC and shams to the resection animals in terms of SGLT1 and GLUT2 protein expression. These effects could be a result of posttranslational regulation as we have previously described,[18] but the most plausible explanation is that, because the magnitude of change in mRNA expression that we observed was so small, it is likely of no clinical significance. Furthermore, the fact that cellular protein expression remained stable across all four groups suggests that the ileal adaptation after a 70% proximal-based, small intestinal resection was not mediated by upregulation of hexose transporter expression within the enterocyte.

Histologically, we observed a marked increase in villus height between NC and sham rats compared to the resection groups, which indicates a cellular proliferation with lengthening of villus height in the resection group. We

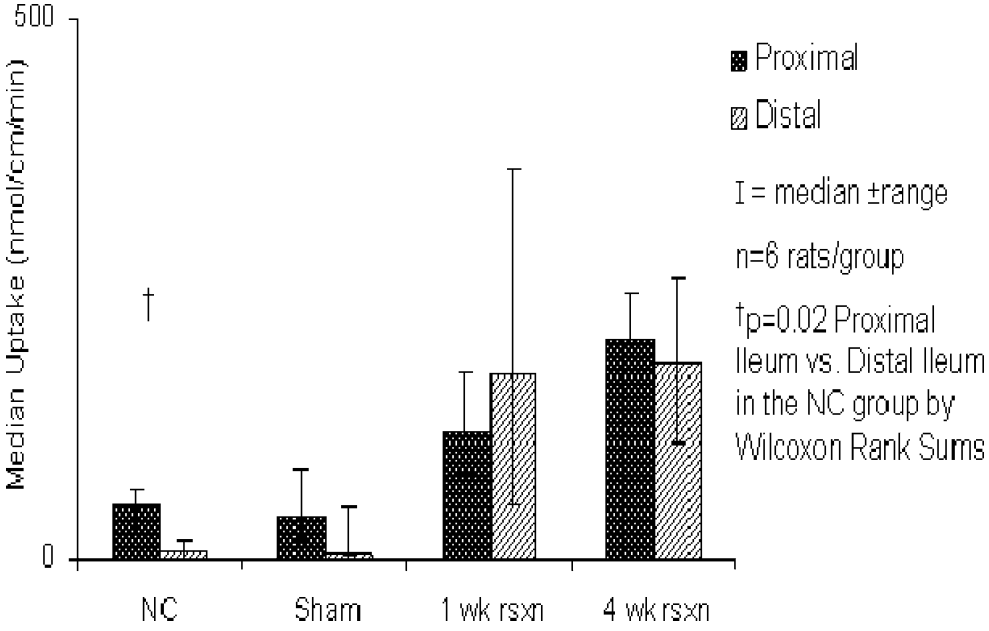

Figure 4 Transporter-mediated glucose uptake in the glucose test solution.

interpret this finding to represent hyperplastic changes in the ileal mucosa after the proximal resection that results in an adaptive response in glucose absorption secondary to more enterocytes rather than each individual enterocyte upregulating hexose transporter expression and function within the apical membrane of the ileal enterocytes. Indeed, changes in transporter-mediated glucose uptake correlated directly with changes in villus height across the four groups and not with protein (or mRNA) expression (Fig. 6).

The intestinal lengths measured after resection further support the concept of intestinal hyperplasia. At 4 wk post-resection, the remnant ileum appears to have increased its length significantly from baseline length, although it is possible that this lengthening represented natural growth of the intestine as the rats grew 4 wk older as opposed to an adaptive response. Another interesting finding was that at 1 wk after resection, the ileum appeared to have shortened. We did not observe a further increase in transporter-mediated glucose uptake between 1 and 4 wk, because the everted sleeve technique measures transport over a 1-cm segment of intestine. It may be that, despite the lack of change in villus height and transporter-mediated glucose uptake per centimeter of tissue between 1 and 4 wk, the ileum's hyperplastic growth from week 1 to week 4 also includes lengthening, and, over time, this lengthening further increases the absolute absorptive capacity. Furthermore, the intestinal diameter also appeared increased; although we did not directly measure this parameter,

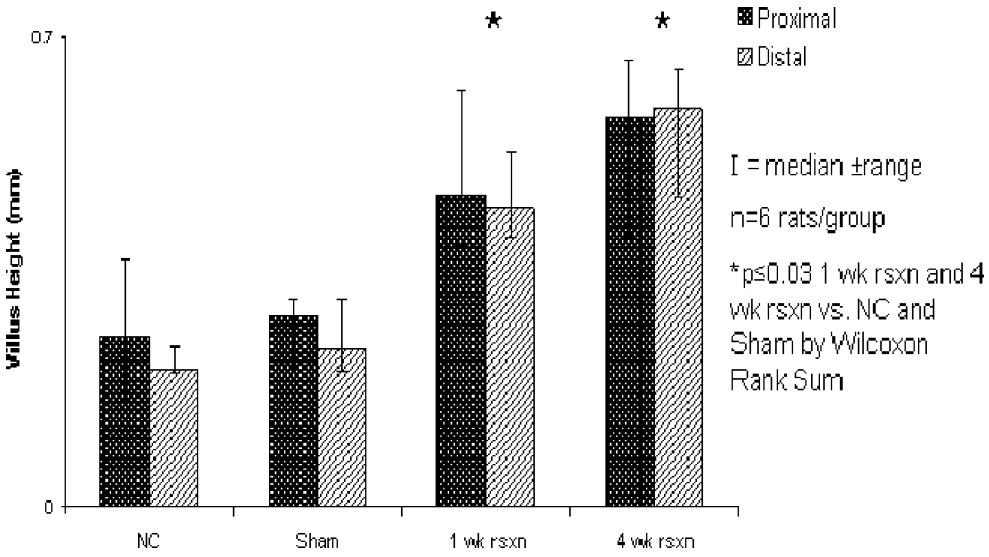

Figure 5 Changes in villus height after 70% proximal small intestinal resection.

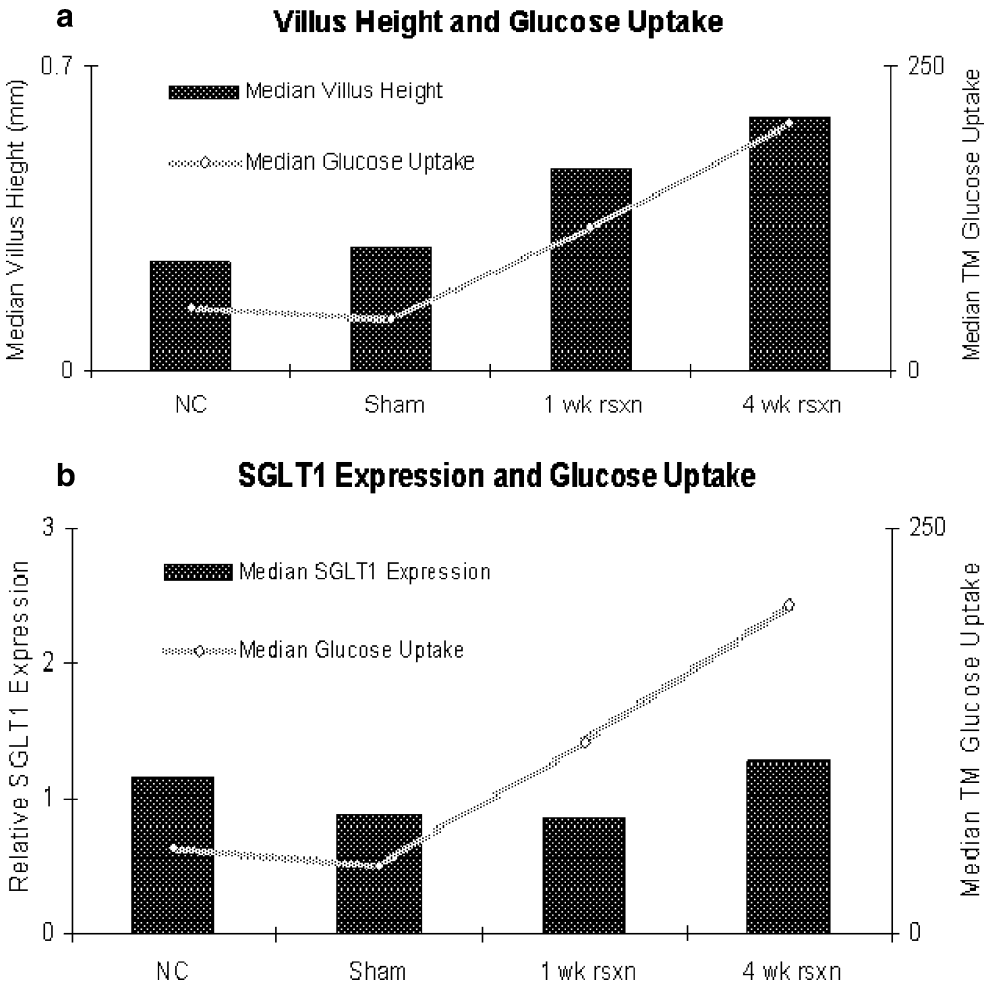

Figure 6 Correlation of transporter-mediated (TM) glucose uptake plotted against (**a**) villus height and (**b**) SGLT1 protein expression by Western blot.

the sleeves required larger bore rods for eversion after resection. This increase in diameter (without any further increase in villus height) did not affect the measured glucose uptake over the 1 cm of tissue that was studied from 1 to 4 wk, but over greater lengths of intestine, where an increase in diameter impacts overall surface area more significantly, intestinal dilation also contributes to a greater absorptive capacity.

Ultimately, these findings suggest that ileal adaptation may not be a good model for studying cellular mechanisms within the enterocyte responsible for regulating hexose transporter expression, at least after proximal resection. In contrast, understanding the mechanisms responsible for increased villus height and intestinal length will be beneficial in treating short bowel syndrome. Our data, however, do suggest that changes in luminal content in the distal ileum after proximal resection did not have a marked effect on enterocyte expression of SGLT1 and GLUT2. If this were the case, one would expect changes in gene expression of SGLT1 and/or GLUT2 protein in this model, because the luminal content of hexoses in the ileum would have increased markedly. The exact mechanism regulating expression cannot be elucidated clearly from our data but could include hormonal or neural mechanisms.

It is accepted widely that SGLT1 is the primary apical glucose transporter in the enterocyte and that GLUT2 functions primarily in the basolateral membrane to transport glucose out of the cell into the systemic circulation. Yet, data from our laboratory and others have suggested the presence of apical GLUT2 in jejunal glucose absorption, and we hypothesized that apical GLUT2 would therefore play an important role in ileal adaptation. When the GLUT2 inhibitor, phloretin, was administered, however, there was no effect on transporter-mediated glucose uptake in any of the groups. This observation suggests strongly that GLUT2 does not play an important role in intestinal apical glucose absorption in the ileum, consistent possibly with the small amount of GLUT2 protein expression we found as well. Moreover, treatment with the SGLT1 inhibitor, phlorizin, resulted in a dramatic, virtually complete inhibition of transporter-mediated glucose uptake, further supporting the belief that, in the ileum, SGLT1 is the predominant apical glucose transporter.

An additional observation was a rebound in transporter-mediated glucose uptake at 4 wk after proximal resection in the phlorizin-treated group. While uptake was still considerably low in the presence of phlorizin at 4 wk after resection, it was significantly greater than the other three groups under the same inhibitory conditions. Because phlorizin is a competitive inhibitor of SGLT1, one explanation might be that the hyperplastic changes at 4 wk after resection resulted in an excess of SGLT1 that was able to overcome the phlorizin inhibition; however, this was not the case at 1 wk after resection, where expression of total cellular SGLT1 protein and histologic data matched that of the 4-wk resection group. It remains possible that an additional transporter is upregulated or newly expressed in a delayed fashion in the ileum, such as GLUT7, a hexose transporter that has been described recently in the literature;[34] however, our data are inadequate to answer this question.

Initially, when we studied the resection animals in a pilot study, we noticed a gross difference between the proximal and distal portion of the remnant ileum 4 wk after resection. The proximal segment appeared to be dilated more than the caliber of the ileum distally. For this reason, our studies were conducted in *both* proximal and distal segments of the remnant ileum. Indeed, we found that there was a significant decrease in transporter-mediated glucose uptake in this distal segment of ileum in the NC rats; the protein expression data for SGLT1 and GLUT2 did not, however, correlate with this finding.

Our study has several limitations. First, our technique for protein analysis cannot distinguish cytoplasmic from apical membranous transporters. Therefore, it is possible that the distal ileum expresses similar total cellular amounts of hexose transporter protein after resection, but more of this protein transporter is trafficked to the apical membrane in the proximal ileum. Our techniques cannot differentiate this possibility. Expression of these proteins in a segment of intestine that is not normally exposed to large amounts of glucose is inefficient, and it may be that expression of these transporters is not regulated by the luminal milieu but by other mechanisms. Again, our data are insufficient to draw a definitive conclusion. Finally, the rats after 70% proximal resection did gain weight, although modest ($\bar{x} = 29$ g), compared to a weight gain in control rats of about 62 g; results might have been different in a more radical proximal resection (>70%), but our interest was more in the regulation of SGLT1 and GLUT expression.

After small bowel resection, the difference in transporter-mediated glucose uptake between proximal and distal ileum was lost, and protein expression and histology were no different either. These data demonstrate that despite different baseline absorptive capacity between proximal and distal ileum with a normal intestinal length, in the setting of short bowel, both the proximal and distal regions of this remnant ileum appear to be equally capable of adaptation through dilation, lengthening, and increased transport of glucose per centimeter length.

Conclusion

The ileum appears to be highly adaptable in its ability to increase glucose absorption via SGLT1 after massive proximal-based small bowel resection—but this increase in absorptive capacity is due to cellular proliferation by villus hyperplasia and intestinal lengthening as opposed to upregulation of glucose transporters within the enterocyte. Despite a lesser SGLT1 activity under normal conditions in the distal ileum compared to the proximal ileum, the distal ileum has a similar capacity to adapt as the proximal portion after 70% proximal-based small bowel resection. There appears to be little or no role of GLUT2 in baseline apical glucose transport in the ileum or after adaptation.

References

1. Vanderhoof JA, Langnas AN. Short-bowel syndrome in children and adults. Gastroenterology 1997;113:1767–1778. doi:10.1053/gast.1997.v113.pm9352883.
2. Georgeson KE, Breaux CW. Outcome and intestinal adaptation in neonatal short-bowel syndrome. J Pediatr Surg 1992;27:344–348. doi:10.1016/0022-3468(92)90859-6.
3. Tavakkolizadeh A, Whang FE. Understanding and augmenting human intestinal adaptation: a call form ore clinical research. J Parenter Nutr 2002;26:251–255. doi:10.1177/0148607102026004251.
4. Scolapio JS, Camilleri M, Fleming CR. Gastrointestinal motility considerations in patients with short-bowel syndrome. Dig Dis 1997;15:253–262.
5. Dekaney CM, Fong JJ, Rigby RJ, Lund PK, Henning SJ, Helmrath MA. Expansion of intestinal stem cells associated with long-term adaptation following ileocecal resection in mice. Am J Physiol Gastrointest Liver Physiol 2007;293:G1013–22. doi:10.1152/ajpgi.00218.2007.
6. Haxhija EQ, Yang H, Spencer AU, Sun X, Teitelbaum DH. Intestinal epithelial cell proliferation is dependent on the site of massive small bowel resection. Pediatr Surg Int 2007;23:379–390. doi:10.1007/s00383-006-1855-9.
7. Baksheev L, Fuller PJ. Gene expression in the adapting small bowel after massive small bowel resection. J Gastroenterol 2006;41:1041–1052. doi:10.1007/s00535-006-1896-9.
8. Nelson DW, Liu X, Holst JJ, Raybould HE, Ney DM. Vagal afferents are essential for maximal resection-induced intestinal adaptive growth in orally fed rats. Am J Physiol Integr Comp Physiol 2006;291:R1256–R1264.
9. Sigalet DL, Bawazir O, Martin GR, Wallace LE, Zaharko G, Miller A et al. Glucagon-like peptide-2 induces specific pattern of adaptation in remnant jejunum. Dig Dis Sci 2006;51:1557–1566. doi:10.1007/s10620-006-9077-5.
10. Helmrath MA, Fong JJ, Dekaney CM, Henning SJ. Rapid expansion of intestinal secretory lineages following a massive small bowel resection in mice. Am J Physiol Gastrointest Liver Physiol 2007;292:G215–G222. doi:10.1152/ajpgi.00188.2006.

11. Ozturk H, Ozturk H, Yagmur Y, Uzunlar KM. Effects of melatonin on intestinal adaptive response after massive bowel resection in rats. Dig Dis Sci 2006;51:333–337. doi:10.1007/s10620-006-3134-y.
12. Martin GR, Wallace LE, Sigalet DL. Glucagon-like peptide-2 upregulation of intestinal blood flow and glucose uptake is nitiric oxide dependent in TPN-fed piglets. Gastroenterology 2003;125:136–147. doi:10.1016/S0016-5085(03)00667-X.
13. Martin GR, Wallce LE, Sigalet DL. Glucagon-like peptide-2 induces intestinal adaptation in parenterally fed rats with short bowel syndrome. Am J Physiol Gastrointest Liver Physiol 2004;286: G964–G972. doi:10.1152/ajpgi.00509.2003.
14. Ferraris RP. Dietary and developmental regulation of intestinal sugar transport. Biochem J 2001;360:265–276. doi:10.1042/0264-6021:3600265.
15. Corpe CP, Burant CF. Hexose transporter expression in rat small intestine: effect of diet on diurnal variation. Am J Physiol Gastrointest Liver Physiol 1996;271:G211–G216.
16. Ferraris RP, Diamond JM. Specific regulation of intestinal nutrient transporters by their dietary substrates. Annu Rev Physiol 1989;51:125–141. doi:10.1146/annurev.ph.51.030189.001013.
17. Ferraris RP, Diamond JM. Regulation of intestinal sugar transport. Physiol Rev 1997;77:257–302.
18. Houghton SG, Iqbal CW, Duenes JA, Fatima J, Kasparek MS, Sarr MG. Coordinated, diurnal hexose transporter expression in rat small bowel: implications for small bowel resection. Surgery 2008;143:79–93. doi:10.1016/j.surg.2007.06.007.
19. Fedorak RN, Cheeseman CI, Thomson AB, Porter VM. Altered glucose carrier expression: mechanism of intestinal adaptation during streptozocin-induce diabetes in rats. Am J Physiol Gastrointest Liver Physiol 1991;261:G585–G591.
20. Helliwell PA, Richardson M, Kellett GL et al. Stimulation of fructose transport across intestinal brush-border membrane by PMA is mediated by GLUT2 and dynamically regulated by protein kinase C. Biochem J 2000;350:149–154. doi:10.1042/0264-6021:3500149.
21. Helliwell PA, Richardson M, Kellett GL et al. Regulation of GLUT5, GLUT2, and intestinal brush-border fructose absorption by the ERK, p38, and PI 3-kinase intracellular signaling pathways: implications for adaptation to diabetes. Biochem J 2000;350:163–169. doi:10.1042/0264-6021:3500163.
22. Au A, Gupta A, Cheeseman CI et al. Rapid insertion of GLUT2 into the rat jejunal brush-border membrane promoted by glucagon-like peptide. Biochem J 2002;367:247–254. doi:10.1042/BJ20020393.
23. Affleck JA, Helliwell PA, Kellett GL. Immunocytochemical detection of GLUT2 at the rat intestinal brush-border membrane. J Histochem Cytochem 2003;51(11):1567–1574.
24. Iqbal CW, Fatima J, Duenes JA, Kasparek MS, Sarr MG. GLUT2 trafficking to the apical membrane of enterocytes via SGLT1 signalling through protein kinase C. Gastroenterology 2007;132: A–891. Abstract M1764.
25. Tavakkolizadeh A, Berger UV, Levitsky LL et al. Diurnal rhythmicity in intestinal SGLT1 function, Vmax, and mRNA expression topography. Am J Physiol Gastrointest Liver Physiol 2001;280:G209–G215.
26. Houghton SG, Zarroug AE, Sarr MG et al. The diurnal periodicity of hexose transporter mRNA and protein levels in the rat jejunum: role of vagal innervation. Surgery 2006;139:542–549. doi:10.1016/j.surg.2005.09.002.
27. Karasov WH, Diamond JM. A simple method for measuring intestinal solute uptake in vitro. J Comp Physiol 1983;152:105–116.
28. Iqbal CW, Sarr MG, Duenes JA, Fatima J, Kasparek MS, Houghton SG. Activity of hexose transporters after small intestinal denervation in the rat: role of intrinsic and extrinsic denervation. J Surg Res 2007;137:160. Abstract 23 doi:10.1016/j.jss.2006.12.032.
29. Manome SH, Kuriaki K. Effects of insulin, phlorizin and some metabolic inhibitors on the glucose absorption from the small intestine. Arch Int Pharmacodyn Ther 1961;130:187–194.
30. Oulianove N, Falk S, Berteloot A. Two-step mechanism of phlorizin binding to the SGLT1 protein in kidney. J Membr Biol 2001;179:223–242. doi:10.1007/s002320010049.
31. Loike JD, Hickman S, Fischbarg J et al. Sodium-glucose co-transporters display sodium- and phlorizin-dependent water permeability. J Membr Biol 2001;179:223–242. doi:10.1007/s002320010049.
32. Forsling ML, Widdas WF. The effect of temperature on the competitive inhibition of glucose transfer in erythrocytes by phenolphthalein, phloretin, and stilboestrol. J Physiol 1968;194:545–554.
33. Boudry G, Cheeseman CI, Perdue MH. Psychological stress impairs Na+-dependent glucose absorption and increases GLUT2 expression in the rat jejunal brush-border membrane. Am J Physiol Regul Integr Comp Physiol 2007;292:R862–R867. doi:10.1152/ajpregu.00655.2006.
34. Qiang L, Manolescu A, Ritzel M, Yao S, Slugoski M, Young JD et al. Cloning and functional characterization of the human GLUT7 isoform SLC2A7 from the small intestine. Am J Physiol Gastrointest Liver Physiol 2004;287:G236–G242. doi:10.1152/ajpgi.00396.2003.

Discussion

David A. Sigalet, M.D. (Calgary, AB, Canada): Your group has used nicely the a classic model of intestinal resection and you have shown us that the hyperplasia versus hypertrophy story still is relevant, despite the application of new technology looking at the potential for GLUT2 involvement. You have nicely demonstrated the increase in SGLT1 expression following resection by the phlorizin/phloretin blocking experiments.

I have two questions. The first is that given the effect of nutrient input, ie the enteral intake of the animals on nutrient absorption, can you give us any background about how these animals were fed and your impression of how this may have impacted their nutrient absorption? And secondly, you have used quite different metrics in your output; the output of absorption per unit length of bowel is necessarily based on bowel surface area, whereas your cellular expression of protein is per cell or per protein measure. So have you tried to reconcile those, in other words, to give us a readout of SGLT1 per unit length of bowel? With this you may find that then you can see a more profound effect of your resection.

Corey W. Iqbal, M.D. (Rochester, MN): In regard to the nutrient influence, the rats were fed a standard rat chow and ad lib. So I really cannot comment on what the specific contributions of nutrients would have been. One of the areas that we are interested in is cellular regulation of the expression and function of all three intestinal hexose transporters, SGLT1, GLUT2, and GLUT5, and the diurnal rhythm that

has been associated with them. Our hypothesis was that the change in the luminal milieu by having the ileum in a more proximal position would affect hexose transporter regulation, and if we had found that SGLT1 and GLUT2 expression changed, then it would be worth investigating further to determine which nutrients regulate hexose transporter expression and function. The fact that there was difference indicates that luminal substrates do not appear to regulate hexose transporter expression and function in the ileum.

With regards to the discrepancies in terms of looking at cellular expression and correlating that with our uptake studies, the everted sleeve is limited to a 1 cm segment of intestine and does not measure transport per cell. However, because the expression data is a ratio, it would not matter if you collected tissue across 1 cm or more, in theory the ratio should be the same, so I feel that our conclusion is still accurate. Additionally, we did find that in the specimens of the remnant ileum, not only did the villus height increase but the length of that remnant also increased, meaning that we left a 14 cm segment of remnant ileum, and four weeks later we found that it had lengthened to a median of 19 cm. Whether that was due to just natural growth over a four week period or part of the adaptive process, we don't have that data to say. The other thing is that the intestine dilates. So there are three mechanisms that seem to increase that surface area, by lengthening, increasing its diameter, as well as the change in villus height which are additional parameters that support our conclusion.

J Gastrointest Surg (2008) 12:1866–1873
DOI 10.1007/s11605-008-0670-0

Reinterventions for Specific Technique-Related Complications of Stapled Haemorrhoidopexy (SH): A Critical Appraisal

Pierpaolo Sileri · Vito Maria Stolfi · Luana Franceschilli · Federico Perrone · Lodovico Patrizi · Achille Lucio Gaspari

Received: 20 February 2008 / Accepted: 8 August 2008 / Published online: 3 September 2008

Abstract
Introduction Stapled haemorrhoidopexy (SH) is an attractive alternative to conventional haemorrhoidectomy (CH) because of reduced pain and earlier return to normal activities. However, complication rates are as high as 31%. Although some complications are similar to CH, most are specifically technique-related. In this prospective audit, we report our experience with the management of some of these complications.
Methods Data on patients undergoing SH at our unit or referred to us are prospectively entered in a database. The onset or duration of specific SH-related complications as well as reinterventions for failed or complicated SH was recorded.
Results From 1/03 to 10/07, 110 patients underwent SH, while 17 patients were referred after complicated/failed SH. Overall early and late complication rates after SH were 12.7% and 27.2%, respectively. Overall reintervention rate was 9.1%. Among the referred SH-group, one patient underwent Hartmann's procedure because of rectal perforation. The remaining 16 patients experienced at least one of the following: recurrence, urgency, frequency, severe persistent anal pain, colicky abdominal pain, anal fissure and stenosis. Four patients underwent CH with regular postoperative recovery. Two patients underwent exploration under anaesthesia because of persisting pain. One patient underwent anoplasty.
Conclusions SH presents unusual and challenging complications. Abuses should be minimized and longer-term studies are needed to further clarify its role.

Keywords Haemorrhoidopexy · Haemorrhoids · Outcome

Introduction

Stapled haemorrhoidopexy (SH) is an attractive alternative to conventional haemorrhoidectomy (CH) because of reduced postoperative pain, shorter hospital stay and earlier return to normal activities. Over the last decade, SH gained wide acceptance, with over 50,000 patients treated in Europe.[1,2]

However, this enthusiastic use has been tempered by increasing reports of unusual complications, including several cases of pelvic life threatening sepsis and deaths.[3,4] Although several complications are similar to CH, some are technique-related such as longer-term anal pain (post-evacuation syndrome or persistent anal pain), longer-term tenesmus with urgency and or frequency, haemorrhoidal recurrence (early as thrombosis or late recurrences), recto-vaginal fistula, anastomotic leakage, rectal perforation and pelvic sepsis.[5–7] In this brief prospective audit, we report our experience with the management of some of these complications after SH.

Presented at the plenary session at the Digestive Disease Week, May 2008, San Diego, CA, USA

P. Sileri · V. M. Stolfi · L. Franceschilli · F. Perrone · L. Patrizi · A. L. Gaspari
Department of Surgery, University of Rome Tor Vergata, Rome, Italy

P. Sileri (✉)
Cattedra Chirurgia Generale, Policlinico Tor Vergata, 6B, Viale Oxford 81, 00133 Rome, Italy
e-mail: piersileri@yahoo.com

Patients and Methods

Between January 2003 and October 2007, 425 symptomatic patients underwent haemorrhoidectomy at our institution

and data entered prospectively in a database. Of those, 110 underwent SH (66 M, 44 F, mean age 44 years, ranging from 21 to 75 years) while 315 underwent conventional haemorrhoidectomy (186 M,129 F, mean age 48 ranging from 24 to 72 years). Mean follow-up period after surgery was similar between the two groups being respectively 25± 14 months after SH and 32±16 months after CH. Before surgery, all patients underwent digital examination and proctoscopy. Preoperative Wexner continence score was performed in all patients. Colonoscopy, anorectal manometry and/or ultrasonography (US) were performed if necessary. All surgeries were performed in a Day Care setting, in lithotomy position under local anaesthesia and, when necessary, general anaesthesia was provided. All patients received a phosphate enema 2 h before the operation.

Antibiotic prophylaxis was administered using intravenous *cephalosporin* (1 g) and *metronidazole* (500 mg) immediately before surgery. Starting May 2006 our protocol was revised and a single-antibiotic regimen replaced the previous one using intravenous *cefotaxime* (2 g).

The procedure was performed according to the technique described by Longo[6] using the PPH01 kit (Ethicon Endo-Surgery) with no modifications or additional procedures.

All resected specimens were sent for pathology examination. Mucosal doughnuts retrieved from the stapler were orientated and sent for pathology. As previously described, the macroscopic appearance of the specimen (shape, size and depth) was recorded. Microscopically, the presence of columnar, transitional and squamous epithelium, the involvement of circular/longitudinal smooth muscle as well as features of mucosal prolapse, was assessed.

Patients were discharged from the unit 4 to 8 h after the procedure with oral and written instructions for postoperative care including medications (non-steroidal anti-inflammatory drugs per os), antibiotics (quinolones twice a day for 5 days per os) and stool softeners for 7 days. Warm sitz baths were suggested.

Patients were seen after 1 week and pain assessed using a 10-cm linear visual analogue scale (VAS). Further controls were scheduled at 1, 3 and 12 months or if required. All patients were contacted annually thereafter. Clinical outcome was assessed by a validated questionnaire on postoperative symptoms and satisfaction supplemented by the Wexner continence score.

During the same period of time, 23 patients were referred to our colorectal unit after complicated CH or SH performed elsewhere: six after CH (four F, two M) and 17 (11F, six M; mean age 47 years) after SH. The onset and duration of specific SH-related complications as well as reinterventions for failed and or complicated SH were recorded.

Results

Operating time between SH and CH was similar being 28.3±8.7 and 26±8.8 min, respectively (p=0.111). Hospitalization rates were similar between SH and CH being 2.7% and 1.6%, respectively (p=0.449).

Likewise, no differences were observed in terms of ER admissions (7.3% vs 3.8%, p=0.214) and hospital readmissions (3.6% and 2.2%, p=0.414) between SH and CH.

Overall early (<30 days from surgery) and late (>30 days) complication rates were similar between SH and CH as shown in Tables 1 and 2.

Despite an increased quote of anal fissure, disabling chronic pain and recurrences were observed after SH when compared to CH, no significative differences were observed in terms of early and late complications between SH and CH as shown in Tables 1 and 2.

Mean pain during the first postoperative week expressed as VAS is shown in Fig. 1. Significant differences were observed from postoperative days 4 to 7.

As shown in Fig. 2, patients who underwent CH experienced more severe pain (expressed as VAS score> 7) than SH at 5, 6 and 7 postoperative days. We did not observed differences between SH and CH in terms of postoperative pain and severe pain (VAS>7) among third and fourth degree haemorrhoids.

Postoperative symptoms duration including pain, bleeding, soiling and hitching lasted more after CH compared to SH reaching significant differences for soling and bleeding as shown in Fig. 3.

Postoperative fever was similar between the two groups. No differences were observed in terms of return to work expressed in days between the two groups. Longer-term follow-up results of symptoms duration is shown in Table 3.

Urgency after 3 months was significantly more frequent after SH compared to CH (8.2% vs 0.6%), despite this difference disappeared at 1 year (0.9% vs 0.3%).

Three patients (2.7%) experienced severe disabling chronic pain after SH that lasted >1 year since surgery without the expected improvement over the follow-up. All patients described the pain as sharp, recurrent, starting

Table 1 Early Complications (<30 days)

Complications	SH (n/%)	CH (n/%)	*P* value
Urinary retention	3/2.7%	5/1.6%	0.449
Bleeding	5/4.5%	9/2.8%	0.394
Faecal retention	1/0.9%	5/1.6%	0.604
Haem. thrombosis	2/1.8%	1/0.3%	0.106
Incontinence	3/2.7%	7/2.2%	0.090
Infection	0	3/0.9%	0.305
Overall	14/12.7%	30/9.5%	0.343

Table 2 Late Complications

Complications	SH (n/%)	CH (n/%)	*P* value
Disabling pain (>1 year)	3/2.7%	2/0.6%	0.082
Recurrence	6/5.4%	5/1.6%	0.133
Stenosis	2/1.8%	10/1.2%	0.460
Anal fissure	6/5.4%	7/2.2%	0.090
Abscess/fistula	0	2/0.6%	0.403
Skin tags	13/11.8%	41/13.2%	0.746
Overall	30/27.2%	67/21.2%	0.197

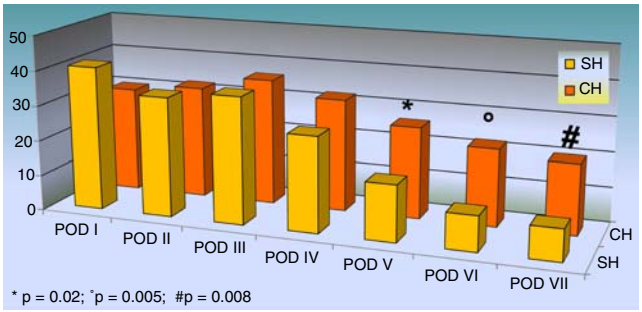

Figure 2 Severe postoperative pain (expressed as % of patients with VAS>7).

within 30 min from defecation and lasting for 2 to 5 h without bleeding or mucous discharge. In all cases, the rectal examination was unremarkable and anal fissure was ruled out. All patients underwent anal manometry that did not show significant abnormalities (only one patient was found to have mild internal anal sphincter hypertonia) as well as endorectal ultrasound that showed normal anatomy in all. A working diagnosis of post-defecation syndrome was made in all and calcium channel blockers ointment given twice a day for 8 weeks. This treatment was effective in all but one who presented worsening persistent pain described as sharper after defecation. In this case oral nifedipine was ineffective and anorectal exploration under anaesthesia was performed. At surgery, the staple line was correctly placed and the only finding was the presence of retained staples which were removed with complete pain resolution within 2 weeks. SH complications and their management resumé is shown in Table 4.

Early haemorrhoidal recurrences (as thrombosis) occurred 4 and 12 days after surgery. Both cases responded to standard medical treatment and did not present any other episode during the follow-up. Six patients developed late haemorrhoidal recurrence after 16±5 months from previous surgery (range 9–26 months). All recurrences were observed in patients who underwent SH for fourth degree haemorrhoids. Main symptoms were bleeding (six patients) and prolapse (four patients). One patient was successfully treated with rubber banding while surgery was offered to the remaining five: one patient refused and four underwent uneventful CH (two closed and two open).

Twelve patients experienced transient urgency (10.9%) that resolved within 4 months in all patients but one in which lasted 13 months. Two patients (1.8%) developed symptomatic rectal stricture with urgency and frequency and responded to anal dilatation with anal dilators. As shown in Table 5, overall reinterventions rate after SH was 9.1% (vs 4.8% of CH, not significant). Figure 4 shows the estimated risk of reinterventions after SH and CH. Table 6 shows summary of complications and management among the referred patients.

Among the referred SH group, one patient developed severe pelvic sepsis after SH performed as a day case procedure. She complained lower quadrants abdominal pain associated to nausea, vomit and fever the night following hospital discharge. She was admitted in our emergency unit because of acute abdomen. Signs of severe sepsis were present and computed tomography (CT) scan showed pneumoretroperitoneum. At laparotomy, mesorectal and retroperitoneal emphysema were present with minimal amount of pus, in absence of an evident low rectal

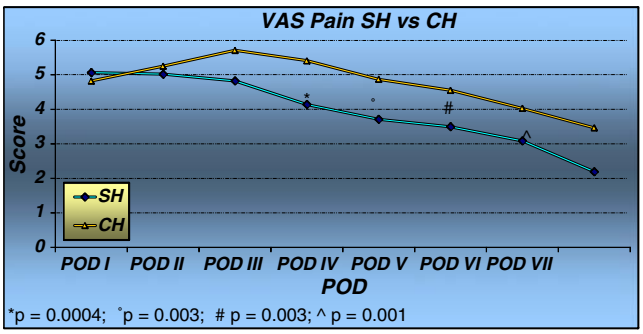

Figure 1 Pain SH vs CH (expressed as VAS score mean).

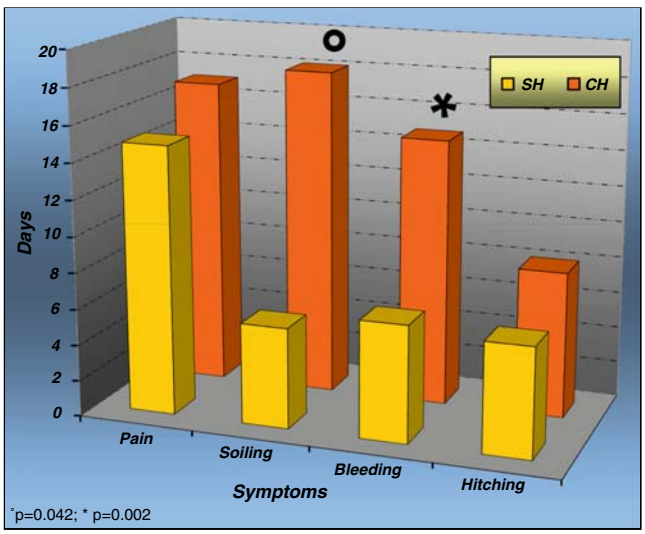

Figure 3 Postoperative symptoms duration.

Table 3 Longer-term Follow-up and Symptoms Duration

Parameter	SH (n/%)	CH (n/%)	*P* value
Fever (>38°C)	4/3.6%	14/4.4%	0.821
Bleeding at 3/12	2/1.8%	5/1.6%	0.870
Urgency at 3/12	9/8.2%	2/0.6%	0.045
Pain at 3/12	3/2.7%	4/1.2%	0.175
Bleeding at 1 yr	1/0.9%	2/0.6%	0.967
Urgency at 1 yr	1/0.9%	1/0.3%	0.436
Pain at 1 yr	3/2.7%	2/0.6%	0.082
Satisfaction (score 4/4)	85%	66%	0.051
Return to work (days)	17.3±11.7	17.5±10.8	0.856

perforation. After accurate washout, a Hartman's procedure was performed and a drain left in the pelvis. Postoperative recovery was uneventful, she was discharged after 8 days and uneventful reversal was performed 6 months later.

Ten of the remaining 16 patients experienced at least one of the following symptoms or complications: recurrence,[6] urgency,[6] severe chronic anal pain,[4] tenesmus,[4] colicky abdominal pain,[1] anal fissure[1] and stenosis.[1]

Recurrences were observed after 17±6 months from surgery (range 9 to 36 months). Main symptoms were bleeding (six patients), prolapse (four patients) and pain (one patient). Four patients accepted surgery and underwent conventional haemorrhoidectomy (three closed, one open) and had a regular postoperative recovery.

Four patients came to our attention because of persistent pain lasting for 7±6 months after SH. In one case, an anal fissure was present and successfully treated with lateral internal sphincterotomy after manometric confirmation of internal sphincter hypertonia and failure of GTN ointment course of 8 weeks. Topical treatment with calcium channel blockers ointment (twice a day for 8 weeks) was started in all. One patient required oral nifedipine. However, conservative medical treatment was ineffective in two patients, who underwent exploration under anaesthesia (EUA). Before reinterventions anorectal manometry and ultrasound were performed in both and pelvic magnetic resonance imaging (MRI) in one. In one patient, the US showed a small (1 cm) submucosal abscess at the stapled line. The abscess was not seen at the MRI, and it was not found at EUA. However, in both patients, surgical removal of retained staples resolved the pain within 4 weeks.

One referred patient with anorectal stricture underwent anoplasty. In this case, asymmetric, very low stapled line was observed at surgery.

Discussion

Our experience confirms that SH is followed by reduced postoperative pain during the first week with overall early and late complications rates similar to CH. Postoperative symptoms duration is shorter after SH with a better patients satisfaction compared to CH. Differently from other authors report, in our experience the mean return to work period (expressed in days) was similar between SH and CH.[8–10] We explain this similarity of results with the fact the our hospital serves a large Government employed (directly or indirectly) population with paid sick leave. Complications rates of SH range from 6.4% to 31%[8,9] with a reintervention rate after 1 year of 11%.[10] Some complications are similar to conventional haemorrhoidectomy such as bleeding, urinary retention, incontinence, fissure and stenosis. Others are specific-related to the technique, such as intrabdominal or retroperitoneal bleeding, pelvic sepsis, tenesmus, severe chronic anal pain (chronic proctalgia or postdefecation syndrome), rectovaginal fistula and damage to sphincterial mechanism.[11–14]

Blouhos et al. reported a case of uncontrollable intra-abdominal bleeding necessitating low anterior rectal resection because of a small laceration in the anterior aspect of the rectum.[15]

The most dangerous complication reported after SH is pelvic sepsis, usually subsequent to rectal perforation or anastomotic leak. In a recent systematic review of life-threatening sepsis following haemorrhoidectomy, McCloud et al. described seven cases of life-threatening complications between 2000 and 2003 including abscesses, fistulae,

Table 4 SH Complications and Management Resume

Complications	Number (*n*)	Management	*n*/%
Bleeding	5	Conservative surgery 1	4/5
Thrombosis (at POD 4 and 12)	2	Conservative	Effective
Disabling pain (US, MRI, manometry)	3	Analgesic/Ca^{2+} CB	Topical,[1] Oral[1]
		EUA	Stapler removal effective[1]
Recurrence (16±5 months)	6	Medical/RBL	1/2 RBL effective; 1 refused
		Surgery-CH	2 Closed/2 open
Fissure	6	Medical (GTN) surgery	Effective 4/6 (66.7%)
			2 LIS, effective
Stenosis	2	Dilators	Effective

Table 5 Number of Patients with a Complication (*N*) Requiring Reintervention (*n*)

Reintervention	SH n/N(%)	CH n/N(%)	*P* value
For pain	1/3(33.3%)	0/2	0.83
For bleeding	1/5(20%)	3/9(33.3%)	0.54
For skin tags	2/13(15.4%)	3/41(7.3%)	0.39
For anal fissure	2/6(33%)	4/7(57%)	0.43
For abscess/Fistula	0	2/2(100%)	0.79
For stenosis	0/2	2/10(20%)	0.84
For recurrence	4/8(50%)	1/5(20%)	0.31
cumulative	10/37(27%)	15/74 (20.3%)	0.64
OVERALL RATE	10/110(9.1%)	15/315(4.8%)	0.06

retroperitoneal sepsis and rectal perforations as well as pneumoretroperitoneum and pneumomediastinum.[5] Six patients required faecal diversion, and one died. These reports tempered the initial enthusiasm for SH and in 2004 Nisar et al. emphasized "potentially devastating complications" of SH in a meta-analysis indicating CH as the gold standard.[16] Since then, an equal number of life-threatening complications after SH have also been reported, the majority requiring faecal diversion with occasional deaths. The number of these adverse events is comparable to those observed after CH over a 40 year period (1964–2003), although severe complications following CH hardly require faecal diversion.[17] Pescatori et al. observed that the risk of these severe complications is higher after SH because it involves the distal rectum with a 'blind' resection and suture, close to the vagina, the prostate and the Douglas pouch, which is also a possible site of an enterosigmoidocele.[17] Although Ravo et al. estimated a life-threatening complications rate of 1:1200 after SH in a large retrospective study, we believe that the real number of life-threatening complications is largely overlooked because of unpublished events. It has been pointed that most of these cases have been performed by general surgeons[17] despite the fact that a consensus paper had recommended that the operation should be carried out only by specialists trained

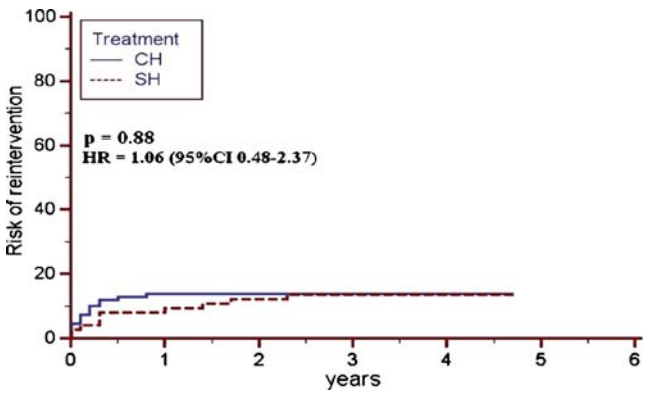

Figure 4 Estimated risk of reinterventions after SH and CH.

Table 6 (Referred Patients): Summary of Complications and Management

Complications	Number (*n*)	Management	Notes/outcome
Rectal perforation	1	Hartmann reversed	4/12 Later
Tenesmus-urgency	10	Biofeedback	
Disabling chronic pain	4	Analgesic/ Ca^{2+} CB	Uneffective 2/4
		EUA (stapler removal)	Effective 2/2
Recurrence	6	Conservative uneffective	6/6
		RB	Effective 1/2
		Surgery-CH	4 (3 closed/1 open)
Stenosis	1	Anoplasty	Asymmetric low stapled line
Fissure	1	Medical (GTN)	Uneffective
		Surgery (LIS)	Effective

in this technique.[18] In case of unexpected severe perineal or abdominal pain, urinary retention or difficulties with micturition, fever and leucocytosis, even if local examination is negative, an abdominal CT scan should be immediately performed. Predominant findings at CT scan are pneumoretroperitoneum, pneumomediastinum and subcutaneous emphysema.[19,20] Despite the fact that successful conservative management has been reported, we believe that anastomotic repair with faecal diversion or a Hartman's procedure should always be performed before worsening of clinical conditions. At exploration (by laparotomy or laparoscopy), very little will be found with oedema of the rectum and pararectal tissues associated to minimal or absent retroperitoneal fluid or pus depending from the onset and duration of symptoms prior surgery. Emphysema along the mesorectum and retroperitoneum can be observed.

Recto-vaginal fistula can also occur, and to date, three cases have been described.[11,21,22] This complication can be avoided by assessing the thickness of the rectovaginal septum before inserting the purse-string suture. Care should be taken not to place too deep a suture anteriorly during the purse-string, and vagina should be examined before firing. If rectovaginal fistula occurs, immediate repair should be attempted after excision of the staples ring, and a faecal diversion should be made.

Three cases of acute rectal obstruction after SH have been reported worldwide secondary to complete closure of the distal rectum by the retained purse string entrapped by the staples (two cases) or secondary to haematoma within the layers of the bowel wall (one case).[23–25] It may require laparotomy and faecal diversion due to subsequent spontaneous or iatrogenic perforation. If immediately recognised a *Delorme* approach could be attempted.[23]

Although we did not observe any, the rectal pocket syndrome may follow SH due to the entrapment of faecoliths leading to transient intramural sepsis.[26] This syndrome may be due to incorrect placement of purse-string suture and requires laying open the pocket.[26]

Several authors suggested possible lesions of the anal sphincterial apparatus mainly secondary to anal dilatation or muscle entrapment at stapler firing. Randomised data have shown that the continence score as well as anorectal manometric and endoanal US findings are similar to those found after CH.[13]

Severe persistent pain after SH has been reported between 2% and 16% and represents the most common cause of reintervention (up to 45% of cases).[10,17,27] In absence of thrombosis or fissure, the pain is described as intense and dull, refractory to treatment and associated variably with tenesmus or urgency (proctalgia). However, pain can be sharp and rapidly increasing after defecation (10–30 min) without evidence of an anal fissure (post-defecation syndrome). Its aetiology is uncertain, and there is clinical evidence of anal sphincter spasm and high anal sphincter pressures on manometry.[28] Calcium channel blockers therapy is effective with restoration of quality of life.[28] In this report, a total of seven patients experienced persistent pain and all initially treated with topical and oral Calcium channel blockers. This treatment was effective in four who presented a clear post-defecation syndrome. Three patients required anal exploration under anaesthesia and, along with other authors, the surgical removal of the retained staples or stitches allowed complete resolution of the pain and associated symptoms.[17] We have previously shown a significant association between longer-term pain and the presence of transitional epithelium in the specimen.[29] Moreover, some authors have indicated that inclusion of smooth muscle in the excised doughnut may be related to the subsequent development of pain, despite clear data are not available.[9] Mlakar et al. suggested that severe longer-term pain may be related to haemostatic stitches at the staple line close to the dentate line.[9] It can be speculated that the metallic staples may act as ongoing inflammatory stimulus responsible for longer term pain.[30] Accurate placement of the staple line is mandatory in order to avoid internal anal sphincter and anodermal tissue involvement.[14]

Tenesmus, frequency and faecal urgency are variably associated and reported between 5% and 40% and are usually transient and self-limiting.[8–11] These symptoms were observed in about 14.5% of our patients, but both tenesmus and urgency were the most frequent complications in the referred group.

According to other authors, we believe that they may arise because of tissue oedema and thrombosis as well as disruption of the anatomy and function of the normal anal cushions as follow-up examination usually do not demonstrate any abnormality such as low placement of the staple line or damage to the dentate line and are usually transitory. However, the reduced rectal capacity may explain frequency and urgency increase as well as tenesmus as observed by Pescatori and Chetham.[12,17]

We observed a high rate of residual and recurrent haemorrhoids (6.3%). Shalaby and Desoky reported a 1% recurrent prolapse, but this study included also patients with second degree haemorrhoids.[2,8,13,19] Conversely, Ganio et al. reported a 20% recurrent prolapse after a telephone follow-up on 50 patients who underwent SH.[2] All our recurrences occurred in patients with fourth degree haemorrhoids. Similarly, Ortiz et al. reported more frequent recurrence in fourth degree haemorrhoids compared to third degree.[31] In our experience, recurrence rate after CH is less than 2% (five out 315 patients) for similar follow up of SH without differences between third degree (three patients out of 196) and fourth degree (two patients out of 119) haemorrhoids. These findings persuaded us to believe that fourth degree haemorrhoids may not represent an appropriate indication for SH, as the success of the operation depends entirely on the resection and reduction of the prolapse by the staple.

In conclusion, the risk of severe life-threatening complications and frequent recurrences explain the reduced use of this technique to treat haemorrhoidal disease. Longer-term and larger studies are needed to further clarify its indications. Meanwhile, abuses should be minimised to reduce unusual and challenging complications.

References

1. Roswell M, Bello M, Hemingway DM. Circumferential mucosectomy versus conventional haemorrhoidectomy: Randomised controlled trial. Lancet 2000;355:779–781. doi:10.1016/S0140-6736(99)06122-X.
2. Ganio E, Altomare DF, Gabrielli F, Milito G, Canuti S. Prospective randomized multicentre trial comparing stapled and open haemorrhoidectomy. Br J Surg 2002;88:669–674. doi:10.1046/j.0007-1323.2001.01772.x.
3. Slawik S, Kenefick N, Greenslade L, Dixon AR. A prospective evaluation of stapled haemorrhoidopexy/rectal mucosectomy in the management of 3rd and 4th degree haemorrhoids. Colorectal Dis 2006;9:352–356. doi:10.1111/j.1463-1318.2006.01163.x.
4. Finco C, Sarzo G, Savastano S, Degregori S, Merigliano S. Stapled haemorrhoidopexy in fourth degree haemorrhoidal prolapse: is it worthwhile? Colorectal Dis 2005;8:130–134. doi:10.1111/j.1463-1318.2005.00912.x.
5. McCloud JM, Jameson JS, Scott ND. Life-threating sepsis following treatment for haemorrhoids: A systematic review. Colorectal Dis 2006;8:748–755. doi:10.1111/j.1463-1318.2006.01028.x.
6. Longo A. Treatment of haemorrhoids disease by reduction of mucosa and haemorrhoidal prolapse with a circular suturing device: a new procedure. Proceedings of the 6th World Congress of Endoscopic Surgery, Rome, 1998; 777–784.

7. George BD, Shetty D, Lindsey I, Mortensen NJ, Warren BF. Histopathology of stapled haemorrhoidectomy specimens: A cautionary note. Colorectal Dis 2001;4:473–476. doi:10.1046/j.1463-1318.2002.00381.x.
8. Kanellos I, Zacharakis E, Kanellos D, Pramateftakis MG, Tsachalis T, Betsis D. Long-term results after stapled haemorrhoidopexy for third-degree haemorrhoids. Tech Coloproctol 2006;10:47–49. doi:10.1007/s10151-006-0250-9.
9. Mlakar B, Kosorok P. Complications and results after stapled haemorrhoidopexy as a day surgical procedure. Tech Coloproctol 2003;7:164–168. doi:10.1007/s10151-003-0029-1.
10. Brusciano L, Ayabaca SM, Pescatori M et al. Reinterventions after complicated or failed stapled haemorrhoidopexy. Dis Colon Rectum 2004;47:1846–1851. doi:10.1007/s10350-004-0721-x.
11. McDonald PJ, Bona R, Cohen CRG. Rectovaginal fistula after stapled haemorrhoidopexy. Colorectal Dis 2004;6:64–65. letter.
12. Cheetham MJ, Mortensen NJ, Nystrom PO, Kamm MA, Philips RKS. Persistent pain and fecal urgency after stapled haemorroidectomy. Lancet 2000;26:730–733. doi:10.1016/S0140-6736(00)02632-5.
13. Ho YH, Seow-Cohen F, Tsang C, Eu KW. Randomized trial assessing anal sphincter injuries after stapled haemorrhoidectomy. Br J Surg 2001;88:1449–1455. doi:10.1046/j.0007-1323.2001.01899.x.
14. Oughriss M, Yver R, Faucheron JL. Complications of stapled haemorrhoidectomy: a french multicentric study. Gastroenterol Clin Biol 2005;29:429–433. doi:10.1016/S0399-8320(05)80798-5.
15. Blouhos K, Vasiliadis K, Tsalis K, Botsios D, Vrakas X. Uncontrollable intra-abdominal bleeding necessitating low anterior resection of the rectum after stapled haemorrhoidopexy: Report of a case. Surg Today 2007;37(3):254–257. doi:10.1007/s00595-006-3363-x.
16. Nisar PJ, Acheson AG, Neal KR, Scholefield JH. Stapled haemorrhoidopexy compared with conventional haemorrhoidectomy: Systematic review of randomized, controlled trials. Dis Colon Rectum 2004;47(11):1837–1845. Reviewdoi:10.1007/s10350-004-0679-8.
17. Pescatori M, Aigner F. Stapled transanal rectal mucosectomy ten years after. Tech Coloproctol 2007;11(1):1–6. doi:10.1007/s10151-007-0318-1.
18. Corman ML, Gravié JF, Hager T, Loudon MA, Mascagni D, Nyström PO, Seow-Choen F, Abcarian H, Marcello P, Weiss E, Longo A. Stapled haemorrhoidopexy: A consensus position paper by an international working party—indications, contra-indications and technique. Colorectal Dis 2003;5(4):304–310. Jul.
19. Ripetti V, Caricato M, Arullani A. Rectal perforation, retropneumoperitoneum, and pneumomediastinum after stapling procedure for prolapsed haemorrhoids: Report of a case and subsequent considerations. Dis Colon Rectum 2002;45(2):268–270. Review, Feb.
20. Filingeri V, Gravante G. Pneumoretroperitoneum, pneumomediastinum and subcutaneous emphysema of the neck after stapled haemorrhoidopexy. Tech Coloproctol. 2005;9(1):86. Apr.
21. Roos P. Haemorrhoid surgery revised. Lancet 2000;355(9215):1648. May 6.
22. Angelone G, Giardiello C, Prota C. Stapled haemorrhoidopexy. Complications and 2-year follow-up. Chir Ital 2006;58(6):753–760. Nov–Dec.
23. Brown S, Baraza W, Shorthouse A. Total rectal lumen obliteration after stapled haemorrhoidopexy: a cautionary tale. Tech Coloproctol 2007; Nov 30
24. Cipriani S, Pescatori M. Acute rectal obstruction after PPH stapled haemorrhoidectomy. Colorectal Dis 2002;4(5):367–370. Sep.
25. Vasudevan SP, Mustafa el A, Gadhvi VM, Jhaldiyal P, Saharay M. Acute intestinal obstruction following stapled haemorrhoidopexy. Colorectal Dis 2007;9(7):668–669. Sep.
26. Pescatori M, Spyrou M, Cobellis L, Bottini C, Tessera G. The rectal pocket syndrome after stapled mucosectomy. Colorectal Dis 2006;8(9):808–811. doi:10.1111/j.1463-1318.2006.00968.x.
27. Ravo B, Amato A, Bianco V et al. Complications after stapled haemorrhoidectomy: Can they be prevented? Tech Coloproctol 2003;6:83–88. doi:10.1007/s101510200018.
28. Thaha MA, Irvine LA, Steele RJ, Campbell KL. Postdefaecation pain syndrome after circular stapled anopexy is abolished by oral nifedipine. Br J Surg 2005;92(2):208–210. doi:10.1002/bjs.4773.
29. Sileri P, Stolfi VM, Palmieri G, Mele A, Falchetti A, Di Carlo S, Gaspari AL. Stapled haemorrhoidopexy: a prospective study from pathology to clinical outcome. J Gastrointest Surg 2007;11(12):1662–1668. Epub 2007 Oct 5, Dec.
30. Filingeri V, Gravante G. Stapled haemorrhoidopexy followed by fecal urgency and tenesmus: methodological complication or surgeon's mistake? Correspondence Tech Coloproctol 2006;10:149–153. doi:10.1007/s10151-006-0271-4.
31. Ortiz H, Marzo J, Armendariz P. Randomised clinical trial of stapled haemorrhoidopexy versus conventional diathermy haemorrhoidectomy. Br J Surg 2002;89:1376–1381. doi:10.1046/j.1365-2168.2002.02237.x.

Discussion

Reinterventions for Specific Technique-Related Complications of Stapled Hemorrhoidopexy (SH): A Critical Appraisal

Susan Gearhart, M.D. (Baltimore, MD, USA): I want to thank you for providing me with the manuscript, and I enjoyed your talk. To summarize a little bit, because I think you are dealing with a couple of different groups of patients, what I have put together is that you have studied patients undergoing stapled haemorrhoidectomy for third and fourth degree haemorrhoids, and you are looking at their complications and how they were managed. There was a 16% complication rate in your own surgical haemorrhoidectomy group, and of that, about 5% of them needed reintervention. I do not quite have a handle on how successful overall you were with your reinterventions and that information could be beneficial for the manuscript. I have a few questions to ask you.

The first is related to pain. You have gone into it in more detail in your talk, and that has been very helpful. You mentioned initially in your paper that in the first 7 days, there is a slight difference but not significantly; but later on, there is more evidence of a difference in pain. That has always been true in all the papers that analysed stapled haemorrhoidectomies, and I wanted to see if you have any additional information to add to that issue.

The other issue you brought up was about the staples being retained, and I think that is an interesting phenomenon that we have not really seen elsewhere. We have not seen it in patients who have colo-anal anastomoses experiencing pain. It is a different technique, but maybe some more information regarding the height of the staple

line would be informative and maybe looking at the pathological specimens in those patients and seeing if there is more muscle involved would be beneficial.

The final question I have is, you touched a little bit about this in your talk, but in your paper, you make the statement that performing a stapled haemorrhoidectomy on fourth degree haemorrhoids would probably not be beneficial and should be avoided. Then, you discussed briefly in your talk the differences between complication rates for third and fourth degree haemorrhoids with respect to bleeding and recurrence. Do you have any information about the differences between third and fourth degree haemorrhoids with respect to pain, reoperative interventions and other parameters?

Pierpaolo Sileri, M.D. (Rome, Italy): The use of VAS score to assess postoperative pain after haemorrhoidectomy is well validated by the literature. According to the majority of the papers, the pain is less since the first postoperative day and so forth up to 14 days. In our experience, the pain is significantly reduced from postoperative days 4 to 7. We believe that some of the reported differences between papers can be the consequence of additional procedures during haemorrhoidopexy such as the removal of anal tags or the use of diathermy on external haemorrhoids or prolapsed haemorrhoids.

Dr. Gearhart: The pain issue was about long-term outcomes. That has not really always been seen in the literature. Is there any other idea? You included just your group and not the other group. Is there any reason why there should be a difference between long-term pain results?

Dr. Sileri: When a patient still suffers with severe pain after 1 year from surgery, still using painkillers, with a normal proctoscopy, a normal ultrasound, usually we offer an anal exploration under anesthesia, and at surgery the only thing we can find is the muco-mucosal anastomosis with some metallic staples within the wall and the scar and so often, we remove the staples. In our and others' experience, this results in pain relief, probably secondary to the removal of the irritant stimulus. Regarding the difference in pain after rectal resection versus stapled haemorrhoidopexy, this is probably due to the complete disconnection of all neuronal pathways present in the wall after rectal resection. On the other hand, when you perform the SH, since it should not be a full thickness resection, the myenteric plexus remains in situ, and this may be responsible for the pain if the staples remain there.

For the third question regarding third versus fourth degree, I do not think I can answer that because of the paucity of complications among our series. According to our experience, despite the insignificance, we observed an increased risk of recurrence and bleeding after haemorrhoidopexy for fourth degree haemorrhoids. This may be the consequence of a more difficult surgery secondary to voluminous piles that occupy the entire anal canal. Moreover, the bleeding risk might be increased due to the trauma on these voluminous piles during the introduction and removal of the dilator. So, in order to better understand if fourth degree haemorrhoids are a good indication for haemorrhoidopexy, more longer-term and larger studies are needed.

J Gastrointest Surg (2008) 12:1874–1879
DOI 10.1007/s11605-008-0559-y

Value of Bronchoscopy after EUS in the Preoperative Assessment of Patients with Esophageal Cancer at or Above the Carina

Jikke M. T. Omloo · Mark van Heijl · Jacques J. G. H. M. Bergman · Mia G. J. Koolen · Mark I. van Berge Henegouwen · J. Jan B. van Lanschot

Received: 13 March 2008 / Accepted: 2 May 2008 / Published online: 5 June 2008

Abstract
Introduction Esophageal cancer is an aggressive disease with a strong tendency to infiltrate into surrounding structures. The aim of the present study is to determine the additional value of bronchoscopy for detecting invasion of the tracheobronchial tree after endoscopic ultrasonography (EUS) in the preoperative assessment of patients with esophageal cancer at or above the carina.
Materials and Methods Between January 1997 and December 2006, 104 patients were analyzed for histologically proven esophageal cancer at or above the carina. All patients underwent both EUS and bronchoscopy (with biopsy on indication) in the preoperative assessment of local resectability.
Results and Discussion After extensive diagnostic workup, 58 of 104 patients (56%) were eligible for potentially curative esophagectomy; nine of these 58 patients (9/58, 15%) appeared to be incurable peroperatively because of ingrowth in the tracheobronchial tree (five patients), ingrowth in other vital structures (two patients) or distant metastases (two patients). Of the 46 non-operable patients, local irresectability (T-stage 4) was identified in 26 patients (26/46, 57%) due to invasion of vital structures on EUS: invasion of the aorta in six patients, invasion of the lung in 11 patients; in 12 patients invasion of the tracheobronchial tree was described, which was confirmed by bronchoscopy in only five patients. No patients with T4 were identified by bronchoscopy alone.
Conclusion For patients with esophageal tumors at or above the carina, no additional value of bronchoscopy (with biopsy on indication) to exclude invasion of the tracheobronchial tree was seen after EUS in a specialized centre. Although based on relatively small numbers, we conclude that bronchoscopy is not indicated if no invasion of the airways is identified on EUS.

Presented at: NVGE/NVGIC (Dutch Society of Gastrointestinal Surgery), October 2007, Veldhoven the Netherlands (oral presentation); United European Gastroenterology Week, October 2007, Paris, France (poster presentation); European Society of Esophagology, September 2007, Dublin, Ireland (poster presentation).

Sources of financial support: JMT Omloo is supported by a grant from Zon Mw Health Care Efficiency Research (945-04-510).

J. M. T. Omloo (✉) · M. van Heijl · M. I. van Berge Henegouwen · J. J. B. van Lanschot
Department of Surgery, Academic Medical Center, University of Amsterdam,
Meibergdreef 9,
1105 AZ Amsterdam, The Netherlands
e-mail: j.m.omloo@amc.uva.nl

J. J. G. H. M. Bergman
Department of Gastroenterology, Academic Medical Centre, University of Amsterdam,
Amsterdam, The Netherlands

M. G. J. Koolen
Department of Pulmonary Diseases, Academic Medical Centre, University of Amsterdam,
Amsterdam, The Netherlands

Present address:
J. J. B. van Lanschot
Department of Surgery, Erasmus Medical Centre,
Rotterdam, The Netherlands

Keywords Esophageal cancer · Bronchoscopy · Endoscopic ultrasonography · Staging

Introduction

Esophageal cancer is an aggressive disease with early lymphatic and hematogeneous dissemination, and a strong tendency to infiltrate into surrounding structures. Despite many improvements in diagnostic and therapeutic strategies, the prognosis is still unfavorable.[1–4]

The proximal part of the intrathoracic esophagus is located between the trachea and the vertebral column. Therefore, esophageal tumors at or above the carina tend to invade the tracheobronchial tree, precluding curative surgery. To assess local resectability endoscopic ultrasonography (EUS) is generally considered the most accurate modality as it is able to visualize distinct esophageal wall layers with an accuracy of more than 90%.[5] Because of the great therapeutic consequences of tracheobronchial ingrowth, the preoperative workup of the patients with these proximal tumors frequently also includes bronchoscopy (with biopsy on indication) to exclude airway invasion.[6,7] The usefulness of bronchoscopy in patients with proximal tumors has been investigated extensively, although not in relation to the accuracy of EUS to determine involvement of the airways.[8,9]

Therefore, the aim of the present study was to determine the additional value of preoperative bronchoscopy (with biopsy on indication) for detecting invasion of the tracheobronchial tree after having performed EUS in a specialized centre.

Patients and Methods

Patients

Patients visiting the outpatient clinic of our hospital for newly diagnosed esophageal cancer between January 1997 and December 2006 were included in this analysis. Eligible patients had histologically proven cancer of the upper and/or middle thoracic esophagus. Patients were excluded if EUS or bronchoscopy was not performed and in case of subcarinal localization of the esophageal tumor.

Endoscopic Ultrasonography

A radial scanner (GF-UM130 or GF-UM160, 5–20 MHz, Olympus Medical Systems, Tokyo, Japan) was used for EUS. In case of a stenotic tumor that did not allow passage of the standard echo-endoscope, a small-caliber probe (Mh-908, 7.5 MHz, Olympus Medical Systems, Tokyo, Japan) was used in an attempt to traverse the tumor. EUS was performed with the patient in a left decubitus position under conscious sedation using 2.5–10 mg midazolam intravenously. All investigations were performed by or supervised by a gastroenterologist experienced in EUS.

A lesion was considered to invade the trachea on EUS if endosonographically the hyper-echoic interphase of the esophagus and trachea was interrupted. Close approximation of the tumor without such interruption was still considered compatible with T3 stage.

Bronchoscopy

Bronchoscopy was performed using a flexible videobronchoscope (BF-P160, Olympus Optical, Tokyo, Japan) via a transnasal approach after premedication with 2% lidocaine spray in nose and throat (up to 50 ml). During the examination 2% lidocaine spray was administered into the trachea and bronchi via the bronschoscope. No systemic medication was used. All investigations were performed by an experienced pulmonary physician. The complete tracheobronchial tree was inspected; laryngeal structures were included in the examination. All direct tumor signs (especially intraluminal growth and mucosal break) and indirect tumor signs (especially mobility of pars membranacea during coughing, bulging/compression) were recorded. Mucosal brushing or biopsies were performed only if mucosal abnormalities were suspected.

No bronchoalveolar lavage was performed; however, rinsing fluid from brushing or biopsies was sent for cytologic examination.

Other Investigations

Computed tomography (CT) of the chest and abdomen and external ultrasonography of the neck were also performed in all patients to exclude distant metastases.

Endoscopic ultrasonography, CT, and external ultrasonography of the neck were performed in a random order; however, bronchoscopy was always performed after EUS. The bronschoscopist was aware of the other clinical data. If EUS showed a T3 tumor, while a T4 tumor was suspected on CT, EUS was used to determine the final T stage. All investigations were performed before any form of therapy was started.

Neoadjuvant Therapy

Due to the time span of this study, different neoadjuvant regimens were applied. In the first period, patients with squamous cell carcinoma received neoadjuvant chemotherapy consisting of two or four cycles of cisplatin and etoposide (depending on the tumor regression on CT after two cycles). In later years, patients received neoadjuvant chemoradiotherapy (five cycles of paclitaxel and carbopla-

tin with concurrent radiation of 41.4 Gy) as part of a randomized clinical trial comparing surgery alone versus neoadjuvant chemoradiotherapy and surgery for squamous cell carcinoma and adenocarcinoma.

Surgical Resection

Because of the high localization of the tumor, in all patients who were considered eligible for potentially curative surgery, an esophagectomy was performed via the extended transthoracic approach with two field lymphadenectomy. A gastric tube was constructed and esophagogastrostomy was performed in the neck without cervical lymphadenectomy.

Tumor extent and airway invasion were assessed intraoperatively. If distant metastases and/or local irresectability due to invasion of vital structures was encountered, resection was abandoned.

Statistical Analysis

Tracheobronchial invasion on EUS, bronchoscopy (with positive biopsy results) and/or during operation was considered the gold standard for the presence of tracheobronchial invasion. No tracheobronchial invasion on EUS and/or bronchoscopy was considered as false negative if local irresectability was encountered during operation.

Results

Clinicopathological Characteristics

Between January 1997 and December 2006, a total of 106 patients presented at our outpatient clinic for analysis of a newly diagnosed histologically proven, esophageal malignancy at or above the carina. Two patients were excluded as EUS was not performed. The clinicopathological characteristics of all 104 patients are summarized in Table 1. The majority of patients were male (64 patients, 62%) and the mean age was 61 years (range 32–85 years). Histology showed squamous cell carcinoma in 93 patients (89%) and adenocarcinoma in 11 patients (11%). Tumors were mainly localized in the middle thoracic part of the esophagus (75 patients, 72%). A total of 98 patients (94%) were referred from another hospital. In total, 24 patients (23%) received neoadjuvant chemotherapy and six patients (6%) received neoadjuvant chemoradiotherapy (of whom one patient was with adenocarcinoma). A complete surgical resection was performed in 49 patients (47%), whereas in nine patients (9%) resection was abandoned as local irresectability or distant metastases were encountered peroperatively. In 46 patients (44%), the treatment was primarily palliative.

Table 1 Clinicopathological Characteristics of 104 Patients Visiting the Outpatient Clinic for Newly Diagnosed Histologically Proven Esophageal Cancer at or Above the Carina between January 1997 and December 2006

	Number of patients (n=104)
Gender	
M/F	64/40 (62%/38%)
Age	
Mean (range) [years]	61 (32–85)
Histology	
Squamous cell carcinoma	93 (89%)
Adenocarcinoma	11 (11%)
Tumor localization	
Cervical esophagus	7 (7%)
Upper thoracic esophagus	22 (21%)
Middle thoracic esophagus	75 (72%)
Referral	
From other hospital	98 (94%)
Therapy	
Preoperative chemotherapy[a]	24 (23%)
Preoperative chemoradiation[b]	6 (6%)
Surgical resection	49 (47%)
Surgical exploration	9 (9%)
Primarily palliative treatment	46 (44%)

M male, *F* female
[a] Two–four cycles of Cisplatin and Etoposide
[b] Five cycles of paclitaxel and carboplatin with concurrent 41.4-Gy radiation

Staging and Treatment

Endoscopic ultrasonography described T-stages 1 to 3 in 78 patients (78/104, 75%; Table 2, Fig. 1). EUS described local irresectability due to: invasion of the tracheobronchial tree in 12 patients (12/104, 12%), invasion of the aorta in six patients (6/104, 6%), invasion of the lung in 11 patients (11/104, 11%). In four patients invasion of multiple structures was seen: in two patients invasion of the aorta and the lung; in one patient invasion of the tracheobronchial tree and the lung; in one patient invasion of the tracheobronchial tree, the aorta, and the lung.

Bronchoscopy showed a fixed pars membranacea in five patients (5/104, 5%), bulging in 36 patients (36/104, 35%), and true invasion of the tracheobronchial mucosa (with positive biopsies) in only five of the patients (5/104, 5%). In five patients, more than one indirect and/or direct sign was seen; in three patients bulging and invasion, in one patient a fixed pars membranacea and bulging, and in one patient a fixed pars membranacea and bulging and invasion was seen.

Distant metastases were found in 12 patients (12/104, 12%). Eight patients were not suitable for surgery due to a poor general health condition (8/104, 8%).

Table 2 Staging and Treatment of 104 Patients Visiting the Outpatient Clinic for Newly Diagnosed Histologically Proven Esophageal Cancer at or Above the Carina between January 1997 and December 2006

	Number of patients (n=104)
EUS	
T1–3	78 (75%)
T4	26 (25%)
Invasion tracheobronchial tree[a]	12 (12%)
Invasion aorta[a]	6 (6%)
Invasion lung[a]	11 (11%)
Other[b]	2 (2%)
Bronchoscopy[c]	
Fixed pars membranacea	5 (5%)
Bulging	36 (35%)
Invasion tracheobronchial tree[d]	5 (5%)
Other contraindications for surgery	
Distant metastases	12 (12%)
Poor general health	8 (8%)
Treatment	
Potentially curative	58 (56%)
Primarily palliative	46 (44%)
Peroperative findings (n = 58)	
Surgical resection	49 (84%)
Surgical exploration/no resection	9 (15%)
Invasion tracheobronchial tree	5 (8%)
Invasion other vital structures	2 (3%)
Distant metastases	2 (3%)

EUS endoscopic ultrasonography

[a] In four patients invasion of multiple structures was seen; in two patients invasion of aorta and lung, in one patient invasion of tracheobronchial tree and lung and in one patient invasion of all three sites was seen

[b] Other: invasion of right carotic artery in one patient, invasion of pericardium in one patient

[c] In five patients more than one indirect and/or direct sign was seen; in three patients bulging and invasion, in one patient fixed pars membranacea and bulging, and in one patient all three signs were seen

[d] Cyto- and/or histologically proven

After completion of the staging procedures, 58 patients were found suitable for potentially curative surgery (56%). In nine patients (9/58, 15%) resection was abandoned peroperatively because of: invasion of the tracheobronchial tree (five patients, 5/58, 8%), invasion of other vital structures (two patients, 2/58, 3%) and distant metastases (two patients, 2/58, 3%). Time between analysis and surgery did not differ between patients undergoing resection and in patients found to be irresectable peroperatively (median 2.9 months and 2.6 months, respectively).

Additional Value of Bronchoscopy

Indirect signs were seen on bronchoscopy in 40 patients (40/104, 38%). Invasion of the tracheobronchial tree was diagnosed or encountered during operation in 17 patients (17/104, 16%) (Table 3). Indirect signs were seen during bronchoscopy in 29% of the patients (25/87) without invasion of the tracheobronchial tree (false positives), and no indirect signs were seen in 12% of the patients (2/17) with invasion of the tracheobronchial tree (false negatives). This results in a sensitivity of 88% and a specificity of 71% of indirect signs seen on bronchoscopy reflecting invasion of the tracheobronchial tree.

Discussion

Preoperative staging in patients with esophageal cancer is an extensive diagnostic process. To detect incurable patients before surgery, various modalities are being used. Invasion of the airways is common in tumors located at or above the carina. Invasion of the tracheobronchial tree can be assessed by different diagnostic modalities, especially CT, magnetic resonance imaging (MRI), EUS, and bronchoscopy. In the literature, CT and MRI both show low accuracy compared to EUS to determine T stage (45% and 60%, respectively).[10,11] Therefore, it was investigated in the present study whether performing bronchoscopy after EUS has any additional value. In this study, bronchoscopy did not detect any patients with airway invasion that was not already detected by EUS. Remarkably, five patients (5/58, 8%) were found to have airway invasion during surgery, which had been missed by both EUS and bronchoscopy.

Bronchoscopy is capable of directly detecting airway invasion if the tumor has breached the epithelium. If a wider definition of invasion would be used and indirect signs (esp. bulging and a fixed pars membranacea) would also be taken into account, the value of bronchoscopy might possibly rise. Baisi et al. evaluated invasion of the tracheobronchial tree in 91 patients with esophageal cancer by bronchoscopy.[12] They concluded that compression of the tracheobronchial tree (bulging) does not necessarily indicate infiltration by the esophageal tumor; however, if also a fixed pars membranacea is seen, there is a frank infiltration, making radical resection highly unlikely. Riedel et al. have investigated 116 patients with bronchoscopy.[13] Remarkably, they found microscopic proof of invasion in only 4% of patients showing indirect signs on bronchoscopy, whereas the remaining 96% of the patients underwent a radical resection. If in the present study, indirect signs were used as well, an unnecessary surgical exploration would have been prevented in two patients (12%). However, 25 patients (29%) would have been wrongly diagnosed with irresectable cancer.

Endoscopic ultrasonography via the esophagus examines the airways from an opposite angle, making it possible to detect airway invasion without a mucosal break, i.e. in an earlier stage. This fundamental difference could explain

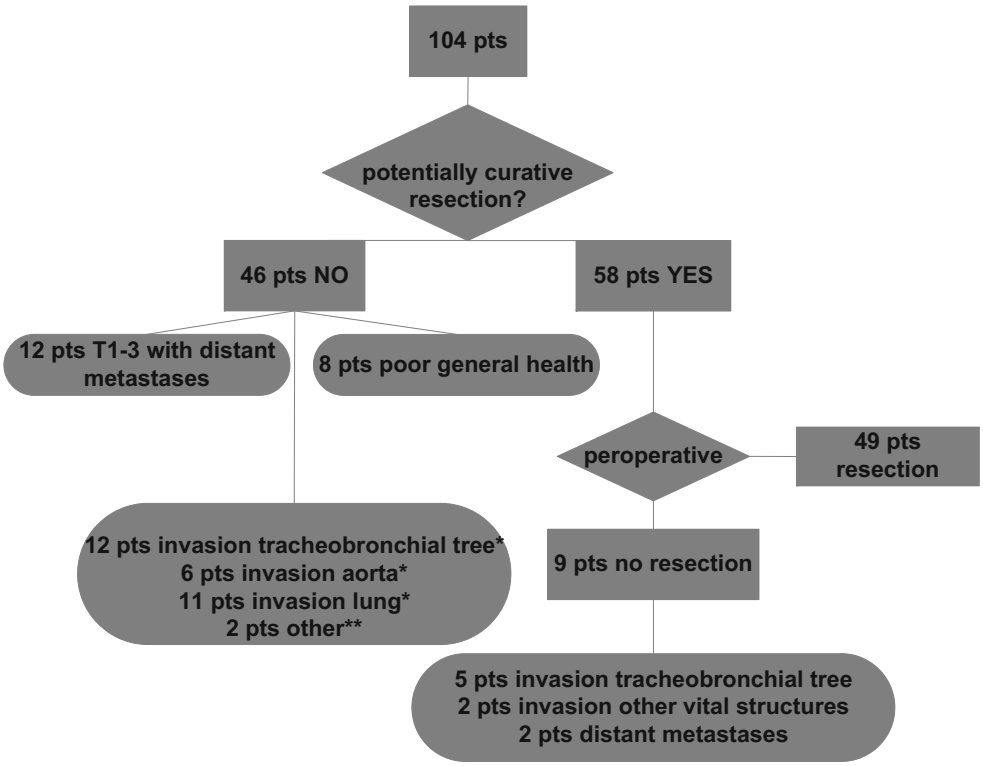

Figure 1 Flowchart of 104 patients visiting the outpatient clinic for newly diagnosed histologically proven esophageal cancer at or above the carina between January 1997 and December 2006. *pts* patients, *NO* not potentially curable, *YES* potentially curable. *Asterisk*: In four patients invasion of multiple structures was seen; in two patients invasion of the aorta and the lung, in one patient invasion of the tracheobronchial tree and the lung, and in one patient invasion of the tracheobronchial tree, the aorta, and the lung was seen. *Two asterisks*, *other*: invasion of the right carotid artery in one patient, invasion of the pericardium and multiple metastatic lymph nodes in the neck, mediastinum, and abdomen in one patient.

why EUS detects more patients with airway invasion compared with bronchoscopy. It should be realized, that EUS uses indirect signs as well in order to describe the T-stage and thus it is very much operator- and experience-dependent. Fockens et al. have described the prognosis of patients diagnosed with irresectable (T4) tumors on EUS, and found that these patients have a very poor prognosis, regardless of further therapy (including potentially curative surgery).[14] In their analysis, 24 of 51 patients (47%) underwent explorative surgery (despite EUS T-stage 4); however, only 13 underwent a surgical resection, and in only three of these patients the resection was microscopically radical.

Table 3 Presence of Indirect Signs on Bronchoscopy of All 104 Patients

	Number of patients (n=104)	
	Invasion tracheobronchial tree	
	Present	Absent
Indirect signs on bronchoscopy		
Present	15	25
Absent	2	62
Total	17	87

"Indirect signs" implies a fixed pars membranacea, bulging and/or invasion of the tracheobronchial tree (cyto-/histologically proven). "Invasion tracheobronchial tree" implies tracheobronchial invasion on EUS, bronchoscopy (with positive biopsy results) and/or encountered during operation

In the present study, bronchoscopic ultrasonography was not addressed. To our knowledge, only one study has compared esophageal ultrasonography, conventional bronchoscopy, and bronchoscopic ultrasonography for detecting airway invasion.[15] Unfortunately, only 44% of the patients underwent esophageal ultrasonography due to stenosis. This study found accuracy rates for invasion of the airways of 91% with bronchoscopic ultrasonography, 78% with conventional bronchoscopy, and 85% with esophageal ultrasonography. The authors conclude that bronchoscopic ultrasonography is a safe and promising technique to determine local resectability. However, it should be taken into account that (bronchoscopic) ultrasonography is an invasive modality and the burden for the patient is relatively high.[16–18]

There are some limitations to the present study. The total number of patients is relatively small. Moreover, the percentage of patients in whom airway invasion was not detected until surgical exploration is relatively high. Time between analysis and surgery was not significantly longer compared with the patients who underwent resection.

In conclusion, bronchoscopy has no additional value in this study as a standard diagnostic modality for staging of patients with esophageal cancer at or above the carina after EUS in a specialized centre. Although based on small numbers, we

conclude that bronchoscopy is not indicated if no invasion of the airways is identified on EUS. However, bronchoscopy (if possible in combination with bronchoscopic ultrasonography) should be performed if because of esophageal stenosis EUS is not feasible. If irresectability is identified during operation, bronchoscopy should rule out direct tumor invasion of the mucosa before radiotherapy is started, to prevent the development of a tracheo-esophageal fistula.

References

1. Burmeister BH, Smithers BM, Gebski V et al. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: A randomised controlled phase III trial. Lancet Oncol 2005;6:659–668.
2. Hulscher JB, van Sandick JW, de Boer AG et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med 2002;347:1662–1669.
3. Lerut T, Coosemans W, Decker G et al. Cancer of the esophagus and gastro-esophageal junction: Potentially curative therapies. Surg Oncol 2001;10:113–122.
4. van Meerten E, Muller K, Tilanus HW et al. Neoadjuvant concurrent chemoradiation with weekly paclitaxel and carboplatin for patients with oesophageal cancer: A phase II study. Br J Cancer 2006;94:1389–1394.
5. Lightdale CJ, Kulkarni KG. Role of endoscopic ultrasonography in the staging and follow-up of esophageal cancer. J Clin Oncol 2005;23:4483–4489.
6. Allum WH, Griffin SM, Watson A, Colin-Jones D. Guidelines for the management of oesophageal and gastric cancer. Gut 2002;50 (Suppl 5):v1–v23.
7. Siersema PD, Rosenbrand CJ, Bergman JJ et al. Guideline 'Diagnosis and treatment of oesophageal carcinoma'. Ned Tijdschr Geneeskd 2006;150:1877–1882.
8. Baisi A, Bonavina L, Peracchia A. Bronchoscopic staging of squamous cell carcinoma of the upper thoracic esophagus. Arch Surg 1999;134:140–143.
9. Riedel M, Stein HJ, Mounyam L et al. Predictors of tracheobronchial invasion of suprabifurcal oesophageal cancer. Respiration 2000;67:630–637.
10. Marsman WA, Fockens P. State of the art lecture: EUS for esophageal tumors. Endoscopy 2006;38(Suppl 1):S17–S21.
11. Wu LF, Wang BZ, Feng JL et al. Preoperative TN staging of esophageal cancer: Comparison of miniprobe ultrasonography, spiral CT and MRI. World J Gastroenterol 2003;9:219–224.
12. Baisi A, Bonavina L, Peracchia A. Bronchoscopic staging of squamous cell carcinoma of the upper thoracic esophagus. Arch Surg 1999;134:140–143.
13. Riedel M, Hauck RW, Stein HJ et al. Preoperative bronchoscopic assessment of airway invasion by esophageal cancer: A prospective study. Chest 1998;113:687–695.
14. Fockens P, Kisman K, Merkus MP et al. The prognosis of esophageal carcinoma staged irresectable (T4) by endosonography. J Am Coll Surg 1998;186:17–23.
15. Nishimura Y, Osugi H, Inoue K et al. Bronchoscopic ultrasonography in the diagnosis of tracheobronchial invasion of esophageal cancer. J Ultrasound Med 2002;21:49–58.
16. Osugi H, Nishimura Y, Takemura M et al. Bronchoscopic ultrasonography for staging supracarinal esophageal squamous cell carcinoma: Impact on outcome. World J Surg 2003;27:590–594.
17. Wakamatsu T, Tsushima K, Yasuo M et al. Usefulness of preoperative endobronchial ultrasound for airway invasion around the trachea: Esophageal cancer and thyroid cancer. Respiration 2006;73:651–657.
18. Becker HD. EBUS: A new dimension in bronchoscopy. Of sounds and images—a paradigm of innovation. Respiration 2006;73:583–586.

J Gastrointest Surg (2008) 12:1880–1887
DOI 10.1007/s11605-008-0607-7

The Integrity of Esophagogastric Junction Anatomy in Patients with Isolated Laryngopharyngeal Reflux Symptoms

Kyle A. Perry · C. Kristian Enestvedt · Cedric S. F. Lorenzo · Paul Schipper · Joshua Schindler · Cynthia D. Morris · Katie Nason · James D. Luketich · John G. Hunter · Blair A. Jobe

Received: 22 April 2008 / Accepted: 8 July 2008 / Published online: 2 August 2008

Abstract
Background Distortion of esophagogastric junction anatomy in patients with gastroesophageal reflux disease produces permanent dilation of the gastric cardia proportional to disease severity, but it remains unclear whether this mechanism underlies reflux in patients with isolated laryngopharyngeal reflux symptoms.
Method In a prospective study, 113 patients were stratified into three populations based on symptom complex: laryngopharyngeal reflux symptoms, typical reflux symptoms, and both laryngopharyngeal and typical symptoms. Subjects underwent small-caliber upper endoscopy in the upright position. Outcome measures included gastric cardia circumference, presence and size of hiatal hernia, and prevalence of esophagitis and Barrett's esophagus within each group.
Results There were no differences in gastric cardia circumference between patient groups. The prevalence of Barrett's esophagus was 20.4% overall and 15.6% in pure laryngopharyngeal reflux patients. Barrett's esophagus patients had a greater cardia circumference compared to those without it. In the upright position, patients with isolated laryngopharyngeal reflux display the same degree of esophagogastric junction distortion as those with typical reflux symptoms, suggesting a similar pathophysiology.
Conclusion This indicates that, although these patients may sense reflux differently, they have similar risks as patients with typical symptoms. Further, the identification of Barrett's esophagus in the absence of typical reflux symptoms suggests the potential for occult disease progression and late discovery of cancer.

Funding: This work was supported in part by NIH grants UL1 RR024140 and K23 DK066165 (BAJ)

K. A. Perry · C. K. Enestvedt · C. S. F. Lorenzo · P. Schipper · J. G. Hunter
Department of Surgery, Oregon Health & Science University, Portland, OR, USA

J. Schindler
Department of Otolaryngology, Oregon Health & Science University, Portland, OR, USA

C. D. Morris
Department of Medical Informatics and Clinical Epidemiology, Oregon Health & Science University, Portland, OR, USA

K. Nason · J. D. Luketich · B. A. Jobe
Division of Thoracic and Foregut Surgery, University of Pittsburgh, Pittsburgh, PA, USA

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

Keywords Gastroesophageal reflux · Laryngopharyngeal reflux · Gastric cardia circumference · Extraesophageal symptoms

Introduction

Laryngopharyngeal reflux (LPR) is a common condition that typically presents with symptoms of excessive throat clearing, cough, hoarseness, and globus pharyngeus.[1–3] Because laryngeal tissues are vulnerable to reflux injury and a smaller volume of refluxate is required to produce symptoms, this condition may present without typical symptoms of gastroesophageal reflux disease (GERD).[4] In addition, the perception of esophageal acid exposure may vary considerably from one patient to another, and therefore, the severity of symptoms may not correlate with disease severity.[5]

There are dangers in failing to recognize LPR, as it has been associated with significantly decreased quality of life and social functioning and increased risk of esophageal cancer.[6–8] However, the same constellation of symptoms can be produced by infection, vocal abuse, allergy, smoking, and alcohol abuse.[9] Currently, no available diagnostic test accurately identifies LPR, and difficulty in developing a sensitive and specific testing modality is complicated by an incomplete understanding of its pathogenesis.

Typical GERD symptoms are most often caused by the reflux of gastric contents through an incompetent lower esophageal sphincter (LES), due in part to the disruption and attenuation of the intragastric portion of the gastroesophageal valve.[10] This portion of the LES is formed by the collar sling musculature and clasp fibers of the distal esophagus and gastric cardia, which normally remain tonically contracted except when signaled to relax during a swallow.[11–14] Repeated episodes of proximal gastric distension lead to permanent disruption of these fibers, which manifests as anatomic distortion of the gastroesophageal junction (GEJ) with subsequent susceptibility to GERD.[15–19] Seltman et al.[20] showed that progressively increasing gastric cardia circumferences accompany increasing severity of GERD, as indicated by the stepwise progression in those with nonerosive disease; GERD; short- and long-segment Barrett's esophagus (BE); and, finally, progression to dysplasia.

Due to their propensity to reflux in the upright position, it remains unclear whether this anatomic distortion also underlies reflux in LPR patients. We theorize that endoscopic examination of the gastric cardia in patients with isolated LPR symptoms will demonstrate evidence of anatomic distortion of the LES manifesting as increased gastric cardia circumference and the presence of hiatal hernia.

Materials and Methods

Patient Selection and Stratification

Patients were selected for this study from prospectively collected data sets from two clinical trials that examined the use of unsedated, small-caliber endoscopy in the outpatient setting at Oregon Health & Science University and Portland VA Medical Center.

1. Gastroenterology Clinic. The initial data set was collected for a trial that compared unsedated small-caliber endoscopy to conventional sedated endoscopy within the context of Barrett's screening.[21] Eligible subjects from gastroenterology clinic included outpatients (≥18 years of age) scheduled for screening endoscopy for typical symptoms of GERD as part of clinical care. Typical symptoms were defined as heartburn, regurgitation, and dysphagia. Between November 2003 and February 2005, scheduled patients were approached by the study coordinator to determine eligibility and gain informed consent. At the time of endoscopy, all patients completed the validated reflux symptom index (RSI) and GERD HRQOL questionnaires, and a detailed medication history was obtained.[22,23] Four hundred and twenty six patients were assessed for eligibility, 274 patients met inclusion criteria, and 134 subjects were enrolled and underwent endoscopy.
2. Otolaryngology Clinic. Patients from the otolaryngology clinic were recruited between February 2005 and March 2007 as part of a BE prevalence study that employed unsedated small-caliber endoscopy as a screening tool. All patients with nonmalignant ENT conditions completed the RSI at the time of their initial appointment. Those patients that scored ≥2/5 on any two symptoms or ≥3/5 on any one symptom were approached for enrollment. Patients were excluded from participation if they had a history of head or neck malignancy, laryngeal trauma, laryngeal surgery, or vocal cord paralysis. A detailed medication history was obtained. At the time of endoscopy, all patients were started on twice daily proton pump inhibitor (PPI) therapy for 4 months and completed the validated RSI and GERD HRQOL questionnaires before and after PPI treatment.[22,23] Three thousand one hundred seventy individuals were assessed for eligibility; 525 patients met inclusion criteria; and 263 subjects were enrolled, underwent endoscopy, and completed the post-PPI treatment RSI. As per protocol, digital images of the gastric cardia were obtained for each subject in both trials.

For the present study, we included all subjects from these data sets who met the following criteria: (1) PPI responsive GERD or LPR symptoms; (2) completion of the entire

endoscopic examination; (3) questionnaire completion; and (4) adequate image of the gastric cardia, which enabled circumference measurement. The RSI is a nine-question, self-administered questionnaire that assesses LPR symptoms (Table 1). Symptoms are graded on a scale of 0 (no problem) to 5 (severe problem), yielding a total score of 0 to 45. Previous studies have validated this questionnaire for the assessment of LPR patients, and defined a score of 14 or higher as abnormal.[22] We used this cutoff score coupled with normalization of RSI score after 4 months of maximum dose PPI therapy to identify patients with LPR in this series.

Subjects were stratified into three study populations based on RSI responses and response to PPI therapy (Table 2). The pure LPR group (N=32) consisted of patients with an abnormal pretreatment RSI score, normalization of RSI after 4 months of PPI treatment, and no typical GERD symptoms. Patients in the typical symptom (GERD) group (N=41) were referred for evaluation of typical reflux symptoms and had documented PPI responsive disease and a normal RSI score at presentation. The mixed group (N=40) consisted of patients with an abnormal RSI coupled with typical GERD symptoms that where either improved or were dependent upon PPI therapy. The pure LPR and mixed groups were derived only from the ENT population because only these patients completed both pre- and post-PPI treatment RSI questionnaires to determine response. The typical GERD symptom population consisted of patients from both clinics (GI=26, ENT=15), as only a normal RSI at presentation and symptomatic relief with PPI treatment were required. Of the 397 patients assessed for eligibility, 195 met the inclusion criteria outlined above, with exclusions made for incomplete response to PPI treatment and abnormal RSI in GI clinic patients. Eight two patients were then excluded due to inadequate views of the gastric cardia to allow cardia circumference measurement.

Table 1 RSI Questions

Within the last month, how did the following problems affect you?
1. Hoarseness or a problem with your voice
2. Clearing your throat
3. Excess throat mucous or postnasal drip
4. Difficulty swallowing food, liquid, or pills
5. Coughing after you ate, or after lying down
6. Breathing difficulties or choking episodes
7. Troublesome or annoying cough
8. Sensation of something sticking in your throat, or a lump in your throat
9. Heartburn, chest pain, indigestion, or stomach acid coming up

Table 2 Definition of Study Populations

	RSI, pre-PPI	PPI Therapy	Typical GERD symptoms
Pure LPR (N=32)	Abnormal	Responsive	Absent
GERD (N=40)	Normal	Responsive	Present
Mixed (N=41)	Abnormal	Responsive	Present

Small-Caliber Endoscopy

Unsedated, small-caliber upper endoscopy was performed on all patients. Examinations were performed in the upright sitting position without sedation using a 4.9- or 5.1-mm-diameter flexible endoscope (Olympus, Melville, NY, USA). The preferred access to the esophagus was via the transnasal route, but transoral scope passage was performed when the endoscope could not be passed easily through either nostril. The entire esophagus and stomach were examined, and the endoscope was placed in retroflexion to obtain views of the gastric cardia. Static images of the entire cardia were obtained with the stomach insufflated so that rugal folds were effaced but discernable.

Study endpoints obtained during endoscopy included gastric cardia circumference measurement, characterization of esophagitis using the Los Angeles (LA) Classification,[24] presence and size of hiatal hernia, and biopsy-proven BE. After evaluation of the esophagus and GEJ, biopsy for suspected BE was performed when the squamocolumnar junction (SCJ) was located proximal to the anatomic GEJ in patients with ZAP classification grade I–III.[25] When indicated, biopsies for BE were obtained every 2 cm in four quadrants from the anatomic GEJ to the SCJ. Pathologic determination of BE was performed by a single pathologist using established diagnostic criteria.[26] Hiatal hernia was defined as the presence of the anatomic GEJ proximal to the crural pinch on "sniff test," and the size was measured at the nares in centimeters.

Gastric Cardia Circumference Measurement

Following endoscopy, static images of the gastric cardia were imported into a Flash (Macromedia, San Francisco, CA, USA) software program developed and validated for performing gastric cardia circumference measurements. A blinded observer performed these measurements according to the protocol developed previously.[20] Briefly, this software uses the known diameter of the endoscope to calibrate to static image and measures the circumference of the gastric cardia at the level of the anatomic GEJ. In patients with a hiatal hernia, measurements are made within the thorax, so as not to approximate the hiatal aperture rather than the circumference of the gastric cardia.

Statistical Analysis

Patient data are maintained in an Access (Microsoft, Redmond, WA, USA) database and were analyzed using SPSS software (SPSS, Chicago, IL, USA). Statistical significance was accepted with a p value less than 0.05, and results are presented as median (range) or percentage as appropriate. Gastric cardia circumferences between patient groups were compared using a one-way ANOVA. Correlation of hiatal hernia size to gastric cardia circumference was made by Pearson correlation, with subgroup comparisons using the Kruskal–Wallis test. Correlation of gastric cardia circumference with esophagitis was made by Spearman's rank-order correlation. Prevalence rates of BE in patient groups were analyzed using the Chi-square test, and the comparison of cardia circumference to the presence of biopsy-proven BE was made by t test. Comparisons of presence and degree of esophagitis were made using Chi-square and Fischer's exact test, respectively.

Results

The demographic data for each patient group are listed in Table 3. No significant differences were present in patient age, gender, race, or body mass index.

Gastric Cardia Circumference in Study Populations

The pure LPR group had a median cardia circumference of 32.7 (19.3–48.3) mm. The median cardiac circumferences for the GERD and mixed groups were 34.5 (24.3–68.3) and 35.1 (14.6–53.6) mm, respectively (Fig. 1). The gastric cardia circumference was not statistically different between these groups (p=0.347, ANOVA).

Figure 2 outlines the distribution of hiatal hernia size by patient group, and no statistically significant differences were present (p=0.404, Kruskal–Wallis). Overall, gastric cardia circumference showed a positive correlation with hiatal hernia size (r=0.219, p=0.02, Pearson's). When hiatal hernia size exceeded 2 cm, the range of cardia circumferences increased markedly.

Overall, gastric cardia circumference positively correlated with both the presence of esophagitis (r=0.199; p=0.03, Spearman's) and severity of esophagitis as indicated by LA classification (r=0.217, p=0.02, Spearman's). The three study populations did not differ in terms of presence (p=0.74, Chi-square) or severity (p=0.584, Chi-square) of esophagitis.

Cardia Circumference and BE

The overall prevalence of biopsy-proven BE in this series was 20.4%. The pure LPR group had a BE prevalence of 15.6%. BE was present in 34.1% of GERD patients and 10% of patients in the mixed group. There were no statistically significant differences in the prevalence of BE between the LPR and GERD groups (p=0.074, Chi-square) or between the LPR and mixed groups (p=0.473, Chi-square). The GERD group did have a higher rate of BE than the mixed group (p=0.009, Chi-square). Long-segment BE (>3 cm) was present in 6.3% of pure LPR patients, 9.8% of typical GERD patients, and 2.5% of mixed patients (p=0.167, Fischer's).

Overall, patients with biopsy-proven BE had a larger mean gastric cardia circumference of 39.1 mm compared with 34.2 mm in patients without pathologic evidence of intestinal metaplasia (p=0.011, t test). The differences in gastric cardia circumference between those with and without biopsy-proven BE in each of the three study populations are shown in Table 4. The mean differences in gastric cardia circumference in the LPR, GERD, and mixed groups were 4.67 (p=0.193), 5.49 (p=0.082), and 2.8 mm (p=0.515), respectively.

Discussion

This study tested the hypothesis that anatomic degradation of the LES is present in patients with known isolated LPR. This series, which utilized a conservative definition of LPR (i.e., PPI responsive LPR symptoms), shows that, in the upright position, this population has the same degree of gastric cardia dilation that is found in patients with typical GERD symptoms and those with a mixed presentation. This finding suggests that the same pathophysiologic disturbance that predisposes typical GERD patients to reflux is present in the upright patient with symptoms of LPR.

Table 3 Patient Characteristics

	LPR (N=32)	GERD (N=41)	Mixed (N=40)	p-value (test)
Age, median (range), years	64 (25–82)	61.5 (38–85)	59 (25–89)	0.203 (ANOVA)
Males, No. (%)	23 (71.9)	36 (87.8)	30 (75)	0.197 (Chi Square)
Caucasians, No. (%)	30 (93.8)	40 (97.6)	40 (100)	0.441 (Chi Square)
BMI, median (Range), kg/m^2	27.3 (18.5–35.6)	29.6 (21.6–47.4)	28 (20.3–73.8)	0.288 (ANOVA)

BMI body mass index

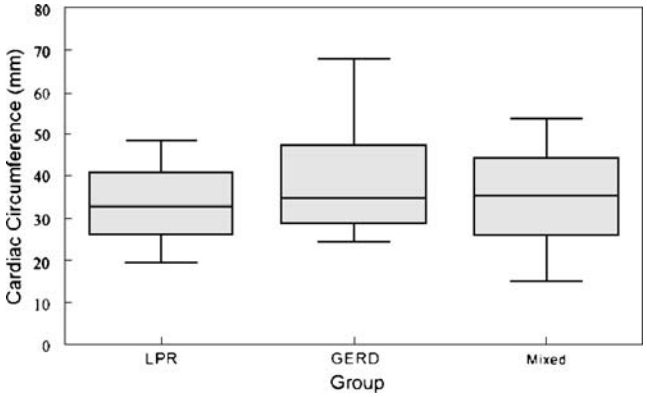

Figure 1 Gastric cardia circumference in LPR, GERD, and mixed populations. *Box*, interquartile range; *line*, median; *bars*, 95% confidence interval.

The population of patients with GERD has been defined by the Genval Working Group as "all individuals who are exposed to the risk of physical complications from gastroesophageal reflux or who experience clinically significant impairment of health-related well being (quality of life) due to reflux-related symptoms."[27] This broad definition reflects the fact that the perception of GERD is highly variable from one patient to the next. In patients with typical GERD symptoms, no frequency or constellation of symptoms can reliably predict the presence of esophagitis of BE.[5] Studies comparing groups of patients with primarily typical or atypical GERD symptoms have found significant crossover of heartburn, regurgitation, and hoarseness in these groups, suggesting that similar underlying pathophysiologies may be present in these two groups.[28]

The current belief that LPR represents a distinct pathophysiologic entity from typical GERD is based on differing patterns of reflux and acid exposure observed with conventional testing. LPR is characterized by upright daytime reflux without the degree of esophageal dysmotility and prolonged periods of acid exposure often seen with GERD.[1,29–33] It has been proposed that LPR represents a malfunction of the upper esophageal sphincter, rather than the LES, but the precise pathophysiologic mechanisms remain unclear.

The underlying pathophysiology of GERD centers around reflux of gastric contents through an incompetent LES.[10] This results from permanent distortion of the clasp and collar sling muscle fibers of the distal LES due to repeated episodes of proximal gastric distension. These changes manifest as dilation of the cardia, effacement of the angle of His, and a funnel-shaped GEJ that results in increased susceptibility to the development of hiatal hernia and GERD.[15–19] This theory is supported by the work of Hill et al., who developed a grading system for the native gastroesophageal flap valve that illustrates this anatomic distortion.[34] Two more recent studies have shown an increase in gastric cardia perimeter and circumference with increasingly severe GERD states.[16,20]

The importance of identifying and diagnosing LPR is clear because of the well documented adverse impact on quality of life and social functioning.[6,7] Subglottic stenosis can result because inflamed laryngeal tissues lack the protective mechanisms against acid reflux that are present within the esophagus.[1,35,36] Perhaps most importantly, a recent study found that extraesophageal symptoms of GERD are more common in patients with EAC than typical GERD symptoms are.[8]

The lack of defensive barriers to acid exposure in the upper aerodigestive tract has led some to postulate that a smaller volume of refluxate may be required to produce LPR symptoms and that a lesser degree of LES dysfunction may help to explain the lack of typical GERD symptoms in these patients.[4] In this series, the degree of anatomic GEJ distortion and prevalence of hiatal hernia between the LPR and typical GERD populations was not significantly different. The absolute measurements obtained in this series are difficult to interpret, however, due to the absence of a control group and differences in the technique of upper endoscopy compared to previous studies of gastric cardia circumference. The data sets from which this study population was derived did not contain a suitable group of control patients with gastric cardia circumference measurements during small-caliber endoscopy. Future prospective studies are required to determine the true normal gastric cardia circumference during small-caliber endoscopic examination in the upright position in a population of control patients with normal pH studies and absence of reflux symptoms.

Also, the previous study of gastric cardia circumference used a conventional 9.8-mm-diameter endoscope, and the procedure was performed in the left lateral decubitus

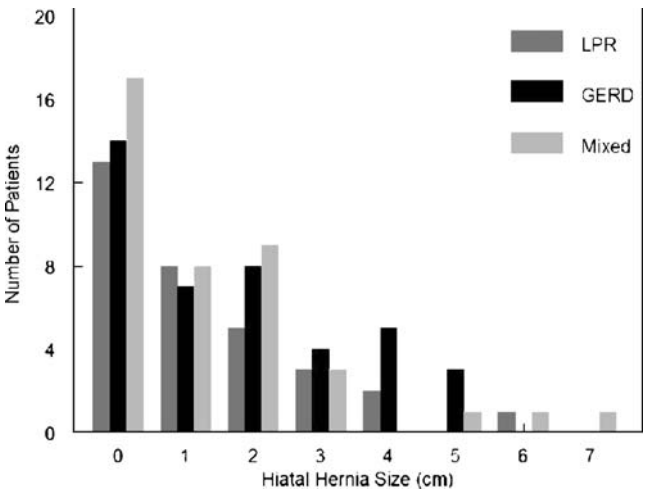

Figure 2 Hiatal hernia size distribution within study populations.

Table 4 Gastric Cardia Circumference and BE

	Overall (N=113)	LPR (N=32)	GERD (N=41)	Mixed (N=40)
BE positive mean CC, mm	39.1	37.6	40.1	37.6
BE negative mean CC, mm	34.2	32.9	34.7	34.8
Mean difference	4.95	4.67	5.49	2.8
p Value (t test)	0.011	0.193	0.082	0.515

CC Gastric cardia circumference

position. While the cardia circumference measurement software should correct for endoscope size because it uses this parameter to calibrate to the image, it is unclear whether the larger endoscope diameter (9.8 mm) used in previous studies may actually stent open the GEJ in patients without significant cardia dilation, resulting in larger median measurements. Also, conventional endoscopy is categorically performed in the left lateral decubitus position, and the effect of body position on the configuration of the GEJ in normal subjects and those with various forms of gastroesophageal reflux remains uncertain. Figure 3 shows supine (A) and upright (B) endoscopic views of the gastric cardia of a patient with LPR and isolated upright reflux on pH testing. Ongoing studies examining the gastric cardia and GEJ in the upright and supine positions during unsedated SCE will assess the role of body position in this patient population and define the normal gastric cardia circumference during SCE.

The dilation of the gastric cardia seen in early GERD is believed to represent the early changes of hiatal hernia development. As expected, we found that gastric cardia circumference increases with increasing hiatal hernia size. With larger hiatal hernias, however, the relationship to gastric cardia circumference became less predictable. This is likely because, as hiatal hernias develop, the attachments to the widening crural aperture contribute to the architecture of the GEJ, whereas, with larger hernias, the gastric cardia resides entirely within the thorax and the cardioesophageal angle is recreated in some cases.[37] Also, with larger hernias, endoscopic visualization of the cardia for the purposes of circumference measurement may become more technically challenging and less uniform.

The most compelling reason to develop a deeper understanding of LPR may be to clarify the risk of esophageal cancer in untreated cases. Reavis et al.[8] demonstrated that LPR symptoms are more commonly found in patients with esophageal adenocarcinoma than typical GERD symptoms are. In our study, most patients were recruited from an otolaryngology clinic and would likely have never been culled for screening endoscopy. Of the patients, 15.6% had biopsy-proven BE in the absence of typical GERD symptoms, and these patients had increased cardia circumference by an average of 4.67 mm compared to LPR patients without BE. The overall difference in gastric cardia circumference between patients with and without biopsy-proven BE of 4.95 mm was statistically significant (Table 4). Although the gastric cardia circumference differences in the subgroup analysis failed to reach statistical significance, the absolute differences are similar to those seen in the entire study population, suggesting the need for larger studies. Furthermore, 6.3% of the patients in the pure LPR group were found to have long-segment BE,

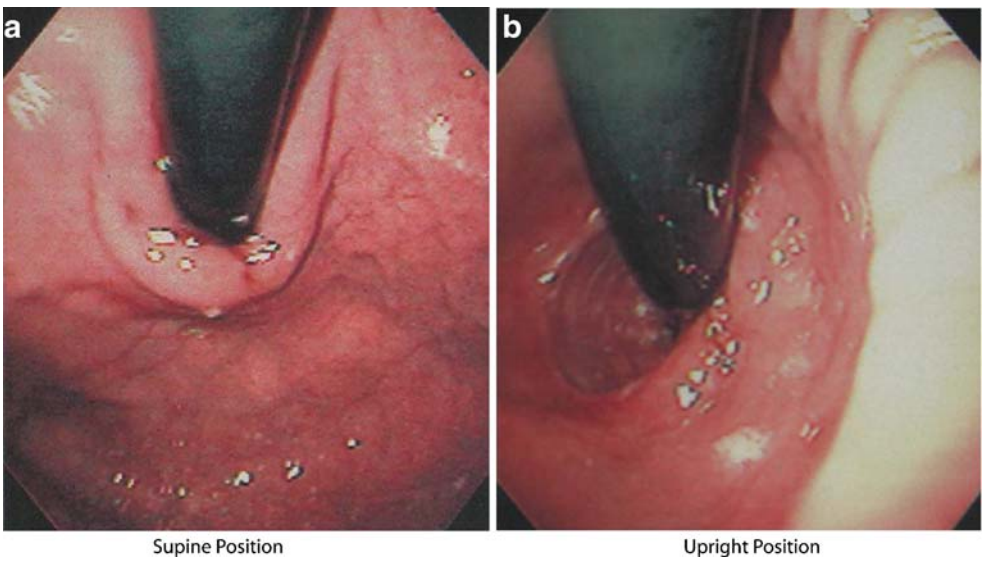

Figure 3 Effect of body position on GEJ architecture in a patient with LPR.

which is not significantly less than the prevalence of 9.8% in the typical GERD group. Taken together, these findings suggest that, while patients with BE secondary to LPR are not uncommon, they are unlikely to be identified and appropriately followed for the development of high-grade dysplasia, and thus are more likely to progress to esophageal cancer. Although this series is not large or diverse enough to comment on the prevalence of BE in the LPR population, these results do underscore the need for population-based studies and the development of accurate diagnostic tools to identify patients with LPR so that they can be screened appropriately.

Conclusion

Patients with LPR display the same degree of EGJ anatomic degradation as those with typical GERD symptoms, suggesting a similar pathophysiology. Further studies are required to quantify the normal gastric cardia circumference and to elucidate the effect of body position on GEJ architecture. These findings also indicate that, although LPR patients may sense reflux differently, they have similar risks to patients with typical symptoms. Further, the identification of BE, accompanied by increased gastric cardia diameter in the complete absence of typical GERD symptoms, suggests the potential for occult disease progression and late discovery of cancer. This study illustrates the need for larger, population-based studies of BE prevalence in the LPR population and more efficient diagnostic testing to identify patients with LPR for early BE screening.

References

1. Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. Laryngoscope 1991;101(4 pt 2 suppl 53):1–78.
2. Hopkins C, Yousaf U, Pedersen M. Acid reflux treatment for hoarseness [protocol]. Cochrane Database Syst Rev 2005; 3 Accession No. 00075320–10000000–03935.
3. Tauber S, Gross M, Issing WJ. Association of laryngopharyngeal symptoms with gastroesophageal reflux disease. Laryngoscope 2002;112:879–86. doi:10.1097/00005537–200205000–00019.
4. Koufman J, Sataloff RT, Toohill R. Laryngopharyngeal reflux: consensus conference report. J Voice 1996;10:215–6. doi:10.1016/S0892–1997(96)80001–4.
5. Avidan B, Sonnenberg A, Schnell TG, Sontag SJ. There are no reliable symptoms for erosive oesophagitis and Barrett's oesophagus: endoscopic diagnosis is still essential. Aliment Pharmacol Ther 2002;16:735–42. doi:10.1046/j.1365–2036.2002.01231.x.
6. Carrau RL, Khidr A, Crawley JA, Hillson EM, Davis JK, Pashos CL. The impact of laryngopharyngeal reflux on patient-reported quality of life. Laryngoscope 2004;114:670–4. doi:10.1097/00005537–200404000–00014.
7. Siupsinskiene N, Adamonis K, Toohill RJ. Quality of life in laryngopharyngeal reflux patients. Laryngoscope 2007;117:480–4. doi:10.1097/MLG.0b013e31802d83cf.
8. Reavis KM, Morris CD, Gopal DV, Hunter JG, Jobe BA. Laryngopharyngeal reflux symptoms better predict the presence of esophageal adenocarcinoma than typical gastroesophageal reflux symptoms. Ann Surg 2004;239:849–56. doi:10.1097/01.sla.0000128303.05898.ee.
9. Ylitalo R, Lindestad PA, Ramel S. Symptoms, laryngeal findings, and 24-hour pH monitoring in patients with suspected gastroesophagopharyngeal reflux. Laryngoscope 2001;111:1735–41. doi:10.1097/00005537–200110000–00013.
10. Csendes A, Burdiles P, Alvarez F, et al. Manometric features of mechanically defective lower esophageal sphincter in control subjects and in patients with different degrees of gastroesophageal reflux. Dis Esophagus 1996;9:290–4.
11. Liebermann-Meffert D, Allgower M, Schmid P, et al. Muscular equivalent of the lower esophageal sphincter. Gastroenterology 1979;76:31–8.
12. Gahagan T. The function of the musculature of the esophagus and stomach in the esophagogastric sphincter mechanism. Surg Gynecol Obstet 1962;114:293–303.
13. Korn O, Stein HJ, Richter TH, et al. Gastroesophageal sphincter: a model. Dis Esophagus 1997;10:105–9.
14. Stein HJ, DeMeester TR, Naspetti R, et al. Three-dimensional imaging of the lower esophageal sphincter in gastroesophageal reflux disease. Ann Surg 1991;214:374–83. doi:10.1097/00000658–199110000–00002.
15. Korn O, Csendes A, Burdiles P, et al. Anatomic dilatation of the cardia and competence of the lower esophageal sphincter: a clinical and experimental study. J Gastrointest Surg 2000;4:398–406. doi:10.1016/S1091–255X(00)80019–0.
16. Skinner DB. Pathophysiology of gastroesophageal reflux. Ann Surg 1985;202:546–56. doi:10.1097/00000658–198511000–00003.
17. Pettersson GB, Bombeck CT, Nyhus LM. Influence of hiatal hernia on lower esophageal sphincter function. Ann Surg 1981;193:214–20. doi:10.1097/00000658–198102000–00016.
18. Pandolfino JE, Shi G, Trueworthy B, et al. Esophagogastric junction opening during relaxation distinguishes nonhernia reflux patients, hernia patients, and normal subjects. Gastroenterology 2003;125:1018–24. doi:10.1016/S0016–5085(03)01210–1.
19. Wajed SA, Streets CG, Bremner CG, et al. Elevated body mass disrupts the barrier to gastroesophageal reflux. Arch Surg 2001;136:1014–8. doi:10.1001/archsurg.136.9.1014.
20. Seltman AK, Kahrilas PJ, Chang EY, Mori M, Hunter JG, Jobe BA. Endoscopic measurement of cardia circumference as an indicator of GERD. Gastrointest Endosc 2006;63:22–31. doi:10.1016/j.gie.2005.07.030.
21. Jobe BA, Hunter JG, Chang EY, et al. Office-based unsedated small caliber endoscopy is equivalent to conventional sedated endoscopy in screening and surveillance for Barrett's esophagus: A randomized and blinded comparison. Am J Gastroenterol 2006;12:2693–703. doi:10.1111/j.1572–0241.2006.00890.x.
22. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the Reflux Symptom Index (RSI). J Voice 2002;16:274–7. doi:10.1016/S0892–1997(02)00097–8.
23. Velanovich V. The development of the GERD-HRQL symptom severity instrument. Dis Esoph 2007;20:130–4. doi:10.1111/j.1442–2050.2007.00658.x.
24. Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: Clinical and functional correlates and further validation of the Los Angeles classification. Gut 1999;45:172–80.
25. Wallner B, Sylvan A, Janunger KG. Endoscopic assessment of the "Z-line" (squamocolumnar junction) appearance: reproducibility

of the ZAP classification among endoscopists. Gastrointest Endosc 2002;55:65–9. doi:10.1067/mge.2002.119876.
26. Lewin K, Appelman H. Tumors of the esophagus and stomach, atlas of tumor pathology. Washington, DC: Armed Forces Institute of Pathology, 1996.
27. Dent J, Brun J, Fendrick AM, et al. An evidence-based appraisal of reflux disease management—the Genval workshop report. Gut 1999;44(suppl 2):S1–16.
28. Poelmans J, Feenstra L, Demedts I, Rutgeerts P, Tack J. The yield of upper gastrointestinal endoscopy in patients with suspected reflux-related chronic ear, nose, and throat symptoms. Am J Gastroenterol 2004;99:1419–26. doi:10.1111/j.1572–0241.2004.30066.x.
29. Koufman J, Sataloff RT, Toohill R. Laryngopharyngeal reflux: consensus report. J Voice 1996;10:215–6. doi:10.1016/S0892–1997(96)80001–4.
30. Ossakow SJ, Elta G, Colturi T, et al. Esophageal reflux and dysmotility as the basis for persistent cervical symptoms. Ann Otol Rhinol Laryngol 1987;96:387–92.
31. Wiener GJ, Koufman JA, Wu WC, et al. Chronic hoarseness secondary to gastroesophageal reflux disease: documentation with 24-h ambulatory pH monitoring. Am J Gastroenterol 1989; 84:1503–8.
32. Richter JE, ed. In Ambulatory esophageal pH monitoring: practical approach and clinical applications. New York: Igaku-Shoin, 1991.
33. Postma GN, Tomek MS, Belafsky PC, et al. Esophageal motor function in laryngopharyngeal reflux is superior to that of classic gastroesophageal reflux disease. Ann Otol Rhinol Laryngol 2001;110:1114–6.
34. Hill LD, Kozarek RA, Kraemer SJ, et al. The gastroesophageal flap valve: in vitro and in vivo observations. Gastrointest Endosc 1996;44:541–7. doi:10.1016/S0016–5107(96)70006–8.
35. Axford SE, Sharp N, Ross PE, et al. Cell biology of laryngeal epithelial defenses in health and disease: preliminary studies. Ann Otol Rhinol Laryngol 2001;110:1099–108.
36. Johnston N, Bulmer D, Gill GA, et al. Cell biology of laryngeal epithelial defenses in health and disease: further studies. Ann Otol Rhinol Laryngol 2003;112:481–91.
37. Wo JM, Branum GD, Hunter JG, Trus TN, Mauren SJ, Waring JP. Clinical features of type III (mixed) paraesophageal hernia. Am J Gastroenterol 1996;91:914–6.

J Gastrointest Surg (2008) 12:1888–1892
DOI 10.1007/s11605-008-0625-5

Inpatient Mortality Analysis of Paraesophageal Hernia Repair in Octogenarians

Benjamin K. Poulose · Christine Gosen · Jeffrey M. Marks · Leena Khaitan · Michael J. Rosen · Raymond P. Onders · Joseph A. Trunzo · Jeffrey L. Ponsky

Received: 24 June 2008 / Accepted: 15 July 2008 / Published online: 14 August 2008

Abstract
Introduction Paraesophageal hernia repair is often performed in an elderly population. Few studies have evaluated perioperative mortality in this group. We identified predictors of inpatient mortality using a nationally representative sample.
Methods Patients ≥80 years old undergoing transabdominal paraesophageal hernia repair were identified in the 2005 Nationwide Inpatient Sample. Congenital diaphragmatic defects and traumatic injuries were excluded.
Results One thousand five discharges (73% female) with mean age 84.7 met inclusion criteria. Mean length of stay was 10.1 days (95% confidence interval 8.9–11.3) with a mortality of 8.2%. Non-elective repair was performed in 43%. For these patients, mortality and mean length of stay (16%; 14.3 days) were increased compared to elective repair (2.5%; 7.0 days, $p<0.05$). Non-elective repair was the sole predictor of inpatient mortality in adjusted analyses (odds ratio 7.1, 95% confidence interval 1.9–26.3, $p<0.05$).
Conclusion Non-elective repair was associated with a six to sevenfold increase in mortality and longer length of stay. Earlier elective repair of paraesophageal hernia may reduce mortality.

Keywords Hiatal hernia · Paraesophageal hernia · Mortality · Octogenarian

Introduction

Although not an infrequent problem dealt with by surgeons, evaluations of paraesophageal hernia (PEH) repair outcomes have been limited to case series of less than 200 patients, with most less than 100 patients. The vast majority of these report results for elective repair. No modern study to date has evaluated the epidemiology of these patients or identified predictors of inpatient morbidity and mortality for both elective and non-elective repair. Both the incidence and the size of the crural defect increase with age.[1,2] Additionally, the probability of complications is higher in older patients.[1] The main objective of this study was to determine the impact that non-elective PEH repair has on inpatient mortality in older patients. The secondary outcome measure included a length of stay comparison between elective and non-elective repair in these patients.

This work was not supported by a research grant.

This work was presented at the 49th annual meeting of the Society for Surgery of the Alimentary Tract, May 19, 2008, San Diego, CA.

B. K. Poulose (✉) · C. Gosen · J. M. Marks · L. Khaitan · M. J. Rosen · R. P. Onders · J. A. Trunzo · J. L. Ponsky
Department of Surgery,
University Hospitals Case Medical Center,
Lakeside 7010, Mailstop 5047, 11100 Euclid Avenue,
Cleveland, OH 44106, USA
e-mail: benjamin.poulose@Vanderbilt.Edu

Materials and Methods

Design Overview

Patients undergoing PEH repair were identified using the 2005 Nationwide Inpatient Sample (NIS) in this observational study. Baseline characteristics of the population were determined. A multivariate logistic regression model was constructed to evaluate the role of gender, hospitals characteristics, comorbidities, and emergent or urgent repair on inpatient mortality. Adjustments were made for possible

confounding variables and for the complex stratified sampling scheme of the NIS. This study was approved by the University Hospitals Case Medical Center Institutional Review Board.

Identification of Paraesophageal Hernia Repair Patients

The NIS is the largest non-federal, all-payer database of inpatient service available in the USA. The 2005 data include 1,054 hospitals from 37 states (AR, AZ, CA, CO, CT, FL, GA, HI, IL, IN, IA, KS, KY, MD, MA, MI, MN, MO, NC, NE, NH, NJ, NY, NV, OH, OK, OR, RI, SC, SD, TN, TX, UT, VT, WA, WI, WV). The sampling design is such that the 7,995,048 discharges in the database represent a national estimate of 39,163,834 discharges when appropriate analysis is performed.[3] This database was selected as most patients who undergo PEH repair are inpatients and the database possesses data elements pertinent to our evaluation including demographics, elective/non-elective admission status, mortality, length of stay, and International Classification of Diseases, Ninth revision, Clinical Modification (ICD-9-CM) codes for determination of comorbid conditions, complications, and procedures.

A coding algorithm was devised to select patients undergoing PEH via transabdominal approach; similar coding schemes have been previously used.[1,4] Inclusion criteria are summarized in Table 1. In addition to examining an older population, the evaluation was limited to patients 80 years old or greater to maximize selection of patients undergoing repair for paraesophageal hernia as opposed to crural repair during elective antireflux procedures. In our experience and literature review, patients above 80 years of age rarely underwent purely elective antireflux procedures.[5,6] Exclusion criteria are listed in Table 2 and included operations for congenital defects, traumatic injuries, or thoracic approaches to repair. Patients were deemed as having emergent or urgent repairs (i.e., non-elective) if any diagnostic code for diaphragmatic hernia with obstruction (552.3) or gangrene (551.3) were detected. In addition, elective and non-elective repairs were further confirmed using the NIS elective admission flag.

Table 1 Inclusion Criteria and ICD-9-CM Codes

Inclusion criteria and codes
Age ≥80 years old
Diaphragmatic hernia code in any diagnosis field
553.3 Diaphragmatic hernia
551.3 Diaphragmatic hernia with gangrene
552.3 Diaphragmatic hernia with obstruction
Transabdominal diaphragmatic repair code in any procedural field
53.7 Abdominal repair, diaphragmatic hernia

International Classification of Diseases, Ninth revision, Clinical Modification

Analysis

To minimize bias in the calculation of national estimates, odds ratios (OR), 95% confidence intervals (95% CI), and p values, analysis of the NIS must account for the complex sampling design inherent to the database structure. For comparisons of means, complex sample, two-sample t test was used. For proportion comparisons, complex sample χ^2 test was used. In-hospital, postoperative crude mortality was calculated by dividing the number of PEH surgery deaths (numerator) by the total number of PEH operations performed (denominator) in the year 2005. Univariate and multivariate complex sample logistic regression was used to identify risk factors for postoperative mortality.

For the multivariate model, an a priori approach was used to determine covariates, considering the number of deaths observed. The final model included variables for gender, congestive heart failure (CHF), and elective/non-elective status. Gender and CHF were included as risks for increased mortality from prior work analyzing surgical procedures using the NIS.[7] Statistical significance was achieved at an alpha level less than 0.05 (two-tailed) or using the 95% CI approach (with significant comparisons not crossing the value of 1). All analyses were performed using STATA version 8.2 (STATA Corporation, College Station, TX, USA).

Results

In the 2005 NIS, a population of 1,005 discharges meeting the defined criteria for PEH repair in patients 80 years old or greater was identified. Demographic characteristics are detailed in Table 3. The majority of patients were women, and procedures were generally performed in large hospitals. Non-elective repair was performed in 43% of patients. Non-elective patients were older and had a higher prevalence of congestive heart failure (Table 3) compared to patients who underwent elective repair. Length of stay was increased for non-elective patients (14.3±0.9 days, mean±SEM) compared to elective patients (7.0±0.7, $p<0.05$).

Overall crude mortality for the population was 8.2% (Fig. 1). Crude mortality was similar in men and women. Non-elective repair was associated with a higher crude mortality (15.7%) compared to elective repair (2.4%, $p<0.05$). To estimate the magnitude of effect on mortality, univariate analyses were performed, which revealed a sevenfold increased odds of death with non-elective repair (Table 4). Gender, hospital bed size, or comorbid conditions did not influence the odds of inpatient mortality after PEH

Table 2 Exclusion Criteria and ICD-9-CM Codes

Exclusion criteria and codes
Diaphragmatic congenital defect or trauma code in any diagnosis field
750.6 Congenital hiatus hernia
756.6 Congenital anomalies of the diaphragm
862.0 Diaphragmatic injury, closed
862.1 Diaphragmatic injury, open
Other diaphragmatic operation code or thoracic approach in any procedural field
34.27 Biopsy of diaphragm
34.81 Excision of diaphragmatic lesion
34.82 Suture of diaphragmatic laceration
34.83 Closure of diaphragmatic fistula
34.84 Other diaphragm repair
34.89 Diaphragm operation NEC
53.8 Thoracic repair, diaphragmatic hernia
53.81 Diaphragm plication

International Classification of Diseases, Ninth revision, Clinical Modification

repair. However, 27% of patients in the non-elective repair group had CHF compared to 15% in the elective group. To adjust for the higher morbidity imparted by an increased prevalence of CHF in the non-elective group, a multivariate analysis was performed. This revealed non-elective repair as the sole predictor of inpatient mortality after PEH repair in patients 80 years of age or older (OR 7.1, 95% CI 1.9–26.3, $p<0.05$; Fig. 2).

Discussion

PEH represents approximately 5% of all hiatal hernia occurrences. Surgical correction remains the mainstay of treatment for symptomatic PEH to prevent complications such as gastric volvulus, strangulation, ulceration, hemorrhage, and death estimated to occur in 10–30% of non-surgically managed patients.[8,9] The results of this study showed that both inpatient mortality and length of stay were increased in patients 80 years or older who underwent non-elective repair compared to elective patients. Surprisingly, nearly half of the patients analyzed (43%) underwent non-elective repair of their PEH.

Controversy still exists regarding the treatment of purely asymptomatic patients with PEH. Stylopoulos et al.[4] performed a decision analysis in 2002 modeling the risks of observation against the risks of surgical repair, favoring watchful waiting for asymptomatic or minimally symptomatic patients. Further, this study suggested that even if non-elective repair were performed, mortality would be relatively low (5.4%). These data were based on earlier versions of the NIS database. Our calculated crude inpatient mortality for patients who underwent non-elective repair was notably higher at 15.7% using the 2005 NIS. This may in part be due to our exclusive analysis of patients 80 years or older. In addition, the study performed by Stylopoulos likely included patients much younger than 80 years but who did not have true paraesophageal hernias based on ICD-9 coding. Patients undergoing repair of sliding hiatal hernia during elective fundoplication may have been included, artificially lowering the mortality risk. This would have underestimated the true mortality for those undergoing the more difficult repair of

Table 3 United States 2005 Paraesophageal Hernia Repair Population Characteristics in Patients 80 years of Age or Older

	Elective	Non-Elective	*p* Value	Total Population
Mean age (years)[a]	83.4±0.3	86.4±0.4	<0.05	84.7±0.4
%Women	71%	76%	NS	73%
%Large hospital[b]	58%	70%	NS	63%
%Diabetes	9%	6%	NS	8%
%Congestive heart failure	15%	27%	<0.05	20%
Total procedures	573	432		1005

Data calculated from the 2005 Nationwide Inpatient Sample database
NS not significant
[a] Mean values are presented ± standard error of the mean; *p* values compare differences between elective and non-elective presentation
[b] Large Hospital as defined by the Healthcare Cost and Utilization Project 2005 Nationwide Inpatient Sample[3]

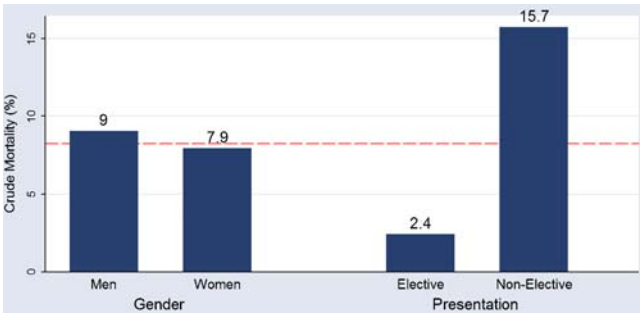

Fig. 1 Crude mortality in 2005 paraesophageal repair population 80 years of age or older: *Dashed line* represents overall crude mortality of 8.2%.

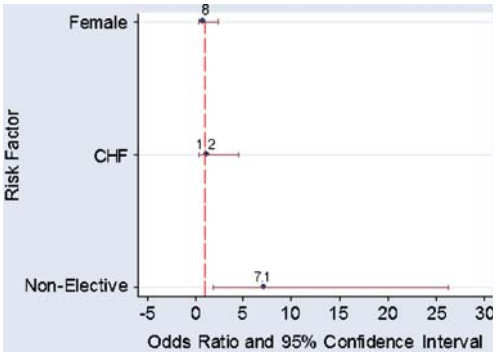

Fig. 2 Adjusted odds of inpatient mortality in 2005 paraesophageal repair population 80 years of age or older: Non-elective repair was the sole predictor of inpatient mortality. *Horizontal bars* represent the 95% confidence interval for the listed odds ratio; *bars that do not cross* 1 (*vertical dashed line*) indicate a significant value ($p<0.05$).

PEH. Other studies quoted overall mortality for paraesophageal hernia repair (both elective and non-elective) ranging from 0% to 8%.[10,11] It is difficult to ascertain mortality risk for the emergent population, as most case series report very small numbers to calculate reliable values. Our study provides one of the first estimates of inpatient mortality in this high risk group (15.7%). Moreover, non-elective repair was the sole predictor of increased inpatient mortality in adjusted analyses, imparting a nearly sevenfold increase in the odds of dying after PEH repair compared to elective operation.

In this study, length of stay was found to be increased for patients undergoing non-elective repair (14.3 days) compared to purely elective repair (7 days). These values are notably higher than those currently described in the literature. Examining case series with larger numbers (100–200 patients), Luketich et al.[12] reported an overall median length of stay of 2 days, and Pierre et al.[13] described a median of 3 days. Gangopadhyay et al.[1] specifically examined length of stay in those 75 years old or greater and found a slightly increased length of stay compared to younger patients (2.8 days versus 1.9 days). The majority of patients in these studies underwent laparoscopic repair, likely accounting for the general shorter length of stay when compared to our results which included all abdominal approaches to PEH repair. Nevertheless, given that our study evaluated those 80 years or older, the results confirmed that older patients in general tend to require a longer length of stay than their younger counterparts. Elective repair of PEH via laparoscopy may be especially well suited to older patients who might otherwise need increased in-hospital days for recovery.

Table 4 Risk Factors for In-Hospital Postoperative Death Following Paraesophageal Hernia Repair in Patients 80 years or Older, 2005 (Univariate, Unadjusted Analysis)

	Odds ratio for death	95% Confidence interval
Gender		
Women	(ref)	(ref)
Men	1.2	0.4–3.4
Hospital bed size		
Small	(ref)	(ref)
Medium	0.3	0.04–1.9
Large	0.8	0.2–3.1
Comorbidities[a]		
Diabetes	0.6	0.1–4.6
CHF	1.7	0.5–5.5
Presentation		
Elective	(ref)	(ref)
Non-elective	7.2	2.1–24.9*

CHF congestive heart failure, *ref* referent group
[a] Comorbidity odds ratios are compared to those without the specified disease
*$p<0.05$ compared to referent group

There are several limitations to this study. Our study examined inpatient mortality only. Patients who were discharged, readmitted, and died would have been excluded from the analysis. As such, the 30-day postoperative mortality would likely be higher than our calculated inpatient mortality. Nonetheless, we discovered a higher mortality than previously published even with this limitation. This study found an increased prevalence of CHF (as a comorbid condition and not a complication) in the non-elective PEH repair group compared to elective patients. This may have confounded the relationship between non-elective repair and mortality. We attempted to adjust for this by using regression techniques; a slightly lower odds of death was observed in the adjusted analysis (odds ratio of 7.1 versus 7.2). Although randomization to elective and non-elective repair would address this issue in a potential clinical trial, it is very unlikely that such a trial would ever be performed given the generally low probability of death overall with PEH repair and resulting lack of power. Thus, even with this limitation using administrative data, the results are robust in detecting relatively rare events such as mortality. The use of administrative data in clinical analysis can result in biased results because of coding errors. To

address this, we attempted to use a coding algorithm to identify PEH patients as previously published.[4] In addition, the identification of patients based on specific surgical procedure codes is fairly robust using large administrative datasets.[14] We also limited our patient population to those 80 years old or greater, further refining our evaluation of those undergoing PEH repair as opposed to elective antireflux procedures. Although large administrative datasets are useful for determining mortality rates for procedure with low mortality risk, no follow-up beyond that of the inpatient stay could be ascertained. As such, no attempt was made to calculate recurrence or readmissions for postoperative complications. Another limitation of this study is that stratification by approach (laparoscopic versus open) is impossible based on ICD-9-CM coding for PEH repair.

This study reports the first large-scale analysis of inpatient mortality after PEH. Patients undergoing non-elective repair were associated with a higher mortality and length of stay than those who underwent elective repair. Notably, crude mortality after PEH repair was higher than previously perceived. Further investigation needs to be performed to evaluate if earlier operative intervention can lead to reduced mortality by avoiding an urgent or emergent operation.

References

1. Gangopadhyay N, Perrone JM, Soper NJ, Matthews BD, Eagon JC, Klingensmith ME, et al. Outcomes of laparoscopic paraesophageal hernia repair in elderly and high-risk patients. Surgery 2006;140:491–498. discussion 498–499 doi:10.1016/j.surg.2006.07.001.
2. Kercher KW, Matthews BD, Ponsky JL, Goldstein SL, Yavorski RT, Sing RF, et al. Minimally invasive management of paraesophageal herniation in the high-risk surgical patient. Am J Surg. 2001;182:510–514. doi:10.1016/S0002-9610(01)00760-7.
3. Nationwide Inpatient Sample HCUP. (NIS). Healthcare Cost and Utilization Project (HCUP): Agency for Healthcare Research and Quality, Rockville, MD. www.hcup-us.ahrq.gov/nisoverview.jsp; 2005.
4. Stylopoulos N, Gazelle GS, Rattner DW. Paraesophageal hernias: operation or observation? Ann Surg. 2002;236:492–500. discussion 500–491 doi:10.1097/00000658-200210000-00012.
5. Cowgill SM, Gillman R, Kraemer E, Al-Saadi S, Villadolid D, Rosemurgy A, et al. Ten-year follow up after laparoscopic Nissen fundoplication for gastroesophageal reflux disease. Am Surg. 2007;73:748–752. discussion 752–743.
6. Kundhal PS, Harnish JL, Urbach DR, Kundhal PS, Harnish JL, Urbach DR. Effect of surgeon on outcome of antireflux surgery. Surg Endosc. 2007;21:902–906. doi:10.1007/s00464-006-9024-8.
7. Poulose BK, Griffin MR, Moore DE, Zhu Y, Smalley W, Richards WO, et al. Risk factors for post-operative mortality in bariatric surgery. J Surg Res. 2005;127:1–7. doi:10.1016/j.jss.2004.12.017.
8. Gantert WA, Patti MG, Arcerito M, Feo C, Stewart L, DePinto M, et al. Laparoscopic repair of paraesophageal hiatal hernias. J Am Coll Surg 1998;186:428–432. discussion 432–423 doi:10.1016/S1072-7515(98)00061-1.
9. Schauer PR, Ikramuddin S, McLaughlin RH, Graham TO, Slivka A, Lee KK, et al. Comparison of laparoscopic versus open repair of paraesophageal hernia. Am J Surg 1998;176:659–665. doi:10.1016/S0002-9610(98)00272-4.
10. Velanovich V, Karmy-Jones R. Surgical management of paraesophageal hernias: outcome and quality of life analysis. Dig Surg 2001;18:432–437. discussion 437–438 doi:10.1159/000050189.
11. Frantzides CT, Madan AK, Carlson MA, Stavropoulos GP. A prospective, randomized trial of laparoscopic polytetrafluoroethylene (PTFE) patch repair vs simple cruroplasty for large hiatal hernia. Arch Surg 2002;137:649–652. doi:10.1001/archsurg.137.6.649.
12. Luketich JD, Raja S, Fernando HC, Campbell W, Christie NA, Buenaventura PO, et al. Laparoscopic repair of giant paraesophageal hernia: 100 consecutive cases. Ann Surg 2000;232:608–618. doi:10.1097/00000658-200010000-00016.
13. Pierre AF, Luketich JD, Fernando HC, Christie NA, Buenaventura PO, Litle VR, et al. Results of laparoscopic repair of giant paraesophageal hernias: 200 consecutive patients. Ann Thorac Surg. 2002;74:1909–1915. discussion 1915–1906 doi:10.1016/S0003-4975(02)04088-2.
14. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613–619. doi:10.1016/0895-4356(92)90133-8.

J Gastrointest Surg (2008) 12:1893–1899
DOI 10.1007/s11605-008-0659-8

Ten-year Outcome of Laparoscopic Antireflux Surgery

M. Fein · M. Bueter · A. Thalheimer · V. Pachmayr · J. Heimbucher · S. M. Freys · K.-H. Fuchs

Received: 24 May 2008 / Accepted: 5 August 2008 / Published online: 3 September 2008

Abstract
Background Reflux recurrence is the most common long-term complication of fundoplication. Its frequency was independent from the type of fundoplication in randomized studies. Results for different techniques of laparoscopic antireflux surgery were retrospectively evaluated after 10 years.
Methods From 1992 to 1997, 120 patients had primary laparoscopic fundoplication with a "tailored approach" (type of wrap chosen according to esophageal peristalsis): 88 received a Nissen, 22 an anterior, and 10 a Toupet fundoplication. Follow-up of 87% of the patients included disease-related questions and the gastrointestinal quality-of-life index (GIQLI).
Results Of the patients, 89% would select surgery again. Heartburn was reported by 30% of the patients. Regurgitations were noted from 15% of patients after a Nissen, 44% after anterior fundoplication, and 10% after a Toupet ($p=0.04$). Twenty-eight percent were on acid-suppressive drugs again. Following Nissen fundoplication, proton pump inhibitors were less frequently used ($p=0.01$) and on postoperative pH-metry reflux recurrence rate was lower ($p=0.04$). The GIQLI was 110±24 without significant differences for the type of fundoplication.
Discussion Ten years after laparoscopic fundoplication, overall outcome is good. A quarter of the patients are on acid-suppressive drugs. Nissen fundoplication appears to control reflux better than a partial fundoplication.

Keywords Gastroesophageal reflux disease · Antireflux surgery · Long-term outcome · Reflux recurrence

The results of the questionnaire have already been published in German in the journal 'Der Chirurg'.

M. Fein (✉) · M. Bueter · A. Thalheimer · V. Pachmayr
Chirurgische Klinik und Poliklinik I,
Klinikum der Universität Würzburg,
Oberdürrbacherstr. 6,
97080 Würzburg, Germany
e-mail: fein@chirurgie.uni-wuerzburg.de

J. Heimbucher
Chirurgie, Marienkrankenhaus,
Kassel, Germany

S. M. Freys
Chirurgische Klinik, DIAKO Ev. Diakonie-Krankenhaus,
Bremen, Germany

K.-H. Fuchs
Allgemeinchirurgische Klinik, Markus-Krankenhaus,
Frankfurt, Germany

Introduction

Antireflux surgery by laparoscopy has undergone a Renaissance despite the availability of proton pump inhibitors. Even after numerous randomized studies on the operative (OP) technique, however, numerous different techniques continue to be used. In addition to the topical question of mesh augmentation of the hiatus, it is still not definitively known whether a 360° Nissen fundoplication or a partial fundoplication—anterior or posterior according to Toupet—is best. Many centers have long used a so-called "tailored approach": In patients with normal esophageal motility, a Nissen fundoplication was applied in those with motility

disorders a partial fundoplication. It was assumed that a partial fundoplication would offer less resistance in patients with reduced pump function, thus lowering the dysphagia rate. Two randomized studies had clearly shown that regardless of the applied technique, the surgical results were not influenced by esophageal motility.[1,2] Even in patients with aperistaltic esophagus, a Nissen fundoplication would be possible.[3] The patients in these studies often complained of bloating and increased flatulence following total fundoplication; the reflux recurrence rates were the same for both OP procedures.

In the evaluation of reflux recurrence rates, the duration of follow-up is highly important. In a randomized study comparing anterior with posterior fundoplication, for example, only 10% of patients reported severe heartburn 1 year after anterior fundoplication, but the rate rose to 22% after 5 years.[4,5] Moreover, in contradiction to those two randomized studies, numerous retrospective studies have shown that a partial fundoplication is less effective against reflux disease over the long-term than a total fundoplication. For example, in a comparison of 235 patients who underwent surgery using the "tailored approach", with 122 patients receiving a Nissen fundoplication independently of esophageal peristalsis, the partial fundoplication was significantly less effective at controlling reflux. And dysphagia was not more common with the Nissen fundoplication, even in patients with poor esophageal peristalsis.[6] So far, however, few studies have reported results from 10 years or more after laparoscopic fundoplication.[7–9]

Against this background, we compared the 10-year outcome of various OP techniques of laparoscopic antireflux surgery with the reflux recurrence rate as the primary endpoint. The goal was to evaluate the long-term effectiveness of the different antireflux surgery techniques.

Patients and Methods

Between March 1992 and July 1997, 134 patients underwent antireflux surgery in the Department of Surgery of the University of Wuerzburg. Fourteen of these patients were excluded from this study, three because they had undergone primary open surgery, 11 for undergoing a redo procedure. A total of 120 patients were therefore studied: 41 females, 79 males, aged 49±14 years.

Endpoints

The long-term outcome was evaluated applying the questionnaire described below and the gastrointestinal quality-of-life index (GIQLI) developed by Eypasch and co-workers,[10,11] which were sent to the patients. If necessary, the patients were contacted by telephone. In the event of complaints, a follow-up examination was offered.

The questionnaire posed 18 questions. In addition to standardized questions regarding gastrointestinal symptoms, which had been obtained prospectively from each patient prior to surgery and were each assigned three degrees of severity, the questions elicited the patients' subjective appraisal of the surgical results and inquired regarding current intake of acid-suppressive drugs. Quality of life was measured with the gastrointestinal quality of life index (GIQLI). This instrument, developed by Eypasch[10,11] represents a generic tool that can be applied to all patients with benign and/or malignant gastrointestinal disorders. It comprises 36 multidimensional items covering symptoms, and physical, emotional, and social dysfunction related to gastrointestinal diseases or their treatments. Each item scores from 0 to 4 points. The GIQLI is calculated by simple addition of all item scores so that an overall score of 0 would constitute the worst, and a score of 144 the best result. Furthermore, each dimension can be analyzed separately. Normal values of the GIQLI were determined in a control group of 150 healthy subjects (120.8±15).[10] Our own comparison values were gathered in a country village of 270 persons (146 males, 124 females).

Preoperative Workup

Prior to surgery all patients underwent gastroscopy, esophageal manometry, and 24-hour esophageal and gastric pH-metry. In some patients, a barium swallow or gastric emptying test was performed. Patient histories were documented using the standardized questionnaire and the GIQLI. All data were gathered prospectively.

The gastroscopy graded the esophagitis according the classification of Savary–Miller and the present size of the hiatus hernia was measured. The pH-metry was applied in standard technique (Medtronic, Minneapolis, MN). In accordance with the tailored approach, the choice of OP procedure was based on the esophageal peristalsis as assessed by the esophageal manometry (Medtronic, Minneapolis, MN) as follows: The examination was carried out using an 8-lm, water-perfused manometry catheter on the reclining, fasting patient. Three days prior to the examination all medications affecting motility were stopped. The position, pressure, and length of the inferior esophageal sphincter were determined with the stationary pull-through manometry. To evaluate the esophageal peristalsis, the lowest channel was placed 3 cm above the upper border of the lower esophageal sphincter and five dry and five water swallows were measured. If the frequency of simultaneous contractions or of amplitudes under 20 mmHg was greater than 30%, then an esophageal motility disorder was diagnosed and, in accordance with the tailored approach, a Nissen fundoplication was not applied so as to avoid too great resistance on the

gastroesophageal junction. Until March 1996, anterior fundoplications were used as partial fundoplication, but due to their recurrence rates, the Toupet fundoplication was employed thereafter.

Surgical Procedure

All procedures were performed laparoscopically. In two patients, a conversion was necessary due to bleeding from the spleen. In every antireflux operation, the distal esophagus in the lower mediastinum was mobilized far enough to lie loosely in the abdominal cavity. The phrenoesophageal ligament was completely cut through so that the entire length of the crura could be identified dorsal to the esophagus. Except for the anterior partial fundoplication, the short gastric vessels were divided starting from the lower margin of the spleen. Every patient received a dorsal hiatoplasty with nonabsorbable sutures, which were tied extracorporeally. A Nissen fundoplication was always applied via a 54 F bougie and attached to the distal esophagus with a U-suture using resorbable pledgets. One to two additional interrupted sutures were made. An anterior fundoplication was attached to the esophagus and on the right to the diaphragm, a posterior fundoplication according to Toupet was attached bilaterally to the crura and to the esophagus right and left of the vagus, in each case with three interrupted sutures.

Postoperative Workup

All patients were asked to have gastroscopy, esophageal manometry, and 24-hour esophageal pH as follow-up investigations one or 2 years after surgery. Patients who presented in the hospital for any reason after these planned reevaluations were also offered 24-hour esophageal pH. The results of esophageal pH-metry were compared with the symptoms and use of acid-suppressive drugs.

Statistics

All data are given as mean with standard deviation. The frequencies of two groups were compared with the Fisher-exact test, for three groups with the χ^2 test. Metric variables were compared with nonparametric tests (Mann–Whitney U test or the Kruskal–Wallis test for three groups). The evaluation was done using the Software SAS (V9.1, SAS Institute, Cary, NC). P-values <0.05 were regarded as significant.

Results

The results of the preoperative workup are listed in Table 1. Patients receiving a Nissen fundoplication had the highest incidence of an incompetent lower esophageal sphincter and the lowest sphincter pressure. Patients receiving anterior fundoplication had slightly less reflux (lower pH score) and less esophagitis. The incidence of hiatal hernia was similar. Preoperative symptoms are listed in Table 2. Remarkably, the group undergoing the Nissen fundoplication reported heartburn significantly more often than other patients. The percentage of patients complaining of dysphagia ranged from 19% to 25%, epigastric pain was reported by 59% of patients, epigastric fullness by 48%, and bloating by 36%, in each instance without intergroup differences. Quality of life was measured since 1995 and the preoperative GIQLI was very low (89.8±27.7) and similar for the three groups.

Postoperative workup was completed in 67 patients (Table 3). The planned reevaluation within the first 2 years was done in 50 of these patients. Eight patients had the follow-up investigation in the third postoperative year, five in the fourth, and four after five and more years. There were no differences in recurrent esophagitis, recurrent hernia, or the presence of an incompetent sphincter. However, reflux recurrence was noted significantly less frequent and the mean pH score was lower following Nissen fundoplication.

Follow-up examinations were completed by 99 of 114 patients (87%). Six patients had died in the intervening years. The follow-up rates were 74/88 (84%) patients for Nissen fundoplication, 16/22 (73%) for anterior fundoplication, and 9/10 (90%) following Toupet fundoplication. Three patients (3%) had undergone a second operation, two after Nissen and one after anterior fundoplication. The

Table 1 Preoperative Endoscopy, Manometry, and ph-metry

Findings	Nissen N=85	Anterior fundopl. N=22	Toupet N=10	p value
Esophagitis	59%	32%	80%	0.107
Hiatal hernia	57%	59%	70%	0.408
Incompetent LES	91%	64%	90%	0.006
LES pressure	4.6±4.0	7.6±5.2	6.1±5.3	0.013
LES total length	3.1±0.8	3.5±1.0	3.3±1.3	0.326
LES total length	1.6±0.8	1.9±0.9	1.6±1.2	0.293
pH-score	45.8±51.5	28.1±25.5	56.5±53.7	0.218

Table 2 Prevalence of Gastrointestinal Symptoms Classified According to OP Procedure (%): Preoperative Findings

Symptoms	Nissen $N = 83$	Anterior fundopl. $N = 20$	Toupet $N = 9$	p value
Heartburn	89.2	65.0	55.5	0.021
Regurgitation	60.2	40.0	55.5	0.418
Dysphagia	19.3	25.0	22.2	0.314
Epigastric pain	60.2	50.0	66.6	0.922
Epigastric fullness	50.6	40.0	44.4	0.401
Vomiting	61.4	25	44.4	0.077
Chest pain	22.9	20.0	33.3	0.143
Bloating	39.8	25.0	22.2	0.051

results in these three patients were assessed according to their first operation.

Subjective Assessment of the Surgical Result

A mean 89% of patients said they would decide to have an antireflux operation again, 90% after Nissen fundoplication, 81% after anterior, and 100% after posterior fundoplication (not significant). Their current health was reported by 37% to be very good, by 55% to be moderate, and by 7% to be poor, again without differences regarding surgical procedure. The majority of patients (55%), however, denied a connection between their current health and the operation. Only two of eight patients attributed their poor health to the operation, whereas 86% of patients reporting very good health did so (Fig. 1). Of the ten patients who would now decline antireflux surgery, only two reported their health as poor, eight as moderate.

Intake of Acid-Suppressive Drugs

Twenty-seven patients (28%) reported they were taking acid-suppressive drugs. Classified by OP procedure, 23% of these patients had undergone Nissen, 44% anterior fundoplication, and 43% Toupet. Of these 27 patients, 74% were taking proton pump inhibitors, 13% H2-blockers, and 13% antacids (Fig. 2). Patients who had undergone anterior fundoplication (38%) or Toupet fundoplication (43%) took proton pump inhibitors ($p<0.01$) significantly more often than patients who underwent Nissen fundoplication (14%). Medications against heartburn were reported to be effective by 75.9% of patients who took them. Of the patients on acid-suppressive drugs, who had a previous pH-metry, 42% had documented recurrent reflux. Of the patients on proton pump inhibitors (PPI), reflux on pH-metry was observed in 54%.

Gastrointestinal Symptoms

An overview of the types and frequencies of gastrointestinal symptoms is given in Table 4. Despite antireflux surgery heartburn was reported by 30% of patients, 13% of whom experienced it weekly. The number of patients complaining of heartburn increased by one to three patients each year on a continual basis throughout the follow-up period. Only 5% of patients complained of at least weekly regurgitations, only 7% of at least weekly dysphagia. The most common postoperative symptoms were epigastric pain and bloating. Comparison of the actual symptoms with the results of previous postoperative pH-metry revealed that 33% of patients with heartburn and 38% of patients with regurgitation had recurrent reflux.

All of the symptoms classified according to OP procedure are shown in Table 5. Whereas in patients with heartburn only slight differences were noted, significantly more patients reported regurgitations after anterior fundoplication. Toupet fundoplication was in this regard just as effective as Nissen fundoplication. In the evaluation of weekly and daily occurrence of symptoms, the rate for heartburn was 13% for all procedures. The rates for regurgitations were 2.7% for the Nissen, and 12.5% for both the anterior fundoplication and Toupet ($p=0.170$). The dreaded symptom dysphagia was reported with equal frequency independently of fundoplication type, weekly and daily dysphagia being mentioned by only seven patients (7%), likewise without differences with regard to fundoplication type. For epigastric pain, epigastric fullness, or bloating a slightly significant difference existed with regard to the frequency of the latter, the other symptoms

Table 3 Follow-up Endoscopy, Manometry, and pH-metry

Findings	Nissen $N=48$	Anterior fundopl. $N=10$	Toupet $N=9$	p value
Esophagitis	4%	0%	0%	0.952
Hiatal hernia	6%	10%	11%	0.151
Incompetent LES	38%	56%	56%	0.454
LES pressure	9.1±4.1	10.6±5.9	7.2±2.8	0.328
LES total length	3.5±0.7	3.1±0.6	2.9±0.3	0.016
LES total length	2.1±0.8	1.7±0.7	1.9±0.6	0.207
pH-score	10.0±18.1	22.5±26.2	26.4±33.2	0.009
Positive pH-score	21%	50%	56%	0.036

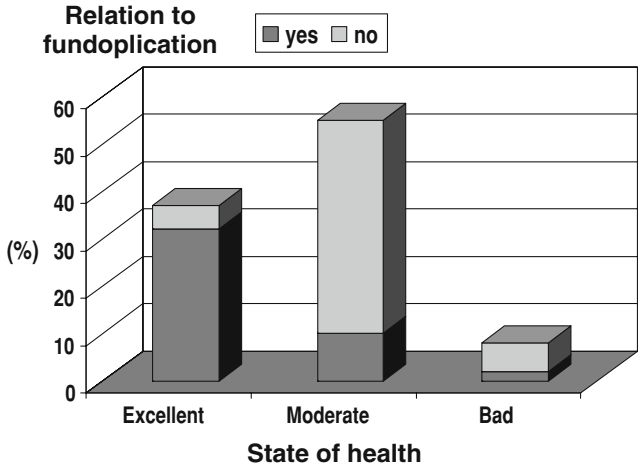

Figure 1 Current health status of patients and its relation to antireflux surgery.

occurring with equal frequency independently of surgical procedure. The rate of weekly or daily bloating was noteworthy at 50% regardless of OP procedure.

Quality of Life

The quality of life as measured by the GIQLI more than 10 years after laparoscopic antireflux surgery is summarized in Table 6. None of the differences regarding the various OP procedures were significant. Compared to the normal values,[10] a nonsignificant discrete reduction in the values in all dimensions was noted, with the lowest values occurring

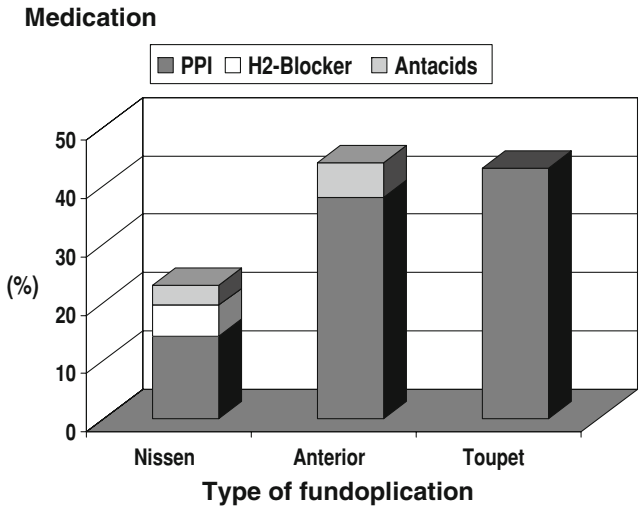

Figure 2 Intake of acid-suppressive drugs in dependence on surgical procedure. Comment: Evaluation of all medications together: comparison of all three groups $p=0.17$, Nissen versus anterior fundoplication and Toupet p=0.06. Evaluation of PPI intake: comparison of all three groups $p=0.04$, Nissen versus anterior fundoplication and Toupet $p=0.01$, Nissen versus anterior fundoplication $p=0.04$, Nissen versus Toupet $p=0.06$.

Table 4 Frequency of Gastrointestinal Symptoms (%): Results at 10-year Follow-up

Symptoms	Never	Rarely	Weekly	Daily
Heartburn	70.4	16.3	6.1	7.1
Regurgitation	79.4	15.5	2.1	3.1
Dysphagia	69.5	23.2	3.2	4.2
Epigastric pain	53.6	34.0	8.3	4.1
Epigastric fullness	39.6	36.5	12.5	11.5
Vomiting	79.4	11.3	4.1	5.2
Chest pain	58.8	28.9	7.2	5.2
Bloating	19.6	29.9	16.5	34.0

in patients following anterior fundoplication. The GIQLI score (121.1±17) of our own control group was almost identical to the normal value. The three lowest GIQLI scores (37, 45, and 49) were observed in patients following Nissen fundoplication, with only one of these patients receiving treatment with acid-suppressive drugs.

Discussion

In the Surgical Clinic of the University of Würzburg laparoscopic fundoplication became an established procedure soon after its introduction,[12] with an ongoing steady increase in OP numbers.[13] In order to evaluate the long-term effectiveness of this procedure, we performed a retrospective study of all patients who underwent the procedure ten or more years ago. As the patients were not randomized for the type of fundoplication, it is important to realize that patients with partial fundoplication were characterized by impaired esophageal motility. However, on preoperative workup disease severity was slightly higher in patients receiving a Nissen fundoplication (Table 1).

As in other studies, the number of patients stating that they would undergo the operation again was very high at 89%.[14,15] About 30% of patients reported persistent heartburn, while 28% were again taking acid-suppressive

Table 5 Prevalence of Gastrointestinal Symptoms According to OP Procedure (%): Results at 10-Year Follow-up

Symptoms	Nissen $N=74$	Anterior fundopl. $N=16$	Toupet $N=9$	p value
Heartburn	29.7	37.5	12.5	0.449
Regurgitation	15.1	43.8	10.0	0.035
Dysphagia	30.6	31.3	28.6	0.992
Epigastric pain	43.8	56.3	50.0	0.651
Epigastric fullness	60.3	62.5	57.1	0.970
Vomiting	18.8	17.8	50.0	0.100
Chest pain	38.4	56.3	37.5	0.410
Bloating	84.9	75.0	50.0	0.051

Table 6 Quality of life According to OP Procedure as Measured by the GIQLI: Results at 10-year Follow-up

Dimension	Nissen N=73	Anterior fundopl. N=14	Toupet N=8	p value
Symptoms	58.2±12.5	57.1±12.3	63.1±11.0	0.541
Psychological	15.4±4.5	13.9±4.7	17.3±2.4	0.235
Physical	19.3±6.1	17.3±6.5	17.6±6.9	0.467
Social	13.4±3.6	12.6±4.1	13.5±3.2	0.884
Medical therapy	3.4±1.0	3.2±0.9	3.6±0.7	0.388
Total[a]	109.8±24.4	104.1±26.9	115.1±21.0	0.696

[a] The GIQLI after 10 years was significantly higher than the preoperative values (p<0.0001).

drugs. Compared to studies with shorter follow-up periods, this rate is relatively high,[14,16] whereas some studies with comparable follow-up times had clearly higher recurrence rates.[9,17] In a randomized study comparing open antireflux surgery with conservative therapy, 62% of the patients undergoing surgery took acid-suppressive drugs over long-term course.[18] The reflux recurrence rate for our first laparoscopic patients was clearly lower, and has declined further with increasing experience. Interesting in this regard is the continual increase in patients complaining or renewed heartburn. Similar to this was the continual increase in the intake of acid-suppressive drugs found in another study with more than 10 years follow-up.[9]

The actual reflux recurrence rate is lower than the data on postoperative symptoms and medication intake suggest. Compared with the previous postoperative pH-metry, less than 50% of patients with reflux symptoms or use of acid-suppressive therapy had documented recurrent reflux. Other studies also show that fewer than 50% of patients experiencing renewed heartburn and/or taking acid-suppressive drugs actually experienced pathological reflux on follow-up pH-metry.[19–21] This discrepancy might be due to a greater likelihood of patients with a history of gastrointestinal complaints being prescribed acid-suppressive drugs. Our findings for reflux recurrence are basically similar to many other follow-up studies.[7–9]

The evaluation of the various procedures is especially relevant with regard to the still frequently performed anterior fundoplication.[15,22] Recurrent reflux was documented more frequently on pH-metry after partial fundoplication. Regurgitations were significantly associated with anterior fundoplication. The results for proton pump inhibitors were similar, they being taken more often by patients after anterior fundoplication or Toupet. However, a comparison of the procedures in this observational series is limited by the fact that the patients were selected according to their motility. A recent 5-year evaluation of a randomized study comparing anterior and posterior fundoplications in 43 and 45 patients, respectively, reported significantly better results for posterior fundoplication, which had fewer reflux-associated symptoms (heartburn and regurgitation, p<0.0001), fewer reoperations, and lower use of acid-suppressive drugs.[5] In contrast to this stands only a randomized study from Adelaide, Australia,[22] in which a comparison of anterior fundoplication and Nissen fundoplication found no significant difference with regard to reflux recurrence.

Similar to the present study, a series of retrospective studies discovered clear drawbacks to partial fundoplication. This was especially conspicuous in patients with severe reflux disease, i.e., an esophagitis grade 3 or 4 according to Savary–Miller, or a Barrett's esophagus.[6,23,24] It should be pointed out, however, that only ten patients were operated on according to Toupet in the follow-up period. For our patients, definitive assessment of the procedure awaits the evaluation of further patients who underwent Toupet after July 1997. As a rule, the effects of each of the applied fundoplication procedures show a gradual steady decline over time. This explains why the technique conferring the greatest benefit initially remains superior in the long-term.

The fear of postoperative dysphagia following Nissen fundoplication is unwarranted. The dysphagia rate for all procedures was low and identical, a result also reported by many other studies. A Nissen fundoplication can be successfully applied even in patients with aperistaltic esophagus.[3,25] A possible drawback to the Nissen fundoplication is the frequency of postoperative bloating.[1,2] Only 15% of patients reported none, while 39.7% complained of daily bloating. However, this appears to have had little effect on the daily life of patients, since no differences in the quality of life were noted.

The quality of life did not differ as between procedures, but was somewhat lower than that reported in other studies.[26] This may be due to the longer follow-up time or to the effects of a learning curve in the present study. However, compared to the very low preoperative values, there was a highly significant increase of quality of life. In assessing the results for quality of life, as for all of the results presented here, it must be remembered that the patient selection was very strict, with the consequence that on average only patients with severe reflux disease were operated on. Retrospective assessment of the three patients with the lowest quality of life revealed that antireflux surgery may not have been the appropriate therapy. This

underscores the necessity of a thorough preoperative evaluation of the indications for fundoplication.

Conclusions

Even the first laparoscopic fundoplications we performed resulted in high patient satisfaction more than 10 years after surgery. A quarter of the patients are on acid-suppressive drugs with documented recurrent reflux in half of these patients. In this observational series, Nissen fundoplication appears to control reflux better than a partial fundoplication. The preferred procedure for surgical treatment of reflux disease in our clinic is therefore laparoscopic Nissen fundoplication.

Disclosure The corresponding author declares that none of the authors has any connections whatsoever with the companies whose products are named in this paper or with any company in competition with those companies. The presentation of the topic is impartial and the contents are entirely product-neutral.

References

1. Lundell L, Abrahamsson H, Ruth M, Rydberg L, Lönroth H, Olbe L. Long-term results of a prospective randomized comparison of total fundic wrap (Nissen-Rossetti) or semifundoplication (Toupet) for gastroesophageal reflux. Br J Surg 1996;83:830–835. doi:10.1002/bjs.1800830633.
2. Fibbe C, Layer P, Keller J, Strate U, Emmermann A, Zornig C. Esophageal motility in reflux disease before and after fundoplication: a prospective, randomized, clinical, and manometric study. Gastroenterology 2001;121:5–14. doi:10.1053/gast.2001.25486.
3. Baigrie RJ, Watson DI, Myers JC, Jamieson GG. Outcome of laparoscopic Nissen fundoplication in patients with disordered preoperative peristalsis. Gut 1997;40:381–385.
4. Hagedorn C, Jonson C, Lonroth H, Ruth M, Thune A, Lundell L. Efficacy of an anterior as compared with a posterior laparoscopic partial fundoplication: results of a randomized, controlled clinical trial. Ann Surg 2003;238:189–196.
5. Engstrom C, Lonroth H, Mardani J, Lundell L. An anterior or posterior approach to partial fundoplication? Long-term results of a randomized trial. World J Surg. 2007;31:1223–1227. doi:10.1007/s00268-007-9004-8.
6. Patti MG, Robinson T, Galvani C, Gorodner MV, Fisichella PM, Way LW. Total fundoplication is superior to partial fundoplication even when esophageal peristalsis is weak. J Am Coll Surg 2004;198:863–869. doi:10.1016/j.jamcollsurg.2004.01.029.
7. Dallemagne B, Weerts J, Markiewicz S, Dewandre JM, Wahlen C, Monami B et al. Clinical results of laparoscopic fundoplication at ten years after surgery. Surg Endosc. 2006;20:159–165. doi:10.1007/s00464-005-0174-x.
8. Dallemagne B, Weerts JM, Jehaes C, Markiewicz S, Lombard R. Laparoscopic Nissen fundoplication: preliminary report. Surg Laparosc Endosc 1991;1:138–143.
9. Kelly JJ, Watson DI, Chin KF, Devitt PG, Game PA, Jamieson GG. Laparoscopic Nissen fundoplication: clinical outcomes at 10 Years. J Am Coll Surg 2007;205:570–575. doi:10.1016/j.jamcollsurg.2007.05.024.
10. Eypasch E, Wood DS, Williams JI, Ure B, Neugebauer E, Troidl H. Der Gastrointestinale Lebensqualitätsindex (GLQI). Ein klinimetrischer index zur befindlichkeitsmessung in der gastroenterologischen Chirurgie. Chirurg. 1993;64:264–274.
11. Eypasch E, Williams JI, Wood DS, Ure BM, Schmulling C, Neugebauer E et al. Gastrointestinal Quality of Life Index: development, validation and application of a new instrument. Br J Surg 1995;82:216–222. doi:10.1002/bjs.1800820229.
12. Fuchs KH, Freys SM, Heimbucher J, Thiede A. Erfahrungen mit der laparoskopischen technik in der antirefluxchirurgie. Chirurg 1993;64:317–323.
13. Fuchs KH, Breithaupt W, Fein M, Maroske J, Hammer I. Laparoscopic Nissen repair: indications, techniques and long-term benefits. Langenbecks Arch Surg. 2005;390:197–202. doi:10.1007/s00423-004-0489-4.
14. Bammer T, Hinder RA, Klaus A, Klingler PJ. Five- to eight-year outcome of the first laparoscopic Nissen fundoplications. J Gastrointest Surg. 2001;5:42–48. doi:10.1016/S1091-255X(01)80012-3.
15. Gockel I, Heintz A, Domeyer M, Kneist W, Trinh TT, Junginger T. Nichterosive und erosive gastroösophageale refluxerkrankung. Langzeitergebnisse der laparoskopischen anterioren Semifundoplikatio. Chirurg 2007;78:35–39. doi:10.1007/s00104-006-1246-8.
16. Kamolz T, Granderath FA, Schweiger UM, Pointner R. Laparoscopic Nissen fundoplication in patients with nonerosive reflux disease. Long-term quality-of-life assessment and surgical outcome. Surg Endosc 2005;19:494–500. doi:10.1007/s00464-003-9267-6.
17. Luostarinen M, Isolauri J, Laitinen J, Koskinen M, Keyrilainen O, Markkula H et al. Fate of Nissen fundoplication after 20 years. A clinical, endoscopical, and functional analysis. Gut 1993;34:1015–1020. doi:10.1136/gut.34.8.1015.
18. Spechler SJ, Lee E, Ahnen D, Goyal RK, Hirano I, Ramirez F et al. Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease: follow-up of a randomized controlled trial. JAMA 2001;285:2331–2338. doi:10.1001/jama.285.18.2331.
19. Lord RV, Kaminski A, Oberg S, Bowrey DJ, Hagen JA, DeMeester SR et al. Absence of gastroesophageal reflux disease in a majority of patients taking acid suppression medications after Nissen fundoplication. J Gastrointest Surg. 2002;6:3–9. doi:10.1016/S1091-255X(01)00031-2.
20. Thompson SK, Jamieson GG, Myers JC, Chin KF, Watson DI, Devitt PG. Recurrent heartburn after laparoscopic fundoplication is not always recurrent reflux. J Gastrointest Surg 2007;11:642–647. doi:10.1007/s11605-007-0163-6.
21. Galvani C, Fisichella PM, Gorodner MV, Perretta S, Patti MG. Symptoms are a poor indicator of reflux status after fundoplication for gastroesophageal reflux disease: role of esophageal functions tests. Arch Surg 2003;138:514–518. doi:10.1001/archsurg.138.5.514.
22. Ludemann R, Watson DI, Jamieson GG, Game PA, Devitt PG. Five-year follow-up of a randomized clinical trial of laparoscopic total versus anterior 180 degrees fundoplication. Br J Surg 2005;92:240–243. doi:10.1002/bjs.4762.
23. Horvath KD, Jobe BA, Herron DM, Swanstrom LL. Laparoscopic Toupet fundoplication is an inadequate procedure for patients with severe reflux disease. J Gastrointest Surg. 1999;3:583–391. doi:10.1016/S1091-255X(99)80079-1.
24. Fernando HC, Luketich JD, Christie NA, Ikramuddin S, Schauer PR. Outcomes of laparoscopic Toupet compared to laparoscopic Nissen fundoplication. Surg Endosc 2002;16:905–908. doi:10.1007/s004640080007.
25. Rydberg L, Ruth M, Abrahamsson H, Lundell L. Tailoring antireflux surgery: a randomized clinical trial. World J Surg 1999;23:612–618. doi:10.1007/PL00012356.
26. Kamolz T, Wykypiel HJ, Bammer T, Pointner R. Lebensqualität nach laparoskopischer Antirefluxchirurgie—Nissen fundoplicatio. Chirurg 1998;69:947–950. doi:10.1007/s001040050519.

J Gastrointest Surg (2008) 12:1900–1906
DOI 10.1007/s11605-008-0674-9

Gastroesophageal Reflux Disease and Connective Tissue Disorders: Pathophysiology and Implications for Treatment

Marco G. Patti · Warren J. Gasper · Piero M. Fisichella · Ian Nipomnick · Francesco Palazzo

Received: 24 July 2008 / Accepted: 8 August 2008 / Published online: 3 September 2008

Abstract
Introduction It has been postulated that in patients with connective tissue disorders (CTD) and gastroesophageal reflux disease (GERD), esophageal function is generally deteriorated, often with complete absence of peristalsis. This belief has led to the common recommendation of avoiding antireflux surgery for fear of creating or worsening dysphagia.
Methods We hypothesized that in most patients with CTD and GERD: (a) esophageal function is often preserved; (b) peristalsis is more frequently absent when end-stage lung disease (ESLD) is also present; (c) a tailored surgical approach (partial or total fundoplication) based on the findings of esophageal manometry allows control of reflux symptoms without a high incidence of postoperative dysphagia. Forty-eight patients with CTD were evaluated by esophageal manometry and 24-hour pH monitoring (EFT). Twenty patients (group A) had EFT because of foregut symptoms, and 28 patients with ESLD (group B) had EFT as part of the lung transplant evaluation. Two hundred and eighty-six consecutive patients with GERD by pH monitoring served as a control group (group C). A laparoscopic fundoplication was performed in two group A patients (total), eight group B patients (three patients total, five patients partial) and in all group C patients (total).
Results Esophageal peristalsis was preserved in all patients with CTD and GERD. In contrast, peristalsis was absent in about half of patients when ESLD was also present. A tailored surgical approach resulted in control of reflux symptoms in all patients. One patient only developed postoperative dysphagia, which resolved with two Savary dilatations.
Conclusion These data show that esophageal motor function is preserved in most patients with CTD, so that they should be offered antireflux surgery early in the course of their disease to prevent esophageal and respiratory complications. In patients with ESLD in whom peristalsis is absent, a partial rather than a total fundoplication should be performed, as it allows control of reflux symptoms while avoiding postoperative dysphagia.

Poster presentation, Society for Surgery of the Alimentary Tract, San Diego, CA, May 19, 2008.

M. G. Patti (✉)
Department of Surgery,
University of Chicago Pritzker School of Medicine,
5841 S. Maryland Ave, MC 5095, Room G-201,
Chicago, IL 60637, USA
e-mail: mpatti@surgery.bsd.uchicago.edu

W. J. Gasper · I. Nipomnick · F. Palazzo
Department of Surgery, University of California, San Francisco,
San Francisco, CA, USA

P. M. Fisichella
Department of Surgery, Loyola University Medical Center,
Maywood, IL, USA

Keywords Connective tissue disorders · Gastroesophageal reflux disease · Esophageal peristalsis · Esophageal manometry · Ambulatory pH monitoring · Laparoscopic fundoplication · End-stage lung disease

Introduction

Connective tissue disorders (CTD) are systemic diseases that can affect several organs. They share the common features of cutaneous and gastrointestinal tract involvement, most commonly esophageal dysmotility and gastroesophageal reflux disease (GERD). Up to 40% to 60% of these patients can develop complications of GERD such as an esophageal

stricture or Barrett's esophagus.[1] In addition, the lungs are often involved by the disease process, and 60% of patients eventually progress to end-stage lung disease (ESLD), which causes severe morbidity and mortality.[2] When GERD is present, patients are usually managed with acid-suppressing medications on the assumption that because esophageal function is routinely deteriorated,[3] antireflux surgery would create or worsen dysphagia. We hypothesize that in most patients with CTD and GERD: (a) esophageal function is preserved; (b) peristalsis is frequently absent only when ESLD is also present; and (c) a tailored surgical approach (total or partial fundoplication) can control reflux symptoms without a high incidence of postoperative dysphagia.

Patients and Methods

Patients with CTD were identified by a retrospective search of a prospectively acquired database of esophageal manometry and ambulatory 24-hour pH monitoring data. We screened a total of 2,973 patients evaluated in the Swallowing Center of the University of California San Francisco between August 1, 2000 and May 31, 2007. We excluded patients whose connective tissue disorder diagnosis had not been confirmed by a rheumatologist, as well as patients who had prior esophageal surgery. A cohort of 286 consecutive patients with GERD (by pH monitoring) who underwent a laparoscopic Nissen fundoplication between October 1, 1992 and May 30, 2004 was used as a control group.[4] Patients who had undergone prior antireflux surgery (open fundoplication, fundoplication for paraesophageal hernia, partial fundoplication, revision fundoplication) or patients who had a diagnosis of connective tissue disorder were excluded from the control group.

Symptomatic Evaluation

All patients referred for esophageal function tests had a standardized interview with a physician or a technician. Patients estimated the severity of their symptoms (heartburn, regurgitation, and dysphagia) according to a 5-point scale.[5] Follow-up was performed in general surgery clinics two and 6 weeks postoperatively, and subsequently in pulmonary clinics or by phone interview every 4 months.

Esophageal Manometry

Patients stopped medications that might interfere with esophageal motility at least 48 hours before the procedure. After an overnight fast, manometry was performed using an 8-lumen manometry catheter, continuously perfused by a pneumohydraulic capillary infusion system connected to a polygraph. Lower esophageal sphincter (LES) position and pressure were determined using the station pull through technique, with 0.5-cm increments between stations. Esophageal peristalsis was measured with ten swallows of 5 mL of water given at 30-s intervals. Peristaltic wave amplitude, duration, and velocity were recorded at 3, 8, 13, and 18 cm above the upper border of the manometrically determined LES. Peristaltic wave amplitude was then independently calculated for the lower esophagus (3 and 8 cm above the LES, DEA) and for the proximal esophagus (13 and 18 cm above the LES, PEA).[6]

Ambulatory pH Monitoring

Acid-reducing medications were stopped 3 days (histamine H_2-receptor antagonists) to 14 days (proton pump inhibitors) before the test. A pH probe was placed in the esophagus to measure acid exposure 5 above the upper border of the manometrically determined LES. Patients were instructed to eat an unrestricted diet and avoid acid-suppressing medications during the study. Based on the collected data, a composite reflux score (i.e., DeMeester score) was calculated for the distal esophagus (normal <14.7).[7] The data were analyzed using a commercial software program (Gastrosoft, Medtronic Functional Diagnostic, Shoreview, MN).

Laparoscopic Fundoplication

An estimate of anesthetic risk was calculated for all patients according to the American Society of Anesthesiologists (ASA) assessment. Standard ASA protocols were used to monitor patients while under general anesthesia. In patients with ESLD, an arterial blood pressure monitoring via a radial artery cannula and central venous catheters were placed as needed by the anesthesiologist. A senior anesthesiologist directed intraoperative management and communicated directly with the attending surgeon during the operation. A senior laparoscopic foregut surgeon performed the operation with the assistance of a senior resident or fellow. The following steps were routinely followed: (1) mobilization of the esophagus in the posterior mediastinum; (2) division of all short gastric vessels; (3) approximation of the right and left pillar of the crus behind the esophagus; (4) creation of a wrap around a 56 French bougie. A total (360°) fundoplication was routinely performed. A partial (240°) fundoplication was instead performed only when peristalsis was absent.[8]

Statistical Analysis

Statistical analysis was performed using Prism statistical software, (Graphpad Software Inc, San Diego, CA). Differences between groups were analyzed using the Fisher's

Exact Test for proportions or Mann–Whitney *U* test for continuous variables. Non-parametric statistical analyses were performed. The study protocol was approved by the University of California San Francisco Committee on Human Research.

Results

Patients

Forty-eight patients with connective tissue disorders (CTD) were evaluated by esophageal manometry and ambulatory 24-hour pH monitoring (EFT). Twenty patients with CTD (group A, 42%) had EFT because of the presence of foregut symptoms (heartburn, regurgitation, or dysphagia), and 28 patients with CTD and end-stage lung disease (ESLD) (group B, 58%) had EFT as part of the lung transplant evaluation. Two hundred and eighty-six consecutive patients with GERD who underwent a laparoscopic Nissen fundoplication (group C) served as a control group for esophageal motility, acid exposure, and surgical outcome. Demographic data for the three groups are shown in Table 1.

Manometric Profile

There was no difference in LES pressure between the three groups (Table 2). The three groups, however, differed substantially when esophageal peristalsis was considered. In groups A and C, the mean wave amplitude was normal, and about one third of patients had abnormal motility (low amplitude waves and/or abnormal propagation). Peristalsis was always present. In contrast, 83% of group B patients had abnormal esophageal motility, and peristalsis was absent in almost half of them.

Reflux Profile

Pathologic reflux was present in 70% and 86% of group A and group B patients (Table 3). All group C patients had abnormal reflux, as this was one of the criteria for a fundoplication. Among patients with pathologic reflux, the DeMeester score was higher in group B patients compared to group A and group C patients. In addition, group B patients had a higher acid exposure in the supine position and a slower acid clearance (higher number of episodes of reflux longer than 5 min).

Laparoscopic Fundoplication

Two patients in group A underwent a total (360°) fundoplication and eight patients in group B underwent either a total (360°; three patients) or a partial (240°; five patients) fundoplication. All group C patients underwent a total fundoplication (Table 4). In one group A patient, the operation was converted to a laparotomy and one patient developed postoperative atrial fibrillation requiring a 6-day hospital stay. In group B, all operations were completed laparoscopically. One patient (previous bilateral lung transplant) developed pneumonia postoperatively and remained in the hospital for 14 days for bronchial stenting and antibiotics. In group C, five operations were converted to laparotomy and there were six intraoperative complications (one gastric perforation, two splenic injuries not requiring splenectomy, and three pneumothoraces requiring tube thoracostomy). In group C, eight patients had postoperative complications (one myocardial infarction, two pleural effusions, one pneumonia, one wound infection, and three urinary retention episodes). The median length of hospital stay after fundoplication was extended in group B because three of the operations were done during

Table 1 Patient Characteristics

	Group A (20 patients)	Group B (28 patients)	Group C (286 patients)
Median age, year (range)	52 (29–73)	48 (25–70)	48 (14–88)
Female sex	18 (90%)	19 (68%)	128 (44%)
Connective tissue disorder			
Scleroderma	4 (20%)	18 (64%)	n/a
Systemic lupus erythematosus (SLE)	8 (40%)	0	n/a
Mixed connective tissue disease	2 (10%)	5 (18%)	n/a
Dermatomyositis/polymyositis	3 (15%)	5 (18%)	n/a
Other	3 (15%)	0	n/a
Symptom prevalence			
Any typical symptom	20 (100%)	20 (71%)	278 (97%)
Heartburn	15 (75%)	18 (64%)	251 (88%)
Dysphagia	15 (75%)	11 (39%)	108 (38%)
Regurgitation	12 (60%)	13 (46%)	204 (71%)

Other diagnoses: Rheumatoid arthritis, one patient; Sjögren's syndrome, two patients.

Table 2 Esophageal Manometry

	Group A	Group B	Group C
LES pressure, median (IQR)	14 (6–20)	10 (6–14)	10 (7–13)
Abnormal peristalsis (%)	5 (36%)*	20 (83%)*·**	103 (36%)**
Absent peristalsis (%)	0*	11 (46%)*·**	0**
PEA (mmHg), median (IQR)	61 (39–99)*	26 (0–46)*·**	53 (38–72)**
DEA (mmHg), median (IQR)	76 (54–139)*	19 (0–54)*·**	79 (51–107)**

"Abnormal peristalsis" was defined as nonspecific esophageal motility disorder (NSEMD), ineffectual esophageal motility (IEM) or no peristalsis.
LES lower esophageal sphincter, *PEA* proximal esophageal amplitude, *DEA* distal esophageal amplitude
*$p<0.05$, A vs. B; **$p<0.05$, B vs. C

the same admission after a lung transplant. For the five patients admitted for an elective fundoplication, the median length of hospital stay was 3 days.

Median duration of follow-up was 25 months for group A, 10 months for group B, and 31 months for group C. Fundoplication resulted in control of reflux symptoms in all group A and group B patients, and in 90% of group C patients. The rate of postoperative dysphagia was very low in all groups (Table 4). One patient in group B (absent peristalsis) developed dysphagia, which resolved after two Savary dilatations. In group C, 15 patients (5.2%) developed dysphagia, and a total of 29 dilatations were performed.

Discussion

The results of our study show that in patients with CTD: (a) peristalsis is usually preserved and esophageal acid exposure is similar to that of patients with GERD only; (b) when end-stage lung disease is also present, peristalsis is absent in about half of the patients, and the esophageal acid exposure is more severe; and (c) a surgical approach tailored to the esophageal motility profile allows control of reflux symptoms with a low incidence of postoperative dysphagia even when peristalsis is absent.

Connective Tissue Disorders and Esophageal Motility

The gastrointestinal tract is frequently involved in patients with CTD, as it represents the second most common manifestation after skin disease. The esophagus is affected in up to 90% of patients, as the disease process causes some degree of atrophy and fibrosis of the smooth muscles in the distal two/thirds of the esophagus. As a consequence of the compromised motility, GERD is frequently present.

It is a common belief that in addition to a hypotensive lower esophageal sphincter (LES), peristalsis is frequently absent.[9,10] Our study, however, shows that peristalsis is preserved in all patients with CTD when no other organs other than the esophagus are involved. Specifically, we demonstrated that in most patients with cutaneous and gastrointestinal manifestations only, the motility profile was similar to that of patients with GERD but without CTD. Group A and group C patients had, in fact, similar LES pressure and frequency of abnormal peristalsis. In addition, peristalsis was always present. Motility instead differed substantially in patients with CTD when ESLD was also present. In group B, peristalsis was indeed abnormal in about 80% of patients both in the distal and proximal esophagus, and peristalsis was absent in about half of them. This finding has been documented by others.[11,12] For instance, Marie and colleagues demonstrated that peristalsis

Table 3 Ambulatory 24-hour pH Monitoring

	Group A	Group B	Group C
Median number of episodes (IQR)	160 (110–232)	234 (150–343)	171 (118–234)
Median number of episodes >5 min (IQR)	8 (4–13)	13 (4–18)*	6 (3–10)*
Median percent of time pH <4, total (IQR)	15 (11–25)	18 (13–31)	12 (8–21)
Median percent of time pH <4, upright (IQR)	16 (9–21)	16 (6–31)	14 (8–21)
Median percent of time pH <4, supine (IQR)	2 (1–37)	24 (11–36)*	9 (2–21)*
Prevalence of distal reflux	70%	86%	100%
Median reflux score for patients with GERD (IQR)	42 (34–87)**	83 (56–119)*	49 (15–77)*

Normal reflux (DeMeester) score: <14.7.
*$p<0.05$, B vs. C; **$p<0.05$, A vs. B.

Table 4 Operative Data and Postoperative Outcome

	Group A	Group B	Group C
Fundoplication			
Total (360°)	2	3	286
Partial (240°)	0	5	0
Intra operative complications	0	0	6 (2.1%)
Conversion to laparotomy	1 (5%)	0	5 (1.8%)
Post operative complications	1 (5%)	1 (3.6%)	8 (2.8%)
Post operative dysphagia	0	1 (3.6%)	15 (5.2%)
Median length of hospital stay, days (IQR)	4 (2–6)	5 (2–14)	1 (1–2)
Control of symptoms (% patients)	100	100[a]	90

LES lower esophageal sphincter, *PEA* proximal esophageal amplitude, *DEA* distal esophageal amplitude
[a] One patient developed postoperative dysphagia, which resolved with two Savary dilatations.

was absent in 52% of patients with systemic sclerosis and interstitial lung disease (ILD),[11] while Johnson documented lack of peristalsis in 77% of similar patients.[12]

As a consequence of the different esophageal function, the reflux profile documented by ambulatory pH monitoring was very different among the three groups of patients. The amount of reflux was similar in group A and group C patients (p=NS). The reflux score was instead higher in group B patients (A vs. B and C vs. B<0.05), who also had more supine reflux and more episodes of reflux longer than 5 min. These findings are very important because supine/nocturnal reflux is more dangerous due to the lack of gravity, the decreased production of saliva, and the less frequent swallowing. The elevated number of reflux episodes longer than 5 min indicates a slower esophageal acid clearance with the possibility of more severe mucosal damage such as strictures, and of a more proximal extent of the refluxate with aspiration.[12,13,14]

Clinical Implications

It has been shown that while abnormal mechanical characteristics (low pressure and decreased length) or abnormal functional behavior (transient relaxations) of the LES has a permissive role that allows gastroesophageal reflux to occur, esophageal peristalsis is the primary determinant of esophageal clearance.[14,15] In addition, there is evidence that when a panesophageal motility disorders is present, acid refluxes all the way to the upper esophagus with an increased risk of aspiration.[12,13] For instance, we found that in group B patients (Table 3) the LES was hypotensive, but in addition peristalsis was impaired not only in the distal (DEA) but also in the proximal esophagus (PEA). Therefore, it is reasonable to suggest that severe esophageal involvement can cause or contribute to the development of pulmonary complications in patients with CTD through repeated episodes of microaspiration. For instance, in a prospective study of patients with systemic sclerosis, Marie and colleagues identified a correlation between the degree of esophageal motility abnormalities (determined by manometry) and evidence for interstitial lung disease (ILD), both by pulmonary function tests and high-resolution computed tomography.[11] In addition, at 2-year follow-up, patients with severe esophageal motility had a faster deterioration of lung function and a higher frequency of ILD on high-resolution CT scans. The findings of this study strongly suggest that GERD may be one of the contributing factors of ILD in patients with systemic sclerosis.[11] Similarly, Afeltra et al. found an 85% prevalence of ILD in patients with connective tissue disease,[16] while Johnson et al. found a correlation between the severity of GERD and pulmonary manifestations in 12 of 13 patients (92%) with systemic sclerosis.[12] When the lungs are involved by the disease process, the prognosis and life expectancy become much worse. For instance, Bryan et al. found that pulmonary disorders were the most common cause of death among patients with systemic sclerosis.[17] During a 5-year follow-up, 21% of patients died of pulmonary complications.[17]

Therapeutic Implications

Proton pump inhibitors have been the main form of treatment for GERD in patients with CTD, while surgery has been rarely considered.[18,19] This approach stems from the belief that peristalsis is absent in most patients with CTD so that a fundoplication must be avoided for fear of creating or worsening dysphagia. This mind-set has several pitfalls because of the following reasons:

- Treatment of GERD in patients with CTD is not able to achieve healing of esophagitis even when high doses are used.[18] Even adding ranitidine at night to omeprazole does not improve nocturnal acid breakthrough and quality of life in these patients.[19]
- Data from impedance studies show that treatment with acid reducing medications only affects acid production

and raises the pH of the gastric refluxate, but reflux still occurs as the frequency and duration of reflux episodes is not affected.[20,21,22] This observation explains the persistence of symptoms and mucosal injury while on proton pump therapy, and it suggests the need for an antireflux operation to restore the competence of the gastroesophageal junction and stop any type of reflux, independent from its pH.[20] For instance, Mainie et al. were able to identify by impedance pH monitoring patients whose cough was due to non-acid reflux while treated by proton pump inhibitors.[22] A laparoscopic Nissen fundoplication was able to cure symptoms in 13 of 14 such patients (93%).[22]

– Finally, our study shows that a fundoplication was effective in resolving reflux symptoms while it was associated to a minimal incidence of postoperative dysphagia. One patient only experienced troublesome dysphagia postoperatively, but it resolved with bougie dilatations. No reoperations were needed. We used a total fundoplication even in patients with weak peristalsis, but chose a partial fundoplication when peristalsis was absent.[8] This approach is similar to that used in patients with achalasia in whom a partial (anterior or posterior) fundoplication is added to the Heller myotomy as a total fundoplication could cause an obstacle to the esophageal emptying because peristalsis is absent.[23] Similarly, Watson et al. performed a laparoscopic fundoplication in 26 patients with GERD (ten had scleroderma) in whom manometry had shown complete absence of peristalsis.[24] At a 5- to 12-year follow-up, a good symptomatic outcome was achieved in 93% of them.[24] In addition, there is evidence that esophageal dysfunction does not always worsen in patients with systemic sclerosis. For instance, Dantas et al. observed that during a median follow-up of 40 months esophageal function worsened in 6% of patients only.[25] Furthermore, it is known that a properly constructed fundoplication increases not only LES pressure but also the strength of esophageal peristalsis.[26,27]

Our study has some limitations. Esophageal manometry was performed one time only, so that the manometric findings are a brief snapshot in time of an individual's esophageal performance, and it is not known if they remain constant over time. In addition, the postoperative follow-up was based on the symptomatic evaluation only, but pH monitoring generally was not repeated postoperatively. Therefore, we do not know if a partial fundoplication determined the same degree of reflux control as a total fundoplication.

Even considering these limitations, we feel that our study supports the notion that patients with CTD should be screened early in the course of their disease by esophageal function tests. If GERD is present, a fundoplication should be offered early to prevent esophageal and extra-esophageal complications.

References

1. Zamost BJ, Hirschberg J, Ippoliti AF, Furst DE, Clements PJ, Weinstein WM. Esophagitis in scleroderma. Prevalence and risk factors. Gastroenterology 1987;92:421–428.
2. Remy-Jardin M, Remy J, Wallaert B, Bataille D, Hatron PY. Pulmonary involvement in progressive systemic sclerosis: sequential evaluation with CT, pulmonary function tests, and bronchoalveolar lavage. Radiology 1993;188:499–506.
3. Shoenut JP, Wieler JA, Micflikier AB. The extent and pattern of gastro-oesophageal reflux in patients with scleroderma oesophagus: the effect of low-dose omeprazole. Aliment Pharmacol Ther 1993;7:509–13.
4. Tedesco P, Lobo E, Fisichella PM, Way LW, Patti MG. Laparoscopic fundoplication in elderly patients with gastroesophageal reflux disease. Arch Surg 2006;141:289–292. doi:10.1001/archsurg.141.3.289.
5. Sweet MP, Herbella FA, Leard L et al. The prevalence of distal and proximal gastroesophageal reflux in patients awaiting lung transplantation. Ann Surg 2006;244:491–497.
6. Patti MG, Fisichella PM, Perretta S. Preoperative evaluation of patients with gastroesophageal reflux disease. J Laparoendosc Adv Surg Tech A 2001;11:327–331. doi:10.1089/10926420152761833.
7. Jamieson JR, Stein HJ, DeMeester TR et al. Ambulatory 24-h esophageal pH monitoring: normal values, optimal thresholds, specificity, sensitivity, and reproducibility. Am J Gastroenterol 1992;87:1102–1111.
8. Patti MG, Robinson T, Galvani C, Gorodner MV, Fisichella PM, Way LW. Total fundoplication is superior to partial fundoplication even when esophageal peristalsis is weak. J Am Coll Surg 2004;198:863–870. doi:10.1016/j.jamcollsurg.2004.01.029.
9. Henry MACA, Harbermann MC, Rocha OM. Esophageal motor disturbances in progressive systemic sclerosis. Dis Esophagus 1999;12:51–53. doi:10.1046/j.1442-2050.1999.00005.x.
10. Airo' P, Della Casa D, Danieli E, Missale G, Cattaneo R, Cestari R. Oesophageal manometry in early and definite systemic sclerosis. Clin Rheumatol 2005;24:370–376. doi:10.1007/s10067-004-1049-6.
11. Marie I, Dominique S, Levesque H, Ducrotte P, Denis P, Hellot MF et al. Esophageal involvement and pulmonary manifestations in systemic sclerosis. Arthritis Rheum 2001;45:346–354. doi:10.1002/1529-0131(200108)45:4<346::AID-ART347>3.0.CO;2-L.
12. Johnson DA, Drane WE, Curran J, Cattau EL, Ciarleglio C, Khan A et al. Pulmonary disease in progressive systemic sclerosis. A complication of gastroesophageal reflux and occult aspiration? Arch Intern Med 1989;149:589–593. doi:10.1001/archinte.149.3.589.
13. Patti MG, debas HT, Pellegrini CA. Clinical and functional characterization of high gastroesophageal reflux. Am J Surg 1993;165:163–166. doi:10.1016/S0002-9610(05)80421-0.
14. Diener U, Patti MG, Molena D, Fsichella PM, Way LW. Esophageal dysmotility and gastroesophageal reflux disease. J Gastrointest Surg 2001;5:260–265. doi:10.1016/S1091-255X(01)80046-9.
15. Kahrilas PJ, Dodds WJ, Hogan WJ. Effect of peristaltic dysfunction on esophageal volume clearance. Gastroenterol 1988;94:73–80.
16. Afeltra A, Zennaro D, Garzia P, Gigante A, Vadacca M, Riggiero A et al. Prevalence of interstitial lung involvement in patients with

connective tissue diseases assessed with high-resolution computed tomography. Scand J Rheumatol. 2006;35:388–394. doi:10.1080/03009740600844381.
17. Bryan C, Knight C, Black CM, Silman AJ. Prediction of five-year survival following presentation with scleroderma: development of a simple model using three disease factors at first visit. Arthritis Rheum 1999;42:2660–2665. doi:10.1002/1529-0131(199912)42:12<2660::AID-ANR23>3.0.CO;2-N.
18. Hendel L, Hage E, Hendel J, Stentoft P. Omeprazole in the long-term treatment of severe gastro-oesophageal reflux disease in patients with systemic sclerosis. Aliment Pharmacol Ther 1992;6:565–577.
19. Janiak P, Thumshirn M, Menne D, Fox M, Halim S, Fried M et al. Clinical trial: the effect of adding ranitidine at night to twice daily omeprazole therapy on nocturnal acid breakthrough and acid reflux in patients with systemic sclerosis—a randomized controlled, cross-over trial. Aliment Pharmacol Ther 2007;26:1259–1265.
20. Tamhankar AP, Peters JH, Portale G, Hsieh CC, Hagen JA, Bremner CG et al. Omeprazole does not reduce gastroesophageal relux: new insights using multichannel intraluminal impedance technology. J Gastrointest Surg 2004;8:888–896. doi:10.1016/j.gassur.2004.08.001.
21. Mianie I, Tutuian R, Shay S, Vela M, Zhang X, Sifrim D et al. Acid and non-acid reflux in patients with persistent symptoms despite acid suppressive therapy: a multicentre study using combined ambulatory impedance-pH monitoring. Gut 2006;55:1398–1402. doi:10.1136/gut.2005.087668.
22. Mainie I, Tutuina R, Agrawal A, Admas D, Castell D. Comibined multichannel intraluminal impedance-pH monitoring to select patients with persistent gastro-esophageal reflux for laparoscopic Nissen fundoplication. Br J Surg 2006;93:1483–1487. doi:10.1002/bjs.5493.
23. Richards WO, Torquati A, Holzman MD, Khaitan L, Byrne D, Lufti R et al. Heller myotomy versus Heller myotomy with Dor fundoplication for achalasia: a prospective, randomized, double blind clinical trial. Ann Surg 2004;240:691–694. doi:10.1097/01.sla.0000136940.32255.51.
24. Watson DI, Jamieson GG, Bessell JR, Devitt PG. Laparoscopic fundoplication in patients with an aperistaltic esophagus and gastroesophageal reflux. Dis Esophagus 2006;19:94–98. doi:10.1111/j.1442-2050.2006.00547.x.
25. Dantas RO, Meneghelli UG, Oliveira RB, Villanova MG. Esophageal dysfunction does not always worsen in systemic sclerosis. J Clin Gastroenterol 1993;17:281–285. doi:10.1097/00004836-199312000-00003.
26. Heider TR, Behrns KE, Koruda MF, Shaheen NF, Lucktong TA, Bradshaw B et al. Fundoplication improves disordered esophageal motility. J Gastrointest Surg 2003;7:159–163. doi:10.1016/S1091-255X(02)00145-2.
27. Herbella FAM, Tedesco P, Nipomnick I, Fisichella PM, Patti MG. Effect of partial and total fundoplication on esophageal body motility. Surg Endosc 2007;21:285–288. doi:10.1007/s00464-006-0108-2.

J Gastrointest Surg (2008) 12:1907–1911
DOI 10.1007/s11605-008-0664-y

Outcomes of Esophagectomy According to Surgeon's Training: General vs. Thoracic

Brian R. Smith · Marcelo W. Hinojosa · Kevin M. Reavis · Ninh T. Nguyen

Received: 20 May 2008 / Accepted: 8 August 2008 / Published online: 3 September 2008

Abstract
Introduction Esophagectomy is performed by general and thoracic surgeons with the type of operation often dictated by the surgeons' training. The objective was to investigate outcomes of esophagectomy to determine if they varied according to surgeon's training.
Methods Clinical data of patients who underwent partial or total esophagectomy for esophageal cancer from 2003 through 2007 were obtained from the University HealthSystem Consortium database. Data were examined between general versus thoracic surgeon and were reviewed for number and type of operations performed, demographics, length of stay, and postoperative morbidity and mortality.
Results During the 54-month period, 2,657 esophagectomies were performed; 1,079 (41%) by general surgeons and 1,578 (59%) by thoracic surgeons. More blunt transhiatal esophagectomies were performed by general surgeons compared to thoracic surgeons (56% vs. 37%, $p<0.01$) while more Ivor Lewis resections were performed by thoracic surgeons (63% vs. 44%, $p<0.01$). Thoracic surgery certification did not significantly affected outcomes with regards to mean hospital and ICU stay, complications, observed mortality, and mortality index.
Conclusions In academic centers, the majority of esophagectomies for carcinoma are performed by thoracic surgeons who favor the Ivor Lewis approach, while general surgeons favor the blunt transhiatal approach. Despite these differences, specialty training does not appear an important factor affecting outcome.

Keywords Esophagectomy · Subspecialty training · Ivor Lewis · Transhiatal

Presented at the 49th annual meeting of the Society for Surgery of the Alimentary Tract May 20, 2008 San Diego, CA, USA.

B. R. Smith · M. W. Hinojosa · K. M. Reavis · N. T. Nguyen
Department of Surgery, University of California,
Irvine Medical Center,
Orange, CA, USA

N. T. Nguyen (✉)
Division of Gastrointestinal Surgery, University of California,
Irvine Medical Center,
333 City Blvd West, Suite 850,
Orange, CA 92868, USA
e-mail: Ninhn@uci.edu

Introduction

Esophageal resection is typically performed in a high-risk, elderly population suffering from many comorbid cardiopulmonary and nutritional conditions. Optimal outcomes for esophagectomy often depend on the presence of an experienced surgical team working in a multidisciplinary program. A dedicated surgical team includes well-trained surgeons, dedicated anesthesiologists, and operative support staff familiar with major abdominal and thoracic surgical procedures. A well-structured program includes a hospital facility capable of handling complex esophageal operations with the presence of appropriate consultative and critical care staff, experienced nursing staff, and a collaborative mutidisciplinary system in place for follow-up.

Two approaches to surgical resection of the esophagus exist, including blunt/transhiatal resection and transthoracic/Ivor Lewis esophagectomy. Both general and cardiothoracic

trained surgeons perform esophagectomy; however, the preference for operative approaches (transhiatal vs. transthoracic) depends on the surgeons' training and experience. Neither operative approach has been shown to confer a clinical or survival advantage. Debate persists as to which operation is the ideal on an oncologic basis. The aim of this study was to determine the volume and types of operation performed by each group of surgeons and determine if the type of surgeon's training affect outcome.

Materials and Methods

Database

The University HealthSystem Consortium (UHC) Clinical Database is an administrative, clinical, and financial database providing comparative data analysis between academic institutions. The UHC database contains patient discharge data from both academic health centers and affiliated community hospitals throughout the United States. It also contains discharge information for inpatient hospital stays such as patient characteristics, postoperative length of stay, 30-day readmission, overall and specific postoperative morbidity, including observed and expected (risk-adjusted) in-hospital mortality, inpatient care costs, and discharge disposition. One of the benefits of the UHC Clinical Database is the availability of risk-adjusted data for comparison between institutions. The database assigns a level of risk severity by grouping patients based on the severity and complexity of secondary diagnoses (comorbidities and complications). The comorbidity severity group is classified as minor, moderate, major, or extreme.

In-hospital mortality was defined as the percentage of patients who did not survive to hospital discharge. The UHC database does not provide information on death occurring after discharge, even if the death occurred within the 30 day perioperative period. Length of stay was defined as the period from the index procedure to hospital discharge. Complications included those related to cardiac, pulmonary, thrombotic, hemorrhagic, iatrogenic, and wound infectious events. In the UHC database cardiac complications include postoperative myocardial infarction as well as arrhythmias and other non-ischemic related cardiac compromise. Pulmonary complications included pneumonia and pulmonary function compromise. Thrombotic complications included both deep venous thrombosis and pulmonary embolism. Hemorrhagic complications included gastrointestinal bleeding as well as extraluminal bleeding episodes. Wound infectious complications included postoperative infections of surgical sites.

Data Analysis

The UHC database was analyzed for discharge data on all patients who underwent esophageal resection with a gastric neo-esophagus for the treatment of malignant esophageal disease between January 1, 2003 and June 30, 2007. Hospitalizations during which an esophageal resection was performed for the treatment of malignant esophageal disease were identified by appropriate diagnosis and procedural codes as specified by the *International Classification of Diseases*, 9th Edition, Clinical Modification (ICD-9-CM). The principal ICD-9 diagnosis codes for esophageal malignancy were used (1500, 1501, 1502, 1503, 1504, 1505, 1508, 1509, 1510, and 2301) as well as that for Barrett's esophagus (53085). The principal ICD-9 procedure codes for partial and total esophageal resection were used (4241, 4251, 4252, and 4242).

Comparative patient characteristics included the type of operation performed, age, gender, race, severity of illness, length of intensive care unit (ICU), and length of hospital stay, as well as overall perioperative complications, in-hospital (observed) mortality and mortality index (observed-to-expected mortality ratio). Hospital volumes were also analyzed for biases towards surgeon subspecialty based on individual institutions. Subspecialty surgical cases were determined by culling database results for individual institutions and categorizing them based on type of surgeon attesting to discharge data. Surgeons in the UHC database, while not listed individually by name, are labeled by the attesting facility according to the physician's specialty or subspecialty training. General surgeon cases were classified as attesting physicians with general, vascular, and oncologic surgical training and certification labels. Cardiothoracic surgeon cases were classified as those attesting physicians with cardiothoracic and/or thoracic surgery training and certification labeling.

Data are expressed as mean±standard deviation where applicable. Continuous variables were analyzed using 2-sample *t*-tests and categorical variables were analyzed with Pearson χ^2 tests. Parameters such as length of ICU stay and hospital stay were given as a mean variable for each institution. These values were weighted according to the number of cases performed at their respective institutions. Statistical analysis was performed on observed and severity-adjusted data with SPSS statistical software, version 12.0 (SPSS Inc., Chicago, IL, USA). *P* values less than 0.05 were considered statistically significant.

Results

Patient Characteristics and Demographics

From January 2003 to June 2007, a total of 2,657 patients underwent esophageal resection for the treatment of malignant

Table 1 Esophagectomy Demographics According to Surgical Subspecialty Training

	General surgeons	Thoracic surgeons	*p* value
Total esophagectomies	1,079	1,578	N/A
Blunt/transhiatal (%)	56	37	<0.01*
Ivor Lewis (%)	44	63	<0.01*
Gender: male (%)	80	81	N/A
Admission status (elective: urgent)	20:1	20:1	1.0
Race (%)			
Caucasian	81	84	0.05*
Black	4	4	0.68
Hispanic	2	1	0.02*
Asian	1	1	0.56
Other	12	10	0.14
Comorbid illness (%)			
Moderate	24.2	28.6	0.01*
Major	55.7	54.5	0.55
Extreme	20.1	16.9	0.04*

*$p \leq 0.05$, Chi-square tests

esophageal disease at 93 academic centers in the United States (Table 1); 1,079 (41%) were performed by general surgeons, while 1,578 (59%) were performed by thoracic surgeons. More blunt transhiatal esophagectomies were performed by general surgeons compared to thoracic surgeons (56% vs. 37%, $p<0.01$) while more Ivor Lewis resections were performed by thoracic surgeons (63% vs. 44%, $p<0.01$). Of the 68 centers where thoracic surgeons performed esophageal resection, 25 (37%) centers were considered to perform high-volume resection rates (≥13 resections/year). There were 77 centers where general surgeons performed esophageal resection, and of those, there were 21 (27%) centers that were considered high-volume. The mean number of cases performed per year in the general surgery group was 216 vs. 316 cases per year for the thoracic surgeon group. The majority of patients were male (81%). The two groups were comparable with respect to age, sex, and admission status. There was a higher proportion of Caucasian within the thoracic surgeon group (84% vs. 81%, $p=0.05$) but there was a higher proportion of Hispanic patients within the general surgeon group (2% vs. 1%, $p=0.02$). There was a significantly higher proportion of patients with moderate comorbidities operated by thoracic surgeons (28.6% vs. 24.2%, $p=0.01$) while there was a significantly higher proportion of extreme comorbid illnesses operated by general surgeons (20.1% vs. 16.9%, $p=0.04$).

Perioperative Outcomes

Overall, there was little difference in perioperative outcomes between the two groups of surgeons (Table 2). The overall complication rate between general and thoracic surgeons was similar (55% vs. 52%, respectively). The mean lengths of hospital stay for general and thoracic surgeons were comparable at 16.6±11.5 days and 16.9± 14.0 days, respectively. Mean ICU stay was 8.4 days for general surgeons, with 87% of patients admitted to the ICU at some point during hospitalization. Mean ICU stay was also 9.7 days for thoracic surgeons, with 73% of patients being admitted to the ICU during hospitalization. The in-hospital mortality rates were also comparable between both general and thoracic surgeons (3.6% and 2.9%, respectively). Mortality index (observed/expected mortality ratio) was similarly comparable between general and thoracic surgeons (0.79 vs. 0.65).

Discussion

Utilizing a large national academic database, the current study was able to demonstrate that thoracic trained surgeons perform more esophageal resections than do general surgeons. Thoracic surgeons favor the Ivor Lewis approach (63% of operations), while general surgeons favor the blunt/transhiatal approach (56% of resections). General surgeons operated on patients with higher comorbid illnesses than did thoracic surgeons. There were more centers that performed high-volume esophagectomy (≥13 operations/year) within the thoracic group compared to the general group (37% versus 27%). Despite all of the these differences, there were no differences in operative outcomes such as length of hospital stay, ICU days, overall morbidity, mortality, or mortality index between the two surgical groups.

Few studies have evaluated the differences in outcomes between subspecialty and non-subspecialty surgeons with regards to any operation. Limited data from lung,[1] gastric, colon[2] and select vascular surgeries[3,4] does exist. However, only one previous study addresses esophageal resections. Dimick et al. evaluated 1,946 esophageal resection patients from the Medicare database spanning the 2-year period from 1998–1999.[5] The intent of that study was to evaluate

Table 2 Perioperative Outcomes of Malignant Esophagectomy Performed by General vs. Thoracic Surgeons

Outcomes	General Surgeons	Thoracic Surgeons	p Value
Mean length of stay (days)	16.6±11.5	16.9±14.0	0.80
Mean ICU stay (days)	8.4	9.7	0.29
Overall complications (%)	55	52	0.11
In-hospital mortality (%)	3.6	2.9	0.31
Mortality index (obs/exp)	0.79	0.65	N/A

the so-called provider-level variable as it pertains to outcomes, as opposed to the hospital volume which has repeatedly been shown to have a significant impact on mortality. They found that in the 32% of patients who had their esophagectomy performed by a thoracic surgeon, mortality rates fell by 37% compared to non-thoracic surgeons. Despite this difference, however, mortality differences between high-volume hospitals and surgeons and low-volume hospitals and surgeons were larger than those between thoracic and general surgeons. They concluded that thoracic surgery training was associated with lower mortality after esophageal resection. These statistics are in stark contrast to our results which showed that 59% of esophagectomy procedures were performed by thoracic surgeon but there were no significant differences in the operative outcomes between the thoracic and general surgery groups. Other studies have evaluated surgeon volume as a predictive factor for mortality. Rouvelas et al. demonstrated, in a prospective study of 607 patients, a correlation between increasing surgeon volume and decreasing mortality.[6] Migliore et al. evaluated nine surgeons performing 195 esophageal cancer resections and found a 4.6-fold lower operative mortality rate in high-volume (>6 cases/year) surgeons than those with a lower volume.[7] The UHC database does not attribute volume to a particular surgeon, and as such, volume outcomes are only able to be examined by individual institutions. As a result, no conclusions for or against individual surgeon volume can be drawn from our study data.

Currently the most important factors affecting outcomes after esophagectomy are the number of operations performed by the surgeon as well as the number of esophageal resections performed by an institution.[8–11] This volume–outcome relationship also extends far beyond esophageal surgery to include various other forms of cancer as well as bariatric surgery.[12–14] According to the Leapfrog group, institutions performing more than 13 esophageal resections per year have the lowest mortality.[15] These guidelines have been broadly accepted by and are resulting in health care organizations promoting regionalization of care for more complex operations. And while little controversy exists over the surgeon–volume outcome relationship, our data represents one of the few studies to evaluate the impact of surgeon specialty training and its role on esophageal resection outcomes.

Data regarding the ideal operative approach to esophageal resection remain unclear, but with some distinct trends. Chang et al. retrospectively utilized the surveillance, epidemiology, and end results (SEER) database to evaluate 868 patients undergoing transhiatal versus transthoracic resection.[16] They found a lower operative mortality rate with transhiatal resection compared to the transthoracic approach (6.7% versus 13.1%). There was also improved short-term survival for transhiatal patients compared to transthoracic (30.5% versus 22.7%) that did not last beyond 5 years. Hulscher et al. evaluated 220 patients randomized to either transhiatal or transthoracic esophageal resection to determine overall and disease-free survival.[17] Transhiatal resection also showed decreased morbidity. However, in contrast to the study by Chang et al., there was a trend towards increased 5-year survival with the transthoracic approach. Similar 5-year trends towards increased survival with the transthoracic approach were found by Omloo et al. in 220 randomized patients.[18] Unfortunately, survival data are not recorded by the UHC database, precluding long-term mortality evaluation of either surgical approach in our study. However, lymph node yield is also significantly higher with Ivor Lewis transthoracic resection compared to transhiatal resection (68% versus 36% $\geq$ 19 nodes).[19] This may be a motivating reason for the higher rate of performance by subspecialists, as shown to account for 63% in our study. On the other hand, some cardiothoracic surgeons still advocate the transhiatal approach.[20]

This study has several noteworthy limitations. The UHC database is generated from discharge data and is limited to in-hospital morbidity and mortality without follow-up data. One example of these limitations relates to complications or deaths arising after discharge, as these data points are not available in this database. The coding of certain complications also has potential to be inaccurate because postoperative adverse events are often subjectively defined by the surgeon and may be coded differently (e.g. leaks) by clerical personnel. In addition, there is the possibility of erroneous labeling of surgeon specialty training by attesting institutions, particularly if a particular high-volume surgeon is consistently mislabeled by his/her own institution in the UHC database. Furthermore, there is also frequent criticism of the use of large databases due to poor uniformity of risk-stratification of patients, making comparisons between hospitals difficult. The UHC database uses an extensive risk adjustment methodology to assign an expected mortality to each patient based on medical comorbidities and operative complexity. This risk stratification process generates at least some level of equalization between patients at various institutions and provides results that are both more analogous and comparable. Our study was also limited to academic centers and the results may not be generalizable to nonacademic institutions. Additionally, it remains unclear what percentage of total annual esophageal resections this database represents, a fact which limits the ability to further generalize these results. Despite these limitations, in-hospital mortality and length of stay are accurate endpoints as these endpoints do not require subjective evaluation, and the large sample size of this study is important to examine the outcome of esophagectomy performed by general vs. thoracic surgeons.

Conclusion

This study analyzed the outcomes of esophagectomy for malignancy according to the surgeon's training using a national administrative database. We found that thoracic surgeons perform more esophagectomy than general surgeons. We also found that thoracic surgeons favored the Ivor Lewis approach while general surgeons favored the blunt transhiatal esophagectomy approach. Despite the differences in operative technique, there was no significant difference in patient's outcome when performed by thoracic trained vs. general surgeons. Therefore, surgical specialty training does not significantly affect outcomes in esophagectomy.

References

1. Goodney PP, Lucas FL, Stukel TA, Birkmeyer JD. Surgeon specialty and operative mortality with lung resection. Ann Surg 2005;241:179–184.
2. Callahan MA, Christos PJ, Gold HT, Mushlin AI, Daly JM. Influence of surgical subspecialty training on in-hospital mortality for gastrectomy and colectomy patients. Ann Surg 2003;238:629–636.
3. Cowan JA Jr, Dimick JB, Thompson BG, Stanley JC, Upchurch GR Jr. Surgeon volume as an indicator of outcomes after carotid endarterectomy: an effect independent of specialty practice and hospital volume. J Am Coll Surg 2002;195:814–821. doi:10.1016/S1072-7515(02)01345-5.
4. Hannan EL, Popp AJ, Feustel P, Halm E, Bernardini G, Waldman J et al. Association of surgical specialty and processes of care with patient outcomes for carotid endarterectomy. Stroke 2001;32:2890–2897. doi:10.1161/hs1201.099637.
5. Dimick JB, Goodney PP, Orringer MB, Birkmeyer JD. Specialty training and mortality after esophageal cancer resection. Ann Thorac Surg 2005;80:282–286. doi:10.1016/j.athoracsur.2005.01.044.
6. Rouvelas I, Jia C, Viklund P, Lindblad M, Lagergren J. Surgeon volume and postoperative mortality after oesophagectomy for cancer. Eur J Surg Oncol 2006;33:162–168. doi:10.1016/j.ejso.2006.10.029.
7. Migliore M, Choong CK, Lim E, Goldsmith KA, Ritchie A, Wells FC. A surgeon's case volume of oesophagectomy for cancer strongly influences the operative mortality rate. Eur J Cardiothorac Surg 2007;32:375–380. doi:10.1016/j.ejcts.2007.04.014.
8. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. N Engl J Med 2003;349:2117–2127. doi:10.1056/NEJMsa035205.
9. Migliore M, Choong CK, Lim E, Goldsmith KA, Ritchie A, Wells FC. A surgeon's case volume of oesophagectomy for cancer strongly influences the operative mortality rate. Eur J Cardiothorac Surg 2007;32:375–380. doi:10.1016/j.ejcts.2007.04.014.
10. Lin HC, Xirasagar S, Lee HC, Chai CY. Hospital volume and inpatient mortality after cancer-related gastrointestinal resections: the experience of an Asian country. Ann Surg Oncol 2006;13:1182–1188. doi:10.1245/s10434-006-9005-0.
11. Metzger R, Bollschweiler E, Vallböhmer D, Maish M, DeMeester TR, Hölscher AH. High volume centers for esophagectomy: what is the number needed to achieve low postoperative mortality? Dis Esophagus 2004;17:310–314. doi:10.1111/j.1442-2050.2004.00431.x.
12. Finlayson EV, Goodney PP, Birkmeyer JD. Hospital volume and operative mortality in cancer surgery: a national study. Arch Surg. 2003;138:721–725. doi:10.1001/archsurg.138.7.721.
13. Birkmeyer JD, Sun Y, Wong SL, Stukel TA. Hospital volume and late survival after cancer surgery. Ann Surg 2007;245:777–783. doi:10.1097/01.sla.0000252402.33814.dd.
14. Nguyen NT, Paya M, Stevens CM, Mavandadi S, Zainabadi K, Wilson SE. The relationship between hospital volume and outcome in bariatric surgery at academic medical centers. Ann Surg 2004;240:586–593.
15. Callcut RA, Breslin TM. Shaping the future of surgery: the role of private regulation in determining quality standards. Ann Surg 2006;243:304–312. doi:10.1097/01.sla.0000200854.34298.e3.
16. Chang AD, Ji H, Birkmeyer NJ, Orringer MB, Birkmeyer JD. Outcomes after transhiatal and transthoracic esophagectomy for cancer. Ann Thorac Surg 2008;85:424–429. doi:10.1016/j.athoracsur.2007.10.007.
17. Hulscher JBF, van Sandick JW, de Boer AGEM, Wijnhoven BPL, Tijssen JGP, Fockens P et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med 2005;347:1662–1669. doi:10.1056/NEJMoa022343.
18. Omloo JMT, Lagarde SM, Hulsher JBF, Reitsma JB, Fockens P, van Dekken H et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus. Five-year survival of a randomized clinical trial. Ann Surg 2007;246(6):992–1001.
19. Bogoevski D, Onken F, Koenig A, Kaifi JT, Schurr P, Sauter G et al. Is it time for a new TNM classification in esophageal carcinoma? Ann Surg 2008;247:633–641.
20. Orringer MB, Marshall B, Chang AC, Lee J, Pickens A, Lau CL. Two thousand transhiatal esophagectomies: changing trends, lessons learned. Ann Surg 2007;246:363–374. doi:10.1097/SLA.0b013e31814697f2.

J Gastrointest Surg (2008) 12:1912–1914
DOI 10.1007/s11605-008-0572-1

Gastrectomy and Lymphadenectomy for Gastric Cancer: is the Pancreas Safe?

Fernando A. Herbella, MD, PhD, TCBC · Ana C. Tineli · Jorge L. Wilson Jr. · Jose C. Del Grande, MD, PhD, TCBC

Received: 3 May 2008 / Accepted: 4 June 2008 / Published online: 9 July 2008

Abstract
Introduction Resection of the capsule of the pancreas is part of the radical operation proposed by oriental authors for the treatment of gastric cancer. It is unclear; however, if resection of the capsule is a safe procedure or even if it is necessary. This study aims to assess in patients treated for gastric cancer the occurrence of: (a) pancreatic fistula and (b) metastasis to the pancreatic capsule.
Methods We studied 80 patients (mean age 61 years, 42 males) submitted to gastrectomy with resection of the pancreatic capsule by hydrodissection. Patients with pancreatic disease, tumoral invasion of the pancreas, submitted to concomitant splenectomy, or anastomotic leakage were excluded. The tumor was located in the distal third of the stomach in 60% of the patients, in the middle third in 27%, and proximally in 12%. Total gastrectomy was performed in 27% of the cases and partial gastrectomy in 73%. In all patients, amylase activity in the drainage fluid was measured on day 2. If initial measurement was abnormal, subsequent measurements were performed in alternated days until normalization. Pancreatic fistula was defined as amylase levels greater than 600. In 25 of these patients (mean age 53 years, 16 males), the pancreatic capsule was histologically analyzed for metastasis.
Results Pancreatic fistula was diagnosed in eight (10%) patients. The mean amylase level was 5,863. Normalization of amylase levels was achieved within 7 days in all patients. No patient developed clinical signs of fistula besides abnormal amylase levels in the drainage fluid, such as intra-abdominal abscesses. Pancreatic fistula was associated to younger age (p=0.03) but not to gender (p=0.1), tumor location (p=0.6), and type of gastrectomy (p=0.8). Metastasis to the pancreatic capsule was not identified.
Conclusion In conclusion, resection of the pancreatic capsule must be discouraged due to subclinical pancreatic fistula in a significant number of the cases and absence of metastasis.

Keywords Pancreas · Gastric cancer · Gastrectomy · Fistula

Presented as poster at the Digestive Disease Week, May 17–22, 2008, San Diego, CA, USA.

F. A. Herbella MD, PhD, TCBC (✉) · A. C. Tineli · J. L. Wilson Jr. · J. C. Del Grande MD, PhD, TCBC
Department of Surgery, Division of Esophagus and Stomach, Federal University of Sao Paulo,
Rua Napoleao de Barros, 715 2nd floor,
Sao Paulo, Sao Paulo 04024-002, Brazil
e-mail: herbella.dcir@unifesp.epm.br

F. A. Herbella MD, PhD, TCBC
Surgical Gastroenterology, Division of Esophagus and Stomach, Hospital Sao Paulo,
Rua Diogo de Faria 1087 cj 301,
Sao Paulo, Sao Paulo 04037-003, Brazil

Introduction

The ideal surgical approach to treat gastric cancer is still a debatable topic. Gastrectomy and extended lymphadenectomy is the standard technique in the East, in opposite to less radical procedures favored in Western countries.[1] Every year, however, several papers are published showing survival benefits to the more radical operation.[2–4]

Resection of the capsule of the pancreas is part of the operation proposed by oriental authors. It is unclear, however, if resection of the pancreatic capsule is a safe procedure or even if it is necessary.

This study aims to assess in patients treated for gastric cancer the occurrence of: (a) pancreatic fistula and (b) metastasis to the pancreatic capsule.

Methods

Patients

We studied 80 patients (mean age 61.5±12.6 years, 42 males) submitted to radical gastrectomy for adenocarcinoma of the stomach with resection of the pancreatic capsule. Patients with pancreatic disease, tumoral invasion of the pancreas, submitted to concomitant splenectomy, or anastomotic leakage were excluded from analysis. Data were obtained from a prospective collected clinical database.

The gastric tumor was located in the distal third of the stomach in 60.0% (n=48) of the patients, in the middle third in 27.5% (n=22), and proximally in 12.5% (n=10).

Surgical Technique

Total gastrectomy was performed in 27.5% (n=22) of the cases and partial gastrectomy in 72.5% (n=58). D2 lymphadenectomy was performed in all cases, according to the Japanese school[5] with removal of the pancreatic capsule by hydrodissection (Fig. 1).

Pancreatic Fistula Assessment

In all patients, amylase activity in the drainage fluid was measured on postoperative day 2. If initial measurement was abnormal, subsequent measurements were performed in alternated days until normalization.

Pancreatic fistula was defined as amylase levels greater than 600.

Pancreatic Capsule Metastasis Assessment

In the last 25 patients (mean age 53±12.6 years, 16 males), the pancreatic capsule was histologically analyzed under hematoxylin–eosin staining for metastasis.

Statistics

Chi-square and Student's t tests were used as indicated. Statistical significance was defined as $p<0.05$.

Results

Pancreatic Fistula

Pancreatic fistula was diagnosed in eight (10%) patients. The mean amylase level was 5,863±11,855 (range 758–33,400) IU/l in these patients on postoperative day 2. Normalization of amylase levels was achieved within 7 days in all patients. No patient developed clinical signs of fistula such as intra-abdominal abscesses.

The presence of pancreatic fistula was not associated to gender (p=0.1), tumor location (p=0.6), and type of gastrectomy (p=0.8). Patients with pancreatic fistula had a younger age (mean age 52.2±10.1 years) compared to patients without fistula (mean age 62.3±12.6 years; p=0.03).

Pancreatic Capsule Metastasis

Metastasis to the pancreatic capsule was not identified.

Discussion

Our results show that: (a) subclinical pancreatic fistula occurs in 10% of the patients submitted to pancreatic capsule removal and (b) metastasis to the pancreatic capsule was not detected.

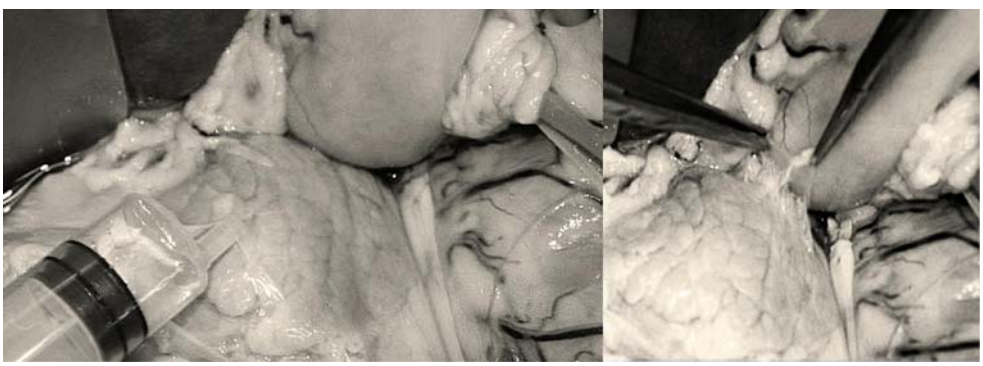

Figure 1 Technique of hydrodissection for removal of the pancreatic capsule.

Gastric Cancer Surgery and the Pancreas

The extent of lymphadenectomy necessary for gastric cancer cure remains controversial as a considerable variation exists between results of different studies.

Extended lymphadenectomy (D2–D3) seems to be associated to a higher index of complications when compared to less radical operations.[6–8] Also, the relative risk ratio for morbidity and mortality is significantly higher if pancreatectomy is associated to the gastrectomy.[7,9] There are no studies showing specific morbidity linked to resection of the pancreatic capsule.

Postgastrectomy pancreatic fistula has an incidence between 0% and 2%[9,10] in the absence of pancreatic resection and between 7% and 22% after distal pancreatosplenectomy.[9] Although the criteria used by different authors to define pancreatic fistula is variable,[9,11,12] our study detected a significant percentage of subclinical pancreatic fistula in the absence of pancreatic resection.

Gastric Cancer Surgery and Bursectomy

Bursectomy is the term created by some authors to describe the en bloc resection of the limits of the bursa omentalis, i.e., the posterior wall of the stomach anteriorly, the hepatogastric ligament superiorly, the superior layer of the transverse mesocolon inferiorly, and the capsule of the pancreas posteriorly. The procedure is recommended in the Japanese Gastric Cancer Treatment Guidelines[13] as part of the radical operation for gastric cancer. The purpose of this procedure is to remove cancer cells and micrometastases disseminated into the retro-stomach space.[14,15]

The real value of the bursectomy, however, has never been adequately assessed. Two studies demonstrated that free cancer cells are rarely found confined to the bursa omentalis[14] and that survival is not different among tumors located in the anterior versus posterior wall of the stomach.[15] Our study focused on the capsule of the pancreas, i.e., only one wall of the bursa omentalis, due to the risk of complications associated to pancreatic fistula. Our results failed to demonstrate microscopic metastasis to the capsule.

Conclusions

We concluded that the dissection of the anterior capsule of the pancreas can lead to potential complications, even if they were not necessarily seen in this small cohort. There certainly is no evidence in this dataset that the additional dissection yielded any benefit to the patients.

References

1. Davis PA, Sano T. The difference in gastric cancer between Japan, USA and Europe: what are the facts? what are the suggestions? Crit Rev Oncol Hematol 2001;40(1):77–94. doi:10.1016/S1040-8428(00)00131-1.
2. Sasagawa T, Solano H, Vega W, Mena F. The effectiveness of extended lymph node dissection for gastric cancer performed in Costa Rica under the supervision of a Japanese surgeon: a comparison with surgical results in Japan. Am J Surg 2008;195 (1):53–60. doi:10.1016/j.amjsurg.2007.01.028.
3. Schwarz RE, Smith DD. Clinical impact of lymphadenectomy extent in resectable gastric cancer of advanced stage. Ann Surg Oncol 2007;14(2):317–328. doi:10.1245/s10434-006-9218-2.
4. Oñate-Ocaña LF, Aiello-Crocifoglio V, Mondragón-Sánchez R, Ruiz-Molina JM. Survival benefit of D2 lymphadenectomy in patients with gastric adenocarcinoma. Ann Surg Oncol. 2000;7 (3):210–217. doi:10.1007/BF02523656.
5. Sakakibara N. Atlas of Advanced Gastric Surgery Techniques. Amsterdam: Harwood, 1997.
6. Danielson H, Kokkola A, Kiviluoto T, Sirén J, Louhimo J, Kivilaakso E
et al. Clinical outcome after D1 vs D2–3 gastrectomy for treatment of gastric cancer. Scand J Surg 2007;96(1):35–40.
7. Hartgrink HH, van de Velde CJ, Putter H, Bonenkamp JJ, Klein Kranenbarg E, Songun I, Welvaart K, van Krieken JH, Meijer S, Plukker JT, van Elk PJ, Obertop H, Gouma DJ, van Lanschot JJ, Taat CW, de Graaf PW, von Meyenfeldt MF, Tilanus H, Sasako M. Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch gastric cancer group trial. J Clin Oncol 2004;22(11):2069–2077.
8. Cuschieri A, Fayers P, Fielding J, Craven J, Bancewicz J, Joypaul V, Cook P. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. The Surgical Cooperative Group. Lancet 1996;347(9007):995–999.
9. Ichikawa D, Kurioka H, Yamaguchi T, Koike H, Okamoto K, Otsuji E et al. Postoperative complications following gastrectomy for gastric cancer during the last decade. Hepatogastroenterology 2004;51(56):613–617.
10. D'Amato A, Santella S, Cristaldi M, Gentili V, Pronio A, Montesani C. The role of extended total gastrectomy in advanced gastric cancer. Hepatogastroenterology 2004;51(56):609–612.
11. Kunisaki C, Makino H, Suwa H, Sato T, Oshima T, Nagano Y et al. Impact of splenectomy in patients with gastric adenocarcinoma of the cardia. J Gastrointest Surg 2007;11(8):1039–1044. doi:10.1007/s11605-007-0186-z.
12. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery. 2005;138:8–13. doi:10.1016/j.surg.2005.05.001.
13. Japanese Gastric Cancer Association. Gastric Cancer Treatment Guidelines. Tokyo: Kanehara, 2004, pp 9–10.
14. Yamamura Y, Ito S, Mochizuki Y, Nakanishi H, Tatematsu M, Kodera Y. Distribution of free cancer cells in the abdominal cavity suggests limitations of bursectomy as an essential component of radical surgery for gastric carcinoma. Gastric Cancer 2007;10 (1):24–28. doi:10.1007/s10120-006-0404-5.
15. Yoshikawa T, Tsuburaya A, Kobayashi O, Sairenji M, Motohashi H, Hasegawa S et al. Is bursectomy necessary for patients with gastric cancer invading the serosa? Hepatogastroenterology 2004;51(59):1524–1526.

J Gastrointest Surg (2008) 12:1915–1923
DOI 10.1007/s11605-008-0619-3

Incidence and Management of Chyle Leaks Following Pancreatic Resection: A High Volume Single-Center Institutional Experience

Lia Assumpcao · John L. Cameron · Christopher L. Wolfgang · Barish Edil · Michael A. Choti · Joseph M. Herman · Jean-Francois Geschwind · Kelvin Hong · Christos Georgiades · Richard D. Schulick · Timothy M. Pawlik

Received: 15 May 2008 / Accepted: 15 July 2008 / Published online: 7 August 2008

Abstract
Background No data on incidence, management, or natural history of chyle leaks following pancreatic resection have been published. We sought to identify possible risk factors associated with chyle leaks following pancreatic resection, as well as determine the natural history of this rare complication.
Methods Between 1993 and 2008, 3,532 patients underwent pancreatic resection at a single institution. Data on demographics, operative details, primary tumor status, and chyle leak were collected. To identify risk factors associated with chyle leak, a matched 3:1 paired analysis was performed.
Results Of 3,532 patients undergoing pancreatic resection, 47 (1.3%) developed a chyle leak ($n = 34$, contained chyle leak versus $n = 13$, diffuse chylous ascites). Chyle leak was identified at median 5 days following surgery. Median drain triglyceride levels were 592 ng/dl. After matching on tumor size, disease etiology, and resection type, the number of lymph nodes harvested and history of concomitant vascular resection predicted higher risk of chyle leak (both $P < 0.05$). Total parenteral nutrition (TPN) was required in more patients with chylous ascites (92.3%) than those with chyle leaks (44.1%) ($P = 0.003$). The median time to resolution was shorter for contained chyle leaks (13 days) versus chylous ascites (36 days) ($P < 0.001$). Patients with chylous ascites tended to have shorter overall survival (3-year, 18.8%) versus patients with no

Presented at the Society for Surgery of the Alimentary Tract, 49th Annual Meeting, San Diego, CA, May 18th, 2008

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

L. Assumpcao · J. L. Cameron · C. L. Wolfgang · B. Edil · M. A. Choti · R. D. Schulick · T. M. Pawlik
Department of Surgery,
The Johns Hopkins University School of Medicine,
Baltimore, MD, USA

J. M. Herman
Department of Radiation Oncology & Molecular Radiation Sciences,
The Johns Hopkins University School of Medicine,
Baltimore, MD, USA

J.-F. Geschwind · K. Hong · C. Georgiades
Department of Radiology, Vascular and Interventional Radiology,
The Johns Hopkins University School of Medicine,
Baltimore, MD, USA

T. M. Pawlik (✉)
Department of Surgery, Johns Hopkins Hospital,
600 North Wolfe Street, Halsted 614,
Baltimore, MD 22187-6681, USA
e-mail: tpawlik1@jhmi.edu

chyle leak (3-year, 46.9%) ($P = 0.12$). In contrast, patients with a contained chyle leak had a similar survival as patients with no chyle leak (3-year, 53.4% versus 46.9%, respectively) ($P = 0.32$).
Conclusion Chyle leak was a rare (1.3%) complication following pancreatic resection that was associated with number of lymph nodes harvested and concomitant vascular resection. In general, chyle leaks were successfully managed with TPN with no adverse impact on outcome. Patients with chylous ascites, however, had a more protracted clinical course and tended to have a worse long-term survival.

Keywords Chyle · Leak · Complications · Pancreas · Surgery

Introduction

Pancreatic resection can be associated with significant potential risks and complications. Although mortality following pancreaticoduodenectomy has decreased over the past 20 years to less than 5%,[1–5] the incidence of peri-operative complications remains relatively high at 30%.[2,4,6,7] Complications from pancreatic resection include delayed gastric emptying, anastomic leak, pancreatic fistula, intra-abdominal abscess formation, and bleeding. Chyle leak has also been reported as a complication following pancreatic resection.[8–14] In general, chyle leak is a very uncommon postoperative surgical complication. In fact, Press et al.[15] reported that chyle leak occurred in only one out of 20,000 hospital admissions for major abdominal or retroperitoneal surgical procedures. Despite its rarity, chyle leak can be associated with significant morbidity including dehydration, wound complications, weight loss, immunosuppression, or even death secondary to sepsis.[16–20]

Postoperative intra-abdominal chyle leak is most likely secondary to surgical disruption of the cisterna chyli or one of its major lymphatic tributaries.[21,22] Surgical procedures that can result in a chyle leak traditionally include retroperitoneal lymph node dissection,[21,23] distal splenorenal shunts,[24] abdominal aortic aneurysm repair,[25,26] and liver transplantation.[27] To date, all data concerning chyle leaks following pancreatic resection have been anecdotal and derived from limited case reports.[8–14] As such, the true incidence of chyle leak has yet to be defined in a large cohort of patients undergoing pancreatic resection. In addition, the natural history, management, and prognostic implications of chyle leak remain poorly defined. Therefore, the objective of the current study was to define the incidence, natural history, and management strategy of chyle leaks in a large single-institution series of patients undergoing pancreatic resection. In addition, we sought to identify possible risk factors associated with chyle leaks as well as assess the relative implications of developing a contained chyle leak versus diffuse chylous ascites following pancreatic resection.

Patient and Methods

Between May 1993 and March 2008, 3,532 patients underwent pancreatic resection at the Johns Hopkins Hospital (total pancreatectomy, $n = 232$; pancreaticoduodenectomy, $n = 2,589$; distal pancreatectomy, $n = 711$). All patients were evaluated preoperatively with a history and physical examination, serum laboratory tests, pancreatic protocol computed tomography, and a chest radiograph. Chyle leak was defined as ≥200 ml/day of milky, white amylase-poor drain effluent with a triglyceride level ≥110 mg/dl.[16,28,29] For the purpose of analyses, chyle leak was further stratified into contained chyle leak versus diffuse chylous ascites. A contained chyle leak was defined as a local peri-pancreatic chyle collection; in contrast, chylous ascites was defined as the presence of diffuse chyloperitoneum.

All data were prospectively collected in a database approved by the Institutional Review Board. The following data were collected for each group: demographics; clinical presentation; primary tumor histology, location, size; operative details; disease status; date and status at last follow-up; and date of death. For the primary tumor, tumor size was defined by the resection specimen. Data on peri-operative complications were also collected for all patients. In addition, detailed data on the specifics of the chyle leak were obtained, including information on time of onset, management, duration, and related complications.

In order to identify potential risk factors associated with chyle leak, a matched-controlled analysis was performed. Specifically, patients without evidence of chyle leak who underwent pancreatic resection were utilized as a matched-control group. Cases (e.g., patients who underwent pancreatic resection and developed a chyle leak) were matched in a 1:3 fashion with the control group (e.g., patients who underwent pancreatic resection and did not develop a chyle leak). Cases and controls were matched on primary tumor characteristics (primary tumor histology, primary site of tumor, primary tumor size) and type of pancreatic resection. Morbidity, mortality, and overall survival were compared among the cases and the control group. Summary statistics were reported using mean or median values as appropriate with the associated standard deviations (SD) or inter-quartile ranges (IQ). Student t tests or analyses of variance were used for mean comparison of variables that were distributed normally. Mann–Whitney test was used to compare skewed continuous variables. Chi-square statistics were used to compare frequencies of categorical variables among groups. Long-term survival was estimated using the nonparametric product-limit method (Kaplan and Meier).[30] Differences in survival were examined using the log-rank test. Statistical

analyses were performed using SPSS software (version 11.5; SPSS Inc., Chicago, IL, USA). Conditional logistic regression estimated odd ratios (OR) with 95% confidence intervals (CIs) for exposure variables were obtained using Intercooled Stata version 9 statistical software (Stata Corp, College Station, TX, USA). *P* values less than 0.05 were considered to be statistically significant for all tests.

Results

Clinicopathologic Characteristics and Surgical Details

Of the 3,532 patients undergoing pancreatic resection, 47 (1.3%) developed a chyle leak following surgery (Table 1). Of the 47 patients with a chyle leak, 34 (72.3%) patients had a contained chyle leak while 13 (27.6%) developed diffuse chylous ascites. Overall, the mean patient age was 64 years (range 55 to 72 years). Most patients ($n = 44$, 93.6%) had an underlying malignancy as the indication for pancreatic resection (adenocarcinoma, $n = 27$, 57.4%; neuroendocrine, $n = 4$, 8.5%; bile duct adenocarcinoma, $n = 4$, 8.6%; other, $n = 9$, 20.4%). In those patients with an underlying malignancy, the primary tumor site was most often located in the pancreatic head ($n = 41$ out of 44, 93.2%). There was no statistical difference in the clinicopathologic characteristics of patients who had a contained chyle leak compared with those who developed diffuse chylous ascites (all $P > 0.05$) (Table 1).

At the time of operation, surgical treatment involved a pylorus preserving pancreaticoduodenectomy ($n = 31$, 65.9%), classic pancreaticoduodenectomy ($n = 10$, 21.3%), classic total pancreatectomy ($n = 3$, 6.4%), pylorus preserving total pancreatectomy ($n = 2$, 4.3%), or distal pancreatectomy ($n = 1$, 2.1%) (Table 2). One patient (2.1%) had synchronous liver metastases and underwent a simultaneous pylorus preserving pancreaticoduodenectomy and non-anatomic hepatic wedge resection. Seven patients (14.9%) required some form of vascular resection and reconstruction to extirpate the tumor (portal-superior mesenteric vein, $n = 6$, 12.7%; inferior vena cava, $n = 1$, 2.1%). The median operative time was 402 min (range 340 to 530 min) and the median estimated blood loss was 750 ml (range 450 to 1,400 ml).

On final pathologic analysis, the median size of the primary tumor was 3.5 cm (range 2.3 to 4.0 cm). No patient had a macroscopically positive margin; the margin status was microscopically positive in 24 patients (51.1%) and microscopically negative in 23 (48.9%) patients. The median number of nodes evaluated was 18 (range 13 to 24). Of the 47 patients who underwent pancreatic resection and subsequently developed a chyle leak, 18 (38.3%) had no metastasis to the peri-pancreatic lymph nodes (N0) while 29 (61.7%) had lymph nodes metastasis (N1). The median number of lymph nodes examined in the N0 group was 15 compared with a median number of 19 lymph nodes in the N1 cohort ($P = 0.267$).

No patient died within 30 days of resection. The median length of stay following pancreatic resection was 13 days (range 10 to 17 days).

Chyle Leak: Natural History and Management

The median time to chyle leak presentation following surgical resection was 5 days (range 4 to 8 days). All patients who had a chyle leak presented with milky output from their abdominal drain. The change in fluid character was typically associated with advancement of the patient's diet. The mean fluid triglyceride level was 592 mg/dl (SD 64 mg/dl); the mean drain amylase level was 71 U/l (SD 42 U/l).

Table 1 Patient Clinicopathologic Characteristics

Variable	Contained chyle leak (n=34)	Chylous ascites (n=13)	Total cases (n=47)
Patient characteristics			
Age (mean±SD in years)	64.3±2.9	60.2±3.9	63.5±5.2
Gender (% Male)	17 (50.0%)	8 (61.5%)	25 (53.2)
Race (% White)	31 (91.2%)	11 (84.6%)	42 (89.4)
Primary tumor			
Cancer as primary diagnosis (%)	32 (94.1%)	12 (92.3%)	44 (93.6)
Tumor size (median; IQR in cm)	3.5 (2.0–4.0)	3.6 (2.1–4.7)	3.5 (2.3–4.0)
Tumor site (%)			
Pancreas head	23 (67.6%)	9 (69.2%)	32 (68.1%)
Pancreas tail	0 (0%)	1 (7.7%)	1 (2.1%)
Duodenum	2 (5.9%)	2 (15.4%)	4 (8.5%)
Distal bile duct	2 (5.9%)	0 (0%)	2 (4.3%)
Ampulla	7 (20.6%)	1 (7.7%)	8 (17%)
T2 or T3 disease (%)	29 (85.2%)	11 (84.5%)	40 (85.1%)
Non-cancer as primary diagnosis (%)	2 (5.9%)	1 (7.7%)	3 (6.4%)

SD standard deviation, *IQR* intra-quartile range

Table 2 Details of Contained Chyle Leak Versus Chylous Ascites

Variable	Contained chyle leak (n=34)	Chylous ascites (n=13)	Total cases (n=47)
Details of operative procedure			
Pancreatic resection (%)			
Classic pancreaticoduodenectomy	6 (17.6%)	4 (30.8%)	10 (21.3%)
PP pancreaticoduodenectomy	25(73.5%)	6 (46.2%)	31 (66%)
Classic total pancreatectomy	2 (5.9%)	1 (7.7%)	3 (6.4%)
PP total pancreatectomy	1(2.9%)	1 (7.7%)	2 (4.3%)
Distal pancreatectomy	0 (0%)	1 (7.7%)	1 (2.1%)
Lymph nodes harvested (mean, range)	18 (12–24)	19 (14–22)	18 (13–24)
Vascular resection+reconstruction (%)	3 (8.8%)	4 (30.8%)	7 (14.9%)
Estimated blood loss (mean±SD in ml)	1,033±207	2,089±606	1,250±215
Operative time (mean±SD in min)	439±25	464±41	444±21
Details of surgical pathology[a]			
Metastatic lymph nodes (mean, range)	3 (1–5)	1 (0–7)	3 (0–5)
Poor-moderate tumor grade (%)	27 (84.4%)	12 (66.6%)	39 (88.6%)
Lympho-vascular invasion (%)	20 (62.5%)	5 (41.6%)	25 (56.8%)
Neural invasion (%)	24 (75%)	8 (66.7%)	32 (72.7%)

PP pylorus preserving, *SD* standard deviation, *ml* milliliters
[a] Only cancer patients (n=32 to chyle leak, n=12 to chyle ascites, n=44 total cases)

All patients were initially treated with conservative management. While most patients (n = 27, 57.4%) were placed on hyperalimentation, total parenteral nutrition (TPN) was utilized more frequently in patients with chylous ascites (n = 12, 92.3%) versus patients with a contained chyle leak (n = 15; 44.1%) (P = 0.003). Median duration of TPN was 15 days (range 19 to 28 days). Somatostatin was employed in eight (17.0%) patients. In a subset of patients (n = 7, 14.9%), lymphoscintigraphy (n = 4) or lymphangiogram (n = 3) was utilized in an attempt to identify the site of chyle leak. Both techniques were largely unsuccessful in detecting the leak (lymphoscintigraphy = one out of four; lymphangiogram = one out of three). Successful sclerotic embolization of the leak site was performed in one patient in whom the leak was identified on lymphangiogram. Three (6.4%) patients subsequently underwent re-operation in an attempt to identify and ligate the cisterna chyli. This was unsuccessful in all three patients; two patients had a peritoneovenous shunt placed. Of note, of the seven patients who failed conservative management and required a more aggressive therapeutic approach (e.g., lymphoscintigraphy, lymphangiogram, or re-operation), only one patient had a contained chyle leak (2.9%) compared with six who had diffuse chylous ascites (46.2%) (P = 0.004).

Complications associated with the chyle leak included abscess (n = 2, 4.3%), concomitant pancreatic fistula (n = 2, 4.3%), malnutrition (e.g., albumin <3.5 mg/dl) (n = 43, 91.5%), peritonitis (n = 3, 6.4%), and sepsis (n = 6, 12.8%).

Overall, the median time to resolution of the chyle leak was 13 days (range 8 to 27 days). For those patients managed conservatively with TPN (n = 27), the chyle leak resolved within a median of 15 days (range, 9 to 28 days). In contrast, those patients that required more aggressive management (e.g., lymphoscintigraphy, lymphangiogram, or re-operation) (n = 7) required a median of 58 days (range 16 to 232 days) for the chyle leak to resolve. In addition, the resolution of the chyle leak was significantly shorter in patients with a contained chyle leak (median 5 days, range 3 to 7 days) versus patients who developed diffuse chylous ascites (median 36 days, range 20 to 50 days) (P < 0.001).

For the entire cohort of patients who developed a chyle leak (n = 47), the median overall survival was 32.1 months and the 1- and 3-year actuarial overall survival rates were 80.2% and 26.9%, respectively (Fig. 1). When only patients with pancreatic adenocarcinoma were considered (n = 24), the 1- and 3-year actuarial overall survival rates were 63.8% and 18.3%, respectively. In assessing the entire cohort (n = 47), patients with chylous ascites tended to have a worse cumulative survival compared with patients who developed a contained chyle leak (P = 0.12) (Fig. 2). Specifically, some patients with chylous ascites suffered early demise that was directly attributable to their chyle complication. This fact was reflected in the 3-year survival

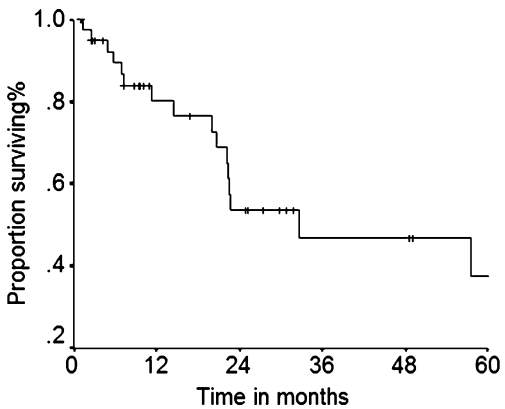

Figure 1 Overall survival of entire cohort of patients who developed chyle leak following pancreatic resection (n=47).

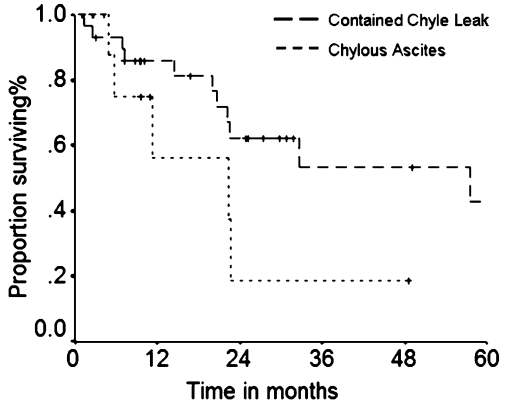

Figure 2 Overall survival comparing patients who developed a contained chyle leak versus patients who developed diffuse chylous ascites following pancreatic resection. Patients with chylous ascites tended to have a worse long-term survival (3-year survival—contained leak, 53.4% versus ascites, 18.8%; P=0.12).

of patients with chylous ascites being only 18.8% versus 53.4% for patients with a contained chyle leak.

Matched Analysis: Risk Factors Associated with Chyle Leak

In order to identify potential risk factors associated with the development of chyle leak, a matched-control analysis was then performed. Table 3 shows the clinicopathologic characteristics of the patients in the case and control groups following the matching process. Matching was successful in identifying cohorts of patients with comparable age, primary tumor characteristics (e.g., histology, tumor size), and type of pancreatic resection performed. For those patients with pancreatic adenocarcinoma, the extent of local disease (e.g., T stage) as well as incidence of neuro-vascular invasion was similar in each group.

Univariate analyses revealed several factors that were associated with the risk of chyle leak (Table 4). Increasing operative time of the pancreatic resection was predictive of increased risk of chyle leak. Specifically, for every 30 min of increased operative time there was an associated 14% increased risk of developing a postoperative chyle leak (OR = 1.14, 95% CI 1.02–1.28; P = 0.01). Similarly, an increasing number of lymph nodes harvested at the time of pancreatic resection was associated with a higher risk of chyle leak. The median total number of lymph nodes harvested in patients developing a chyle leak was 18 compared with 16 in the control group (P = 0.06). For each additional lymph node harvested, the risk of chyle leak increased by 6% (OR = 1.06, 95% CI 1.01–1.11; P = 0.01). In contrast, the number of lymph nodes with metastatic disease was not associated with the risk of chyle leak (P = 0.57). Another factor associated with the risk of chyle leak was concomitant vessel resection at the time of surgery. In fact, vascular resection and reconstruction was the factor most strongly associated with the risk of chyle leak (OR = 4.81, 95% CI 1.41–16.6; P = 0.01). On multivariate analysis, number of lymph nodes harvested as well as vascular resection and reconstruction remained associated with risk of chyle leak (Table 4). Patients who underwent vascular resection and reconstruction had over an eightfold increased risk of chyle leak (OR = 8.25, 95% CI 1.99–34.6; P = 0.004).

Table 3 Clinicopathologic Characteristics and Operative Procedures: 1:3 Match

Variable	Cases (chyle leak) N=47	Controls (no chyle leak) N=141
Patient characteristics		
Age (mean±SD in years)	63.5±11.5	61.91±11.9
Gender (% Male)	25 (53.2%)	99 (70.2%)
Race (% White)	42 (89.4%)	122 (86.5%)
Primary tumor		
Cancer as primary diagnosis (%)	44 (93.6%)	129 (91.5%)
Tumor size (median; IQR in cm)	3.5 cm (2–3.7)	3.5 cm (2–4)
Tumor site (%)		
Pancreas head	32 (68.1%)	96 (68.1%)
Pancreas tail	1 (2.1%)	3 (2.1%)
Duodenum	4 (8.5%)	12 (8.5%)
Distal bile duct	2 (4.3%)	6 (4.3%)
Ampulla	8 (17%)	24 (17%)
Non-cancer as primary diagnosis (%)	3 (6.4%)	12 (8.5%)
Operation for primary tumor site		
Pancreatic resection (%)		
Classic pancreaticoduodenectomy	10 (21.3%)	26 (18.4%)
PP pancreaticoduodenectomy	31 (66%)	98 (69.5%)
Classic total pancreatectomy	3 (6.4%)	10 (7.1%)
PP total pancreatectomy	2 (4.3%)	4 (2.8%)
Distal pancreatectomy	1 (2.1%)	3 (2.1%)

IQR intra-quartile range, *PP* pylorus preserving

Table 4 Prognostic Factors Associated with Chyle Leak

	Univariate analysis			Multivariate analysis		
Prognostic factor	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Age (years)	1.01	0.98–1.04	0.52	–	–	–
Sex (male)	2.15	1.01–4.3	0.03	–	–	–
No. lymph nodes harvested	1.06	1.01–1.11	0.01	1.07	1.02–1.13	0.007
No. metastatic lymph nodes	1.02	0.94–1.13	0.71	–	–	–
Lympho-vascular invasion	1.58	0.66–3.8	0.30	–	–	–
Neural invasion	1.02	0.38–2.94	0.96	–	–	–
Vascular resection	4.81	1.41–16.6	0.01	8.25	1.99–34.6	0.004
Operative time[a]	1.14	1.02–1.28	0.01	–	–	–

No. number
[a] Odds calculated using 30-min intervals

Regarding overall survival, patients who developed postoperative chylous ascites tend to have a shorter overall survival (3-year, 18.8%) compared with patients who did not develop any type of chyle leak following pancreatic resection (3-year, 46.9%) ($P = 0.12$) (Fig. 3a). In contrast, the overall survival of patients with a contained chyle leak was not different from the overall survival of patients with no chyle leak (3-year, 53.4% versus 46.9%, respectively) ($P=0.35$). When analyses were restricted to only patients with a diagnosis of pancreatic adenocarcinoma, a similar survival pattern was observed (Fig. 3b).

Discussion

Chyle leaks are a recognized but rarely reported complication following abdominal and retroperitoneal surgery. Most causes of chyle flow disruption include neoplastic,[31] cirrhosis,[32] infectious,[33] or inflammatory etiologies;[34,35] however, chyle leaks can also occur as a postoperative complication. The preponderance of reports on chyle leak as a postoperative complication have included patients who underwent retroperitoneal lymph node dissection,[21,23] distal splenorenal shunts,[24] abdominal aortic aneurysm repair,[25,26] or liver transplantation.[27] Few reports have included patients who underwent pancreatic resection. Data on chyle leak following pancreatic resection is, therefore, largely unavailable and based on case reports or anecdotal information that exist in the literature.[8–14] The current study is important because it represents an attempt to systematically examine chyle leak as a complication following pancreatic resection. The current study is unique because it not only described the natural history of chyle leak following pancreatic resection but also identified potential intra-operative risk factors as well as defined the long-term impact of chyle leak. To our knowledge, the current study is the largest and most definitive report on chyle leak following pancreatic resection to date.

The overall incidence of chyle leak remains poorly defined. Press et al.[15] reported an overall incidence of approximately one in 20,000 following major abdominal surgery. In contrast, Baniel et al.[23] reported an incidence of

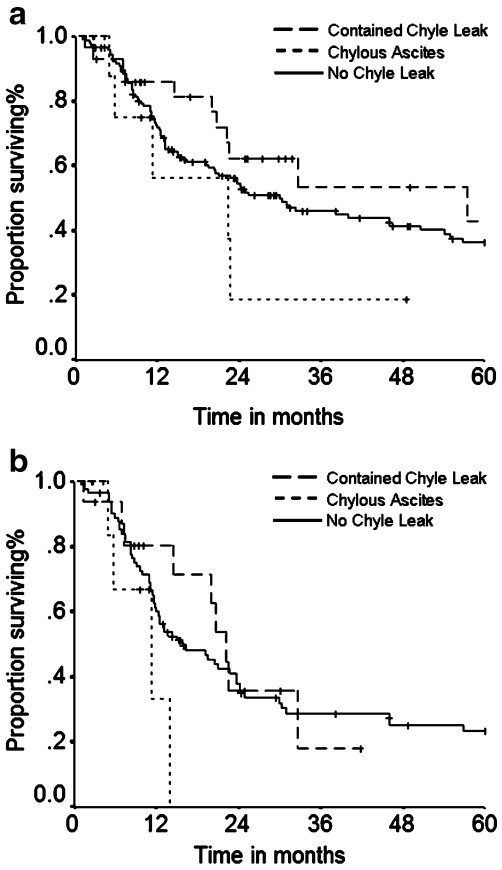

Figure 3 Results of matched survival analysis. **a** Patients with a contained chyle leak had a similar overall survival compared with patients who did not have a chyle leak (3-year, 53.4% versus 46.9%, respectively) ($P=0.35$). In contrast, the overall survival of patients with chylous ascites was worse than the overall survival of patients with no chyle leak (3-year, 18.8% versus 53.4%, respectively) ($P=0.12$). **b** When analyses were restricted to only patients with a diagnosis of pancreatic adenocarcinoma, a similar survival pattern was observed.

2% following retroperitoneal lymph node dissection and Leibovitch et al.[36] noted an incidence of 1% following abdominal aneurysm repair. The incidence of chyle leak following pancreatic resection is largely unknown but has been reported to range from 2.2% to 6.7%.[8,9] These estimates are difficult to interpret, however, as these studies included only a small number of patients who underwent pancreatic resection ($n<150$). In the current study, we report an overall incidence of chyle leak following pancreatic resection of 1.3% (47 out of 3,532). In addition, we noted that the incidence of chyle leak was highest in patients who underwent pancreaticoduodenectomy (1.8%). The higher incidence of chyle leak with pancreaticoduodenectomy may be due to the close proximity of the cisterna chyli to the head of the pancreas.[8] Of note, the one patient who did develop a chyle leak following distal pancreatectomy also underwent a concomitant aorto-caval lymphadenectomy for metastatic neuroendocrine disease.

The number of lymph nodes harvested and a history of concomitant vascular resection and reconstruction were predictive of chyle leak (Table 4). Various investigators have reported that extensive lymphadenectomy in conjunction with neck dissection,[37] esophagectomy,[38] or gastrectomy[39] was associated with an increased risk of chyle leak. Yol et al.[39] reported that a D3 extended lymphadenectomy at the time of gastric resection was associated with a higher incidence of chyle leak. Similarly, in the current study, those patients who underwent a more extensive lymph node harvest at the time of pancreatic resection had an incremental increased risk of chyle leak. The other risk factor for chyle leak was vascular resection and reconstruction. The skeletonization of adjacent vascular structures, as well as the more extensive retroperitoneal dissection required in the setting of concomitant pancreatic resection and portal-superior mesenteric vein reconstruction, may in part explain the increased risk of chyle leak. It is important to note, however, that given the very low baseline risk of chyle leak, while the relative risk was increased in these subgroups of patients, the absolute risk remained low.

Similar to other studies[21,23] that have reported a 75% to 80% success rate, we noted that 40 out of 47 (85.1%) patients had successful resolution of their chyle leak with conservative measures. In fact, only seven (14.9%) patients failed conservative management and required a more aggressive therapeutic approach such as lymphoscintigraphy, lymphangiogram, sclerotic therapy, or re-operation. While lymphoscintigrapy and lympangiogram remain the gold standard in defining the site of lymphatic leak, the efficacy of these studies in the postoperative setting is poorly defined.[28] In the current study, lymphoscintigrapy and lympangiogram were able to document the site of lymph leak in only the minority of cases. In the setting of a persistent chyle leak, some investigators have advocated repeat laparotomy with ligation of the leaking lymph vessels.[40,41] However, similar to the experience presented in the current study, other investigators[17] have reported that repeat exploration to identify and ligate the leak is rarely successful. When the site of the chyle leak cannot be identified, placement of a peritoneovenous shunt may be another option. This approach was utilized in two patients. Peritoneovenous shunting should, however, be used selectively as it may be associated with potential complications including fluid shifts, electrolyte imbalance, sepsis, and shunt occlusion.[22,42]

Although most reports on chyle leak have failed to stratify the extent of the leak (e.g., contained leak versus diffuse ascites), this distinction may have important therapeutic and prognostic implications.[31,43] As such, we specifically sought to analyze the natural history and prognostic implications of a contained chyle leak versus diffuse chyloperitoneum following pancreatic resection. Importantly, we found that the consequences of developing a contained chyle leak versus chylous ascites were dramatically different. Whereas contained chyle leaks frequently resolved after a short duration of conservative management (median 5 days), patients who developed chylous ascites had a much more protracted clinical course (median 36 days). In addition, patients who developed chyloperitoneum were more likely to fail conservative management and need additional therapeutic interventions (e.g., lymphoscintigraphy, lymphangiogram, or re-operation). A dramatic difference in overall survival was also noted. In fact, when analyses were restricted to only patients with a diagnosis of pancreatic adenocarcinoma, no patient with chylous ascites was alive at 18 months (Fig. 3b). These data are consistent with previous reports that have noted high mortality rates associated with chylous ascites.[15,31,44] In aggregate, these data strongly suggest that, while a contained chyle leak following pancreatic resection may have a short natural history and not impact long-term outcome, diffuse chylous ascites is associated with both a prolonged clinical course and increased mortality.

The current study had several limitations. Despite having the largest pancreaticobiliary surgical experience in the country, only a relatively small sample size of patients could be identified for this study. As such, the current study has limited statistical power; due to this constraint, statistical analyses and inferences were limited. Another possible limitation involved our combining of contained chyle leak and diffuse chylous ascites into a composite outcome for the purposes of reporting general outcome parameters. While we demonstrated that natural history and mortality were different in the chyle leak and chylous ascites groups, risk factor analyses were performed using a composite endpoint of "chyle leak." This approach was chosen in order to increase the number of patients that

could be included in the covariate adjusted analyses. Although unlikely, the risk factors associated with the development of chyle leak versus diffuse chylous ascites may be different.

In conclusion, chyle leak was a rare (1.3%) complication following pancreatic resection. Factors predictive of chyle leak included increasing number of lymph nodes harvested and concomitant vascular resection. In general, chyle leaks were successfully managed with TPN with no adverse impact on outcome. Patients with chylous ascites, however, had a more protracted clinical course and had a worse long-term survival. Data from the current study should provide guidance in helping to clinically manage this rare, but clinically important, postoperative complication.

References

1. Cameron JL, Pitt HA, Yeo CJ, Lillemoe KD, Kaufman HS, Coleman J. One hundred and forty-five consecutive pancreaticoduodenectomies without mortality. Ann Surg 1993;217:430–435. discussion 435–438. doi:10.1097/00000658-199305010-00002.
2. Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. Ann Surg 1997;226:248–257. discussion 257–260. doi:10.1097/00000658-199709000-00004.
3. Crist DW, Sitzmann JV, Cameron JL. Improved hospital morbidity, mortality, and survival after the Whipple procedure. Ann Surg 1987;206:358–365. doi:10.1097/00000658-198709000-00014.
4. Winter JM, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J et al. 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. J Gastrointest Surg 2006;10:1199–1210. discussion 1210–1191. doi:10.1016/j.gassur.2006.08.018.
5. Trede M, Schwall G, Saeger HD. Survival after pancreatoduodenectomy. 118 consecutive resections without an operative mortality. Ann Surg 1990;211:447–458. doi:10.1097/00000658-199004000-00011.
6. Balcom JHt, Rattner DW, Warshaw AL, Chang Y, Fernandez-del Castillo C. Ten-year experience with 733 pancreatic resections: changing indications, older patients, and decreasing length of hospitalization. Arch Surg 2001;136:391–398. doi:10.1001/archsurg.136.4.391.
7. Rios G, Conrad A, Cole D, Adams D, Leveen M, O'Brien P et al. Trends in indications and outcomes in the Whipple procedure over a 40-year period. Am Surg 1999;65:889–893.
8. Madanur MA, Battula N, Azam MO, Heaton N, Rela M. Chylous ascites after pancreatico-duodenectomy cholangiocarcinoma xenografts in nude mice. Hepatobiliary Pancreat Dis Int 2007;6:416–419.
9. Malik HZ, Crozier J, Murray L, Carter R. Chyle leakage and early enteral feeding following pancreatico-duodenectomy: management options. Dig Surg 2007;24:418–422. doi:10.1159/000108324.
10. Walker WM. Chylous ascites following pancreatoduodenectomy. Arch Surg 1967;95:640–642.
11. Cope C. Diagnosis and treatment of postoperative chyle leakage via percutaneous transabdominal catheterization of the cisterna chyli: a preliminary study. J Vasc Interv Radiol 1998;9:727–734.
12. Kollmar O, Schilling MK, Buchler MW. Treatment of chyloperitoneum after extended lymphatic dissection during duodenopancreatectomy. Int J Pancreatol 2000;27:83–87. doi:10.1385/IJGC:27:1:83.
13. Li S, Pei YQ, Du FT, Zhuang GY, Li CY, Song QH et al. Surgical treatment for uncinate process carcinoma of the pancreas. Hepatobiliary Pancreat Dis Int 2002;1:592–594.
14. Gallagher MC, Shankar A, Groves CJ, Russell RC, Phillips RK. Pylorus-preserving pancreaticoduodenectomy for advanced duodenal disease in familial adenomatous polyposis. Br J Surg 2004;91:1157–1164. doi:10.1002/bjs.4527.
15. Press OW, Press NO, Kaufman SD. Evaluation and management of chylous ascites. Ann Intern Med 1982;96:358–364.
16. Kaas R, Rustman LD, Zoetmulder FA. Chylous ascites after oncological abdominal surgery: incidence and treatment. Eur J Surg Oncol 2001;27:187–189. doi:10.1053/ejso.2000.1088.
17. Jayabose S, Kogan S, Berezin S, Slim M, San Filippo JA, Godine L et al. Combined occurrence of chyloperitoneum and chylothorax after surgery and chemotherapy for Wilms' tumor. Cancer 1989;64:1790–1795. doi:10.1002/1097-0142(19891101)64:9<1790::AID-CNCR2820640905>3.0.CO;2-V.
18. Silk YN, Goumas WM, Douglass HO Jr, Huben RP. Chylous ascites and lymphocyst management by peritoneovenous shunt. Surgery 1991;110:561–565.
19. Bhat AL, Lowery GL. Chylous injury following anterior spinal surgery: case reports. Eur Spine J 1997;6:270–272. doi:10.1007/BF01322450.
20. Nagai H, Shimizu K, Shikata J, Iida H, Matsushita M, Ido K et al. Chylous leakage after circumferential thoracolumbar fusion for correction of kyphosis resulting from fracture. Report of three cases. Spine 1997;22:2766–2769. doi:10.1097/00007632-199712010-00013.
21. Evans JG, Spiess PE, Kamat AM, Wood CG, Hernandez M, Pettaway CA et al. Chylous ascites after post-chemotherapy retroperitoneal lymph node dissection: review of the M. D. Anderson experience. J Urol 2006;176:1463–1467. doi:10.1016/j.juro.2006.06.016.
22. Ablan CJ, Littooy FN, Freeark RJ. Postoperative chylous ascites: diagnosis and treatment. A series report and literature review. Arch Surg 1990;125:270–273.
23. Baniel J, Foster RS, Rowland RG, Bihrle R, Donohue JP. Management of chylous ascites after retroperitoneal lymph node dissection for testicular cancer. J Urol 1993;150:1422–1424.
24. Edoute Y, Nagachandran P, Assalia A, Ben-Ami H. Transient chylous ascites following a distal splenorenal shunt. Hepatogastroenterology 2000;47:531–532.
25. Meinke AH 3rd, Estes NC, Ernst CB. Chylous ascites following abdominal aortic aneurysmectomy. Management with total parenteral hyperalimentation. Ann Surg 1979;190:631–633. doi:10.1097/00000658-197911000-00011.
26. Busch T, Lotfi S, Sirbu H, Dalichau H. Chyloperitoneum: a rare complication after abdominal aortic aneurysm repair. Ann Vasc Surg 2000;14:174–175. doi:10.1007/s100169910030.
27. Asfar S, Lowndes R, Wall WJ. Chylous ascites after liver transplantation. Transplantation 1994;58:368–369.
28. Pui MH, Yueh TC. Lymphoscintigraphy in chyluria, chyloperitoneum and chylothorax. J Nucl Med 1998;39:1292–1296.
29. Archimandritis AJ, Zonios DI, Karadima D, Vlachoyiannopoulos PG, Kiriaki D, Hatzis GS. Gross chylous ascites in cirrhosis with massive portal vein thrombosis: diagnostic value of lymphoscintigraphy. A case report and review of the literature. Eur J Gastroenterol Hepatol 2003;15:81–85. doi:10.1097/00042737-200301000-00014.
30. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–481. doi:10.2307/2281868.

31. Aalami OO, Allen DB, Organ CH Jr. Chylous ascites: a collective review. Surgery 2000;128:761–778. doi:10.1067/msy.2000.109502.
32. Rector WG Jr. Spontaneous chylous ascites of cirrhosis. J Clin Gastroenterol. 1984;6:369–372.
33. Keaveny AP, Karasik MS, Farber HW. Successful treatment of chylous ascites secondary to *Mycobacterium avium* complex in a patient with the acquired immune deficiency syndrome. Am J Gastroenterol 1999;94:1689–1690. doi:10.1111/j.1572-0241.1999.01165.x.
34. Cappell MS, Friedman D, Mikhail N. Chyloperitoneum associated with chronic severe sarcoidosis. Am J Gastroenterol 1993;88:99–101.
35. Goldfarb JP. Chylous effusions secondary to pancreatitis: case report and review of the literature. Am J Gastroenterol 1984;79:133–135.
36. Leibovitch I, Mor Y, Golomb J, Ramon J. The diagnosis and management of postoperative chylous ascites. J Urol 2002;167:449–457. doi:10.1016/S0022-5347(01)69064-5.
37. Mallen RW, Kudryk WH. Case report: Chylous fistula following right radical neck dissection. Can J Otolaryngol 1975;4:177–179.
38. Omloo JM, Lagarde SM, Vrouenraets BC, Busch OR, van Lanschot JJ. Compartimentalization for chylothorax originating from the abdomen after extended esophagectomy. Report of two cases and review of the literature. Dig Surg 2006;23:86–92. doi:10.1159/000093499.
39. Yol S, Bostanci EB, Ozogul Y, Ulas M, Akoglu M. A rare complication of D3 dissection for gastric carcinoma: chyloperitoneum. Gastric Cancer 2005;8:35–38. doi:10.1007/s10120-004-0312-5.
40. Williamson C, Provan JL. Chylous ascites following aortic surgery. Br J Surg 1987;74:71–72. doi:10.1002/bjs.1800740126.
41. Ohri SK, Patel T, Desa LA, Spencer J. The management of postoperative chylous ascites. A case report and literature review. J Clin Gastroenterol 1990;12:693–697. doi:10.1097/00004836-199012000-00021.
42. Voros D, Hadziyannis S. Successful management of postoperative chylous ascites with a peritoneojugular shunt. J Hepatol 1995;22:380. doi:10.1016/0168-8278(95)80296-7.
43. Cardenas A, Chopra S. Chylous ascites. Am J Gastroenterol 2002;97:1896–1900.
44. Vasko JS, Tapper RI. The surgical significance of chylous ascites. Arch Surg 1967;95:355–368.

J Gastrointest Surg (2008) 12:1924–1929
DOI 10.1007/s11605-008-0644-2

Surgical Management of Failed Endoscopic Treatment of Pancreatic Disease

Kimberly A. Evans · Colby W. Clark · Stephen B. Vogel · Kevin E. Behrns

Received: 1 July 2008 / Accepted: 28 July 2008 / Published online: 15 August 2008

Abstract
Introduction Endoscopic therapy of acute and chronic pancreatitis has decreased the need for operative intervention. However, a significant proportion of patients treated endoscopically require definitive surgical management for persistent symptoms.
Objective Our aim was to determine which patients are likely to fail with endoscopic therapy, and to assess the clinical outcome of surgical management. Patients were identified using ICD-9 codes for pancreatic disease as well as CPT codes for endoscopic therapy followed by surgery.
Material and Methods Patients with documented acute or chronic pancreatitis treated endoscopically prior to surgical therapy were included (N=88). The majority of patients (65%) exhibited chronic pancreatitis due to alcohol abuse. Common indicators for surgery were: persistent symptoms, anatomy not amenable to endoscopic treatment and unresolved common bile duct or pancreatic duct strictures. Surgical salvage procedures included internal drainage of a pseudocyst or an obstructed pancreatic duct (46%), debridement of peripancreatic fluid collections (25%), and pancreatic resection (31%).
Results Death occurred in 3% of patients. The most common complications were hemorrhage (16%), wound infection (13%), and pulmonary complications (11%). Chronic pancreatitis with persistent symptoms is the most common reason for pancreatic surgery following endoscopic therapy. Surgical salvage therapy can largely be accomplished by drainage procedures, but pancreatic resection is common.
Conclusion These complex procedures can be performed with acceptable mortality but also with significant risk for morbidity.

Keywords Endoscopic retrograde cholangiopancreatography (ERCP) · Endoscopic therapy · Acute and chronic pancreatitis · Salvage surgery

Presented at the 49th Annual Meeting of the Society for Surgery of the Alimentary Tract, San Diego, CA, May 21, 2008.

K. A. Evans · C. W. Clark · S. B. Vogel · K. E. Behrns (✉)
Division of General Surgery, Department of Surgery,
University of Florida,
P.O. Box 100286, 1600 SW Archer Road,
Gainesville, FL 32610, USA
e-mail: Kevin.Behrns@surgery.ufl.edu

Introduction

Pancreatitis is an expansive disease that may be debilitating and managed medically, endoscopically or by surgical approaches. In acute pancreatitis, up to 20% of patients suffer considerable morbidity and/or mortality.[1] Acute severe pancreatitis is characterized by a robust systemic inflammatory response that may result in pulmonary, renal, and hepatic compromise that progresses to multi-system organ failure and decreased immune function.[2–9] This impaired host response may result in infected pancreatic necrosis that can be treated by either endoscopic or surgical management; however, either approach has significant complications.[1,10,11] In contrast to the dramatic presentation

of severe acute pancreatitis, chronic pancreatitis is associated with waxing and waning abdominal pain, steatorrhea, anorexia, malabsorption, weight loss, and diabetes mellitus.[12] Although the course of disease and the clinical presentation of chronic pancreatitis differs markedly from acute pancreatitis, both endoscopic and surgical management may effectively reduce recalcitrant abdominal pain and effectively treat complications such as pseudocysts in select patient populations.[13–18] However, recent randomized trials have demonstrated that the surgical management of chronic pancreatitis results in improved outcomes compared to endoscopic treatment.[19,20]

Endoscopic approaches to acute and chronic pancreatitis are varied and include sphincterotomy and stone extraction for gallstone pancreatitis,[21] pancreatic duct stenting in acute recurrent and chronic pancreatitis,[22–24] and endoscopic ultrasound (EUS)-guided transmural or transpapillary drainage of fluid collections and pseudocysts. Previous work has demonstrated that pancreatic duct stenting can decrease recurrence rates of acute pancreatitis[23] and reduce the pain associated with chronic pancreatitis.[25] However, abatement of symptoms too frequently has a short duration following endoscopic therapy, and the underlying pathophysiology of a fibrotic pancreatic duct is not significantly altered by endoscopic therapy. Conversely, EUS-guided pseudocyst drainage has low complication and mortality rates and is highly successful.[15]

Surgical therapy for pancreatitis includes procedures that decompress the pancreatic duct or resect the diseased parenchyma. In the past, decompressive and pancreatic parenchyma-sparing procedures were favored; however, resection of an enlarged, inflamed pancreatic head accompanied by duct drainage has been a valuable addition to decrease neurogenic pancreatic pain in patients with chronic pancreatitis. Decompressive procedures include cystgastrostomy, cystenterostomy, lateral pancreatojejunostomy, and sphincteroplasty. Pancreatic resection is accomplished by pancreatoduodenectomy, distal pancreatectomy, local resection of the pancreatic head, and total pancreatectomy with islet cell transplantation. Puestow and Gillesby described the first widely effective drainage procedure in 1958.[26] This procedure was modified by Partington and Rochelle by sparing the spleen and tail of the pancreas.[17] In chronic pancreatitis, short-term pain relief is achieved in 60–95% of patients with a reported 0–5% mortality rate using decompression procedures.[18,27–29] Alternatively, a resection that preserves substantial pancreatic tissue can be performed.[30] Furthermore, patients with a non-dilated pancreatic duct and/or refractory pain are candidates for pancreatic resection.[27] Complete pain relief with resection can be achieved in 70–100% of patients with a mortality of 0–4%.[31–35]

The aims of this study were to determine which patients are likely to fail endoscopic therapy and to assess the clinical outcome of surgical management following initial endoscopic therapy. The findings of this study suggest that patients with chronic pancreatitis may have persistent symptoms following endoscopic therapy and that surgical salvage therapy has low mortality but significant morbidity.

Materials and Methods

Patients were identified by searching institutional databases for ICD-9 pancreatic disease codes (577.0–577.2) and current procedural terminology codes for endoscopic therapy and surgical procedures for pancreatic diseases. Nine hundred twenty-five patients with pancreatic disease and interventional management were identified over the period extending from 28 March 1997 to 14 February 2007. Patients with well-documented acute or chronic pancreatitis treated endoscopically prior to surgical therapies were included for analysis. Patients with neoplastic disease or suspected neoplastic disease preoperatively were excluded. Eighty-eight (10%) patients met the study criteria.

Following patient identification, medical records were retrospectively reviewed for demographic data, etiology of pancreatitis, endoscopic management, and surgical therapy. The etiology of pancreatitis was classified as induced by alcohol, gallstones, hyperlipidemia, pancreatic divisum, trauma, or genetic causes. Additional cases not ascribed to these categories were deemed idiopathic. As documented in the medical record, pancreatitis was described as chronic, acute, or acute necrotizing pancreatitis; acute on chronic pancreatitis; or acute recurrent pancreatitis. Endoscopic management was identified as cystgastrostomy, endoscopic retrograde cholangiopancreatography (ERCP) with stent placement, or sphincterotomy or EUS-guided stent placement. The indications for surgery were persistent symptoms, anatomy not amenable to further endoscopic treatment, common bile duct or pancreatic duct strictures, persistent pseudocysts, infection or clinical deterioration, obstructing pancreatic lithiasis, pancreatic fistula, post-ERCP pancreatitis, hemorrhage, or duodenal stenosis. Each procedure was identified and the medical records were reviewed for complications. Means plus or minus the standard deviation were determined for continuous variables. Other results were summarized as percentages of the patient population.

Results

A summary of the demographic characteristics of the study group is listed in Table 1. Of the 88 patients with pancreatitis that received surgical therapy following endoscopic management, the mean age at time of surgery was

Table 1 Patient Demographics

Characteristics	*N*	Percent
Age	49±14	
Male/Female	45:43	
Etiology		
Alcohol	40	45.4
Idiopathic	18	20.4
Gallstones	17	19.3
Iatrogenic	4	4.5
Hyperlipidemia	4	4.5
Pancreatic Divisum	3	3.4
Trauma	1	1.0
Genetic	1	1.0
Viral	1	1.0
Type of Pancreatitis		
Chronic	57	64.7
Acute/Acute Necrotizing	14	15.9
Acute on Chronic	9	10.2
Acute Recurrent	7	7.9
Not Documented	1	1.0

49±14 years and the male-to-female ratio was 45:43. Sixty-five percent (65%) of patients had chronic pancreatitis with alcohol-induced disease in 40 of 88 patients. The next most common etiologies were idiopathic causes, gallstones, hyperlipidemia, and pancreatic divisum. Trauma, genetic, and cytomegalovirus-induced pancreatitis were less frequent causes of pancreatitis.

Of the endoscopic therapies that preceded surgical intervention, nearly all (96%) patients were treated with ERCP. In 53% of patients, stents were placed, 10% of patients underwent cystgastrostomy with the remaining patients undergoing ERCP with sphincterotomy of either the bile or pancreatic ducts. Three patients had pancreatic stones extracted while three additional patients had transpapillary pseudocyst drainage (Table 2).

The common indications for surgery were: persistent symptoms (28%), anatomy not amenable to further endoscopic therapy (26%), common bile duct or pancreatic duct strictures (18%), infection or clinical deterioration (16%), and a persistent pseudocyst (15%) (Table 3).

Surgical salvage procedures included internal drainage of a pseudocyst or an obstructed pancreatic duct in 40 (46%) patients, debridement or pancreatic abscess drainage in 22 (25%) patients, and pancreatic resection in 27 (30%) patients (Table 4). The most common drainage procedures were lateral pancreaticojejunostomy (22%) and cystojejunostomy (19%). Eight (9%) patients had duodenal-sparing pancreatic head resections, while 15% of patients had associated procedures such as cholecystectomy or cholecystojejunostomy performed.

An overall complication rate of 56% was observed (Table 5). There were three deaths in the series. One death resulted after a lesser sac marsupialization for pancreatic and retroperitoneal abscess drainage requiring a repeat operation for drainage of a pelvic abscess. This patient developed multi-system organ failure manifested by *Pseudomonas* pneumonia, renal failure, sepsis, and adult respiratory distress syndrome. Another death resulted after external drainage. This patient had bleeding postoperative day 6 requiring reoperation and transfusion of 10 units of

Table 2 Endoscopic Procedures

Endoscopic Treatment	*N*	Percent
ERCP	84	95.5
Stent Placement	47	53.4
Cystgastrostomy	9	10.2
Stone extraction	3	3.4
Transpapillary drainage of pseudocyst	3	3.4
Celiac plexus nerve Block	1	1.0

Table 3 Indications for Surgery Following Endoscopic Treatment

Indication	*N*	Percent
Persistent/new onset symptoms	25	28.4
Unacceptable anatomy	23	26.1
CBD/PD Stricture	16	18.2
Persistent pseudocyst	13	14.7
Infection or clinical deterioration	14	15.9
Impacted stones	5	5.7
Pancreatic fistula	2	2.3
Post ERCP pancreatitis	1	1.0
Hemorrhage	1	1.0
Duodenal stenosis	1	1.0

Table 4 Spectrum of Operations

Operation	*N*	Percent
Internal Drainage	40	45.5
Pancreaticojejunostomy	19	21.6
Cystjejunostomy	17	19.3
Cholecystojejunostomy	14	15.9
Hepaticojejunostomy	6	6.8
Choledochojejunostomy	3	3.4
Transduodenal sphincteroplasty	2	2.3
Pancreatocystojejunostomy	1	1.0
Debridement/Drainage	22	24.7
Pancreatic Resection	27	30.7
Distal pancreatectomy with Splenectomy	13	14.8
Distal pancreatectomy without Splenectomy	1	1.0
Local pancreatic head resection	8	9.1
Subtotal Pancreatectomy	4	4.5
Pancreatoduodenectomy	1	1.0
Associated Procedures		
Cholecystectomy	13	14.8
Gastrojejunostomy	10	11.4

Table 5 Complications

Complications	*N*	Percent
All Complications	50	56.8
Hemorrhage	14	15.9
Wound infection	11	12.5
Pulmonary	10	11.4
Sepsis	6	6.8
Reoperation	4	4.5
Ileus	3	3.4
UTI	3	3.4
Dehiscence	2	2.3
Infected pancreatic fluid	2	2.3
GI bleed	2	2.3
Urinary retention	2	2.3
Colitis	2	2.3
Neurologic	2	2.3
Thoracic duct injury	1	1.0
DVT	1	1.0
Stroke	1	1.0
Renal Failure	1	1.0
Death	3	3.4

red blood cells, but he subsequently died. The third death resulted after an operation including splenectomy and drainage of a fluid collection. The operation was complicated by bleeding followed by respiratory insufficiency, sepsis, and multi-organ failure in the postoperative period. Overall, repeat operations were necessary in 4% of patients.

Discussion

In this study, our aim was to examine the outcome of patients that had initial endoscopic treatment but required surgical salvage therapy for ongoing symptoms from pancreatic disease. Both acute and chronic pancreatitis may result in extensive tissue destruction with difficult-to-treat symptoms and complications. Both endoscopic and surgical approaches may result in resolution of symptoms, but often endoscopic therapy is chosen because it is less invasive and has a limited recovery period compared to surgery. Few data exist to determine whether endoscopy or surgery is most appropriate for advanced pancreatic disease. Moreover, the outcome of surgical therapy after failed endoscopic therapy has not been documented. In this study, the findings indicate that chronic pancreatitis with persistent or newly developed symptoms is the most common reason for pancreatic surgery following endoscopic therapy. While pancreatic resection may be required, surgical salvage therapy can often be accomplished by drainage procedures. These complex procedures can be performed with acceptable mortality but significant risk for morbidity.

The results of our study suggest that patients with chronic pancreatitis that are treated with endotherapy are the most likely patients that will require salvage surgery. These findings are in agreement with recent randomized trials that demonstrated surgical therapy for obstructive chronic pancreatitis resulting in more durable pain relief.[19,20] Dite et al. concluded that endotherapy may remain the first line therapy and that surgery should be performed following failed endotherapy. However, their study does not completely address the risks associated with complex procedures in a group of patients with chronic illness and substantial co-morbidities. The current study suggests that overall mortality rates are low (3.4%), but that the overall complication rates are high (56.8%) and that some of the complications may result in permanent sequelae. It is also important to note that many of the patients undergoing endotherapy require multiple procedures that extend over several months. Furthermore, a Dutch trial reported a 58% complication rate in patients treated endoscopically.[19] Without correction of the underlying pancreatic pathology, many of these patients are unable to obtain adequate nutrition and over time, lose significant weight and further increase their risk of postoperative complications.[36] In addition, even though this work does not provide direct evidence that early initial operative therapy will decrease patient morbidity, Cahen et al. illustrates a morbidity rate of 35% in a group of surgical patients that had a duration of symptoms of only 21 months.[19] In our study, nearly all surgical patients had two to five endoscopic procedures performed over 2–3 years prior to surgery. Thus, extended endoscopic therapy may affect the morbidity of salvage surgery for chronic pancreatitis. Given these findings, we suggest that surgery be considered as a first-line therapy for select patients with chronic pancreatitis.

While successful long-term outcomes following endotherapy for patients with chronic pancreatitis have been difficult to achieve, endotherapy for the complications of acute pancreatitis has been employed with increasing success. Pancreatic pseudocyst drainage by either the transpapillary or transmural approach has replaced surgical therapy and percutaneous drainage as the first-line treatment option in appropriately selected patients.[37,38] Furthermore, aggressive endotherapy with transmural stent placement and vigorous irrigation of lesser sac pancreatic abscesses has been increasingly successful.[37] Pancreatic fistulae are readily identified and treated with ERCP followed by transpapillary stenting.[37] In years past, each of these complications of acute pancreatitis was thought to be best managed by surgical therapy, yet these operations were difficult and associated with high morbidity. Therefore, endotherapy for appropriately selected patients with pancreatic pseudocysts and fistulae is appropriate. Although some patients with pancreatic abscesses or necrosis may be successfully treated by skilled, dedicated endoscopic therapists, these complications of acute pancreatitis require

long-term therapy with multiple interventions that can result in treatment over several months. In patients with significant necrosis and tissue destruction, surgical pancreatic debridement remains the mainstay of therapy.

Surgical outcomes for pancreatic resection and drainage procedures have improved markedly in the last decade with significantly decreased mortality rates. However, despite the improved mortality in these ill patients, the risks of complications remain significant. More recent complete reporting has demonstrated that over 50% of patients undergoing pancreatic surgery have complications.[39] Furthermore, evidence suggests that thorough preoperative evaluation and preparation of patients may decrease the risk of complications.[40] Therefore, assessment of patients for endotherapy or surgical therapy for pancreatic disease must include a complete risk assessment and evaluation of the likely long-term outcomes of either an endotherapeutic approach or surgical management. Failed endotherapy may not be a prerequisite for surgical therapy of acute or chronic pancreatitis.

Conclusion

In conclusion, because of the significant risk of complications, only patients who are likely to have a long-lasting beneficial effect from endotherapy should undergo this type of therapy initially for chronic pancreatitis or pancreatic necrosis. Patients with complex disease and are unlikely to respond to endotherapy should have primary surgical therapy. This approach may decrease cost, treatment duration, patient discomfort, and potentially limit subsequent surgical complications.

References

1. Frossard JL, Steer ML, Pastor CM. Acute pancreatitis. Lancet 2008;371:143–152. doi:10.1016/S0140-6736(08)60107-5.
2. Birgisson H, Moller PH, Birgisson S, Thoroddsen A, Asgeirsson KS, Sigurjonsson SV et al. Acute pancreatitis: A prospective study of its incidence, aetiology, severity, and mortality in Iceland. Eur J Surg 2002;168:278–282. doi:10.1002/ejs.46.
3. Carnovale A, Rabitti PG, Manes G, Esposito P, Pacelli L, Uomo G. Mortality in acute pancreatitis: Is it an early or a late event? JOP 2005;6:438–444.
4. Company L, Saez J, Martinez J, Aparicio JR, Laveda R, Grino P et al. Factors predicting mortality in severe acute pancreatitis. Pancreatology 2003;3:144–148. doi:10.1159/000070083.
5. Floyd A, Pedersen L, Nielsen GL, Thorladcius-Ussing O, Sorensen HT. Secular trends in incidence and 30-day case fatality of acute pancreatitis in North Jutland County, Denmark: A register-based study from 1981–2000. Scand J Gastroenterol 2002;37:1461–1465. doi:10.1080/003655202762671369.
6. Frey CF, Zhou H, Harvey DJ, White RH. The incidence and case-fatality rates of acute biliary, alcoholic, and idiopathic pancreatitis in California, 1994–2001. Pancreas 2006;33:336–344. doi:10.1097/01.mpa.0000236727.16370.99.
7. Gislason H, Horn A, Hoem D, Andren-Sandberg A, Imsland AK, Soreide O, Viste A. Acute pancreatitis in Bergen, Norway. A study on incidence, etiology and severity. Scand J Surg 2004;93:29–33.
8. McKay CJ, Evans S, Sinclair M, Carter CR, Imrie CW. High early mortality rate from acute pancreatitis in Scotland, 1984–1995. Br J Surg 1999;86:1302–1305. doi:10.1046/j.1365-2168.1999.01246.x.
9. Renner IG, Savage WT III, Pantoja JL, Renner VJ. Death due to acute pancreatitis. A retrospective analysis of 405 autopsy cases. Dig Dis Sci 1985;30:1005–1018. doi:10.1007/BF01308298.
10. Werner J, Feuerbach S, Uhl W, Buchler MW. Management of acute pancreatitis: From surgery to interventional intensive care. Gut 2005;54:426–436. doi:10.1136/gut.2003.035907.
11. Bradley EL III. Management of infected pancreatic necrosis by open drainage. Ann Surg 1987;206:542–550. doi:10.1097/00000658-198710000-00015.
12. Gourgiotis S, Germanos S, Ridolfini MP. Surgical management of chronic pancreatitis. Hepatobiliary Pancreat Dis Int 2007;6:121–33.
13. Smits ME, Badiga SM, Rauws EA, Tytgat GN, Huibregtse K. Long-term results of pancreatic stents in chronic pancreatitis. Gastrointest Endosc 1995;42:461–467. doi:10.1016/S0016-5107(95)70051-X.
14. Kozarek RA, Ball TJ, Patterson DJ, Brandabur JJ, Traverso LW, Raltz S. Endoscopic pancreatic duct sphincterotomy: indications, technique, and analysis of results. Gastrointest Endosc 1994;40:592–598.
15. Will U, Wegener C, Graf KI, Wanzar I, Manger T, Meyer F. Differential treatment and early outcome in the interventional endoscopic management of pancreatic pseudocysts in 27 patients. World J Gastroenterol 2006;12:4175–4178.
16. Hookey LC, Debroux S, Delhaye M, Arvanitakis M, Le MO, Deviere J. Endoscopic drainage of pancreatic-fluid collections in 116 patients: A comparison of etiologies, drainage techniques, and outcomes. Gastrointest Endosc 2006;63:635–643. doi:10.1016/j.gie.2005.06.028.
17. Partington PF, Rochelle RE. Modified Puestow procedure for retrograde drainage of the pancreatic duct. Ann Surg 1960;152:1037–1043.
18. Prinz RA, Greenlee HB. Pancreatic duct drainage in chronic pancreatitis. Hepatogastroenterology 1990;37:295–300.
19. Cahen DL, Gouma DJ, Nio Y, Rauws EA, Boermeester MA, Busch OR et al. Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. N Engl J Med 2007;356:676–684. doi:10.1056/NEJMoa060610.
20. Dite P, Ruzicka M, Zboril V, Novotny I. A prospective, randomized trial comparing endoscopic and surgical therapy for chronic pancreatitis. Endoscopy 2003;35:553–558. doi:10.1055/s-2003-40237.
21. Neoptolemos JP, Carr-Locke DL, London NJ, Bailey IA, James D, Fossard DP. Controlled trial of urgent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy versus conservative treatment for acute pancreatitis due to gallstones. Lancet 1988;2:979–283. doi:10.1016/S0140-6736(88)90740-4.
22. Lans JI, Geenen JE, Johanson JF, Hogan WJ. Endoscopic therapy in patients with pancreas divisum and acute pancreatitis: A prospective, randomized, controlled clinical trial. Gastrointest Endosc 1992;38:430–434.
23. Jacob L, Geenen JE, Catalano MF, Geenen DJ. Prevention of pancreatitis in patients with idiopathic recurrent pancreatitis: A prospective nonblinded randomized study using endoscopic stents. Endoscopy 2001;33:559–562. doi:10.1055/s-2001-15314.
24. Smits ME, Badiga SM, Rauws EA, Tytgat GN, Huibregtse K. Long-term results of pancreatic stents in chronic pancreatitis.

Gastrointest Endosc 1995;42:461–467. doi:10.1016/S0016-5107(95)70051-X.
25. Smits ME, Badiga SM, Rauws EA, Tytgat GN, Huibregtse K. Long-term results of pancreatic stents in chronic pancreatitis. Gastrointest Endosc 1995;42:461–467. doi:10.1016/S0016-5107(95)70051-X.
26. Puestow CB, Gillesby WJ. Retrograde surgical drainage of pancreas for chronic relapsing pancreatitis. AMA Archives of Surgery 1958;76:898–907.
27. Warshaw AL, Banks PA, Fernandez-Del CC. AGA technical review: Treatment of pain in chronic pancreatitis. Gastroenterology 1998;115:765–776. doi:10.1016/S0016-5085(98)70157-X.
28. Holmberg JT, Isaksson G, Ihse I. Long term results of pancreaticojejunostomy in chronic pancreatitis. Surg Gynecol Obstet 1985;160:339–346.
29. Wilson TG, Hollands MJ, Little JM. Pancreaticojejunostomy for chronic pancreatitis. Aust N Z J Surg 1992;62:111–115.
30. Markowitz JS, Rattner DW, Warshaw AL. Failure of symptomatic relief after pancreaticojejunal decompression for chronic pancreatitis. Strategies for salvage. Arch Surg 1994;129:374–379.
31. Traverso LW, Kozarek RA. Pancreatoduodenectomy for chronic pancreatitis: Anatomic selection criteria and subsequent long-term outcome analysis. Ann Surg 1997;226:429–435. doi:10.1097/00000658-199710000-00004.
32. Beger HG, Schlosser W, Friess HM, Buchler MW. Duodenum-preserving head resection in chronic pancreatitis changes the natural course of the disease: A single-center 26-year experience. Ann Surg 1999;230:512–519. doi:10.1097/00000658-199910000-00007.
33. Eddes EH, Masclee AA, Lamers CB, Gooszen HG. Duodenum preserving resection of the head of the pancreas in painful chronic pancreatitis. Eur J Surg 1996;162:545–549.
34. Evans JD, Wilson PG, Carver C, Bramhall SR, Buckels JA, Mayer AD et al. Outcome of surgery for chronic pancreatitis. Br J Surg 1997;84:624–629. doi:10.1002/bjs.1800840512.
35. Fahy BN, Frey CF, Ho HS, Beckett L, Bold RJ. Morbidity, mortality, and technical factors of distal pancreatectomy. Am J Surg 2002;183:237–241. doi:10.1016/S0002-9610(02)00790-0.
36. Curtis CS, Kudsk KA. Nutrition support in pancreatitis. Surg Clin North Am 2007;87:1403–1415. viii doi:10.1016/j.suc.2007.08.010.
37. Baron TH. Treatment of pancreatic pseudocysts, pancreatic necrosis, and pancreatic duct leaks. Gastrointest Endosc Clin N Am 2007;17:559–579. doi:10.1016/j.giec.2007.05.013.
38. Neuhaus H. Therapeutic pancreatic endoscopy. Endoscopy 2004;36:8–16. doi:10.1055/s-2004-814119.
39. DeOliveira ML, Winter JM, Schafer M, Cunningham SC, Cameron JL, Yeo CJ et al. Assessment of complications after pancreatic surgery: A novel grading system applied to 633 patients undergoing pancreaticoduodenectomy. Ann Surg. 2006;244:931–937. doi:10.1097/01.sla.0000246856.03918.9a.
40. Winter JM, Cameron JL, Yeo CJ, Alao B, Lillemoe KD, Campbell KA et al. Biochemical markers predict morbidity and mortality after pancreaticoduodenectomy. J Am Coll Surg 2007;204:1029–1036. doi:10.1016/j.jamcollsurg.2007.01.026.

J Gastrointest Surg (2008) 12:1930–1937
DOI 10.1007/s11605-008-0620-x

Survival Rates and Cause of Death in 174 Patients with Chronic Pancreatitis

Sergio Pedrazzoli · Claudio Pasquali · Stefano Guzzinati · Mattia Berselli · Cosimo Sperti

Received: 16 May 2008 / Accepted: 15 July 2008 / Published online: 3 September 2008

Abstract
Background The natural history after surgery for chronic pancreatitis is rarely reported.
Methods Between 1970 and 1999, 174 patients underwent surgery for chronic pancreatitis and were followed until December 2006. They were divided in four groups: (1) *resection* 62; (2) *drainage* 82; (3) *external drainage* 7; (4) *non-pancreas-directed surgery* 23. A second procedure was required by 25 patients and a third by four: *group 1*=6+0, *group 2*=10+2, *group 3*=3+1, *group 4*=6+1.
Results Hospital mortality was four of 174 (2.3%). *Fifty-seven* patients are alive; 49 of 170 developed cancer, and 38 died: lung (22), oral, pharynx, larynx (eight), esophagus, kidney, pancreas, colon, liver (two each), breast, stomach, mediastinum, prostate, melanoma, chronic myelogenous leukemia, squamous cancer of the auricle (one each), liver metastasis from unknown primary (two). Fifteen patients died of liver cirrhosis, 13 of myocardial infarction/decompensation, six of vascular problems, five each of acute renal insufficiency or cerebral diseases, four each of acute pancreatitis, accidental trauma, complications of diabetes, bronchopneumonia, and 19 of other causes. The overall 5-, 10-, 15-, 20-, 25-, and 30-year survival rate was 84.7, 65.6, 51.6, 38.0, 28.1, and 23.5.
Conclusions Incidence of pancreatic cancer was 1.2%. The high incidence of smoking cancers (18.8%) is explained by the smoking habits of almost 100% of our patients. Eliminating smoking and increasing tests on organs at risk may prolong survival.

Keywords Chronic pancreatitis · Surgery · Pancreaticojejunostomy · Pancreaticoduodenectomy · Frey procedure

Grant support: This study has been supported by the Ministero dell'Università e Ricerca Scientifica (Cofin 2005060715_001), Rome, Italy.

S. Pedrazzoli (✉) · C. Pasquali · M. Berselli · C. Sperti
Department of Medical and Surgical Sciences,
Clinica Chirurgica IV, University of Padova,
Via Giustiniani, 2,
35128 Padova, Italy
e-mail: sergio.pedrazzoli@unipd.it

S. Guzzinati
Venetian Tumor Registry, Istituto Oncologico Veneto, IRCCS,
Padova, Italy

Introduction

The phrase "chronic pancreatitis" refers to a syndrome of progressive destructive, inflammatory conditions of the pancreas leading to an exocrine and endocrine insufficiency in most patients. Significant progress has been made in recent years on the pathogenesis of chronic pancreatitis[1,2] with the identification of new genetic[3] and environmental factors and a deeper understanding of the pathobiology of the disease.[4] The predominant symptom of chronic pancreatitis is pain, which affects more than 85% of patients. Pain control was the main problem that prompted the majority of the studies on medical,[5,6] endoscopic,[7,8] and surgical[9,10] treatment of chronic pancreatitis.

The very long-term fate of chronic pancreatitis patients *has been less well studied*. The reported general death rate after 5, 10, 20, and 30 years was highly variable and *reported* between 4% and 14%, 8% and 35%, 20% and

77%, and 72% and 92%, respectively, while the death rate related to chronic pancreatitis was between 0.9% and 18.6%.[11–16] The very long-term survival of chronic pancreatitis patients shows a mortality rate of around 80% after 20 years in smokers and *after* 30 years in non-smokers.[17] Data on mortality rate and long-term survival are difficult to interpret, as etiology and mean observation times vary from study to study, with a mean and median follow-up that rarely reach 10 years and an incidence of *loss* to follow-up between 0% and 44.6%.[11–16]

The aim of our study was to evaluate the long-term course of 174 chronic pancreatitis patients that underwent surgical treatment between 1970 and 1999.

Patients and Methods

Patients and Indications for Surgery

From January 1970 to December 1999, 193 patients underwent surgical treatment with the diagnosis of chronic pancreatitis. After careful review 19 patients were excluded: In 16 patients, a posttraumatic (4) or post-severe acute pancreatitis (12) pseudocyst was drained in the gastrointestinal (GI) tract; two patients had a stenosis of Vater's papilla and one intraductal papillary mucinous tumor. Chronic pancreatitis was confirmed by histology in 134 patients and by surgical exploration and follow-up in 40 patients. There were 152 men and 22 women with a mean age of 45±10.2, range 24–75 years. Preoperative alcohol intake was absent in only three patients, and only 25 had stopped drinking before surgery for a mean of 45 months (median 24, range 6–276). Preoperative smoking habit was absent in only nine of 170 patients (5.3%) surviving surgery, while 16 patients had stopped smoking before surgery for a mean of 15 months (median 8, range 1–120). The mean preoperative duration of the disease was 4.1 years (median 3, range 0.1–21). The severity of the disease was evaluated "a posteriori" according to the parameters reported in Table 1. Pain was absent in five, mild in nine, moderate in 20, severe in 70, very severe in 67, and unendurable in three. Diabetes was absent in 132, controlled by diet in 19, on oral antidiabetics in six, and on insulin treatment in 17. Diarrhea was absent in 128 patients, mild in 21, moderate in 20, and severe in five. Appetite was normal in 131, alternate normal/decreased in 29, and decreased in 14. The leading indications for surgery in the 174 patients were pain in 61, pseudocyst in 39, suspicion of a pancreatic cancer in 25, jaundice in 24, hemosuccus pancreaticus in six, internal pancreatic fistula in five, duodenal or intestinal occlusion in four, and other in ten.

Surgery and Perioperative Management

According to the procedure performed, the surgical treatment was divided in four groups:

Resection was performed in 62 patients (*group 1*). A Whipple pancreaticoduodenectomy (PD) was performed in 41 patients, a distal pancreatectomy with (six) or without (13) pancreaticojejunostomy in 19, and a Dean Warren procedure in two.

Drainage was performed in 82 patients (*group 2*). A Puestow was performed in 20 patients, a pancreaticojejunostomy according to Partington Rochelle or Frey procedure in 44, a personal procedure[18] in four, a cystojejunostomy in 12, a cystoduodenostomy, and a fistulojejunostomy in one each.

An external drainage of a pancreatic pseudocyst (*group 3*) was performed in seven patients in the early 1970s.

Table 1 Parameters Used to Evaluate the Severity of the Disease

Parameter	Score					
	0	1	2	3	4	5
Pain	Absent	Mild	Moderate[a]	Severe[b]	Very severe[c]	Unendurable[d]
Appetite	Normal-increased	Alternate normal decreased	Decreased	Absent		
Diarrhea	Absent	Mild Occasional	Moderate Controlled by enzymes	Severe Partially controlled by enzymes	Very severe Uncontrolled by enzymes	
Diabetes	Absent		Controlled by diet		Oral antidiabetics	IDDM

[a] Lesser than or equal to three attacks controlled by nonsteroidal anti-inflammatory drugs (NSAIDs)
[b] Greater than or equal to four attacks controlled by NSAIDs
[c] One or more attacks uncontrolled by NSAIDs
[d] Need of opioid treatment

Table 2 Second and Third Operative Procedures Performed

Procedure (second and third)	Group 1 Resection (62 patients)	Group 2 Drainage (82 patients)	Group 3 External drainage (seven patients)	Group 4 Non-pancreas-directed surgery (23 patients)	Total (174 patients)
Bilioenteric anastomosis	2	2		1	5
Distal pancreatectomy	2[a]	2+1		2	6+1
Pancreaticoduodenectomy				1	1
Pancreaticojejunostomy				1	1
Toilette of a necrotic collection	1	1			2
Cholecystectomy	1	1			2
Closure of a colonic stoma		1		1+1	2+1
Total pancreatectomy		1[b]			1
Gastroenterostomy		1			1
Lysis of peritoneal adhesions		1			1
Fistulojejunostomy			3[c]		3
Posterior splanchnicectomy		0+1	0+1		0+2
Total	6	10+2	3+1	6+1	25+4

[a] One performed 2 months after an emergency salvage cystojejunostomy (Fig. 1)
[b] Performed after the diagnosis of "scar cancer" on the specimens of a Frey's procedure. The final diagnosis was chronic pancreatitis.
[c] Together with a bilioenteric anastomosis in one patient.

Non-pancreas-directed surgery was performed in 23 patients (*group 4*). A procedure on the main bile duct was performed in 19 patients, a cholecystectomy, a bilateral splanchnicectomy, an embolization of a bleeding pseudoaneurysm, and a remaking of the hepaticojejunostomy 8 years after a Whipple procedure performed elsewhere in one each.

Overall, 25 patients underwent a second and four a third surgical procedure (Table 2).

Follow-up

All 170 patients surviving surgery were regularly followed mostly in the form of outpatient visit or, when not possible, with telephone contact to the patient. The questionnaires used varied along the 37 years, elapsed between 1970 and December 2006. When patients missed *program follow-up*, their actual status was traced through the registry office, and in case of death, any effort was made to trace the actual

Table 3 Postoperative Deaths

Pat.	Year	Age	Sex	ASA	Surgical procedure	Complication	Cause of death	PO day
1	1976	33	M	3	DP, PJ, MCA	GI hemorrhage	Liver insufficiency	23
2	1980	43	M	3	PD	Pancreatic and biliary fistula	Candida pneumonia, MOF	37
3	1984	60	M	3	Cholecystectomy, hepaticojejunostomy, GEA, splenectomy	Perforated diverticulum of the left colon (13 days); perforated diverticulum of the right colon (20 days)	MOF	21
4	1997	75	M	3	PD	Hypovolemic shock from hemorrhagic gastritis (17 days)[a]. GI hemorrhage from a pseudoaneurysm of the RHA (38 days)[b]	MOF	42

DP distal pancreatectomy; *PJ* pancreaticojejunostomy; *MCA* mesentericocaval shunt with jugular vein interposition; *PD* pancreaticoduodenectomy; *RHA* right hepatic artery; *MOF* multiple-organ failure
[a] Total gastrectomy
[b] Suture ligation of the RHA

cause of death, at least until the law on privacy prevented us to find complete information in some patients.

For this study, the results of the last follow-up until December 2006 were considered. Median postoperative follow-up in the 170 patients surviving surgery was 186.3 months (95% confidence interval [CI]=160.1–222.1), mean 200.3±9.7, range 3.1–441.6 months, first quartile=92.1, and third quartile=336.3.

Statistics

All perioperative and outcome data were entered into a computerized database (SPSS 13.0 per Windows, SPSS Inc., Illinois, USA). Life tables for the general population of the Veneto region (northeast of Italy) for men and women were obtained by the National Institute of Statistics (Istituto Nazionale di Statistica) to calculate the expected survival curves using the Kaplan–Meier method.

The relative risk of cancer was estimated by the standardized incidence ratio (SIR), defined as the ratio of the observed (32 men with sites of oral cavity, pharynx, esophagus, larynx, and lung) to expected number of patients with cancer. To estimate the expected cases, we applied incidence rates from the same sites taken from the Veneto Cancer Registry database by 10-year age classes and 5-year calendar period, multiplied by 10, because all

Table 4 Long-Term Cause of Death

Cause of death	Group 1 (62 patients)	Group 2 (82 patients)	Group 3 (7 patients)	Group 4 (23 patients)	Total (174 patients)
Cancer of					
Lung	6	12	0	2	20
Mouth, pharynx, larynx	3	3	1	0	7
Esophagus	1	0	0	0	1
Pancreas	1[a]	1	0	0	2
Liver metastases[b]	2	0	0	0	2
Mediastinum	1	0	0	0	1
Liver (in cirrhosis)	0	0	0	1	1
Prostate	0	0	0	1	1
Chronic myeloid leukemia	0	1	0	0	1
Stomach	0	1	0	0	1
Monoclonal gammopathy[c]	0	1	0	0	1
Liver cirrhosis	3	8	2	2	15
MI or cardiac decompensation	2	8	1	2	13
Vascular problems	3	2	1	0	6
Acute renal insufficiency	3	2	0	0	5
Cerebral ictus, subdural hematoma	1	1	0	3	5
Acute pancreatitis	2	1	0	1	4
Diabetes or hypoglycemia	2	0	1	1	4
Car crash or accidental trauma	2	2	0	0	4
GI hemorrhage	0	3	0	0	3
Liver or pancreatic abscess	1	1	0	0	2
Septicemia	0	1	0	0	1
Suicide	0	0	0	1	1
Epilepsia in alcoholic	0	1	0	0	1
Intestinal occlusion	0	1	0	0	1
Perforated GD ulcer	0	1	0	0	1
Intestinal volvulus	1	0	0	0	1
Alzheimer	0	1	0	0	1
Cachexia from undernourishment	0	1	0	0	1
Unknown[d]	4	2	0	0	6
Total	38	55	6	14	113

[a] Small pancreatic cancer at first surgery, unresectable pancreatic cancer 18 years later
[b] Unknown primary
[c] With lymphoid infiltration of the bone marrow
[d] Two patients lost of follow-up (one emigrated abroad), one patient reached cadaver at first aid, no autopsy performed. Privacy prevented us to retrieve complete data of three patients.

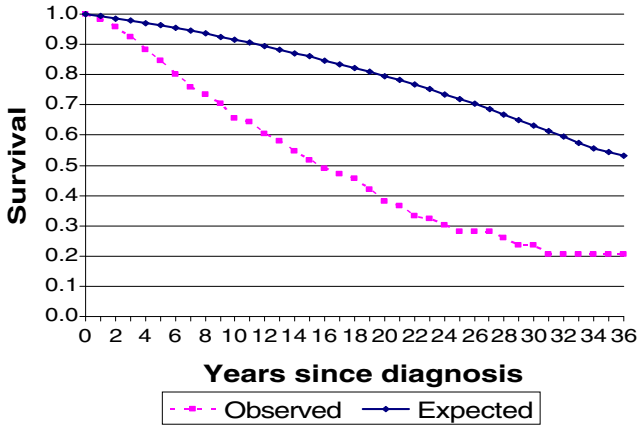

Figure 1 Observed and expected overall survival of the 170 chronic pancreatitis patients that survived surgery. The mean and median survival rate were 16.7±0.8 and 15.5 years (95% CI=13.3–18.5), first quartile 7.7 and third quartile 28.0. The death rate after 5, 10, 15, 20, 25, and 30 years was 15.3, 34.4, 48.4, 62.0, 71.9, and 76.5 instead of the expected 3.7, 8.5, 14.0, 20.5, 28.1, and 36.8 ($p<0.0001$).

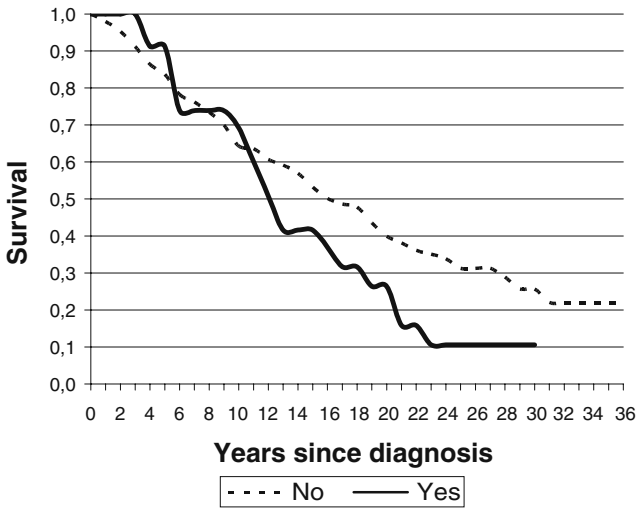

Figure 3 Observed survival of the 170 chronic pancreatitis patients that survived surgery according to the preoperative diabetes (*Yes* 23, *No* 147 patients. $p=0.1896$).

the observed cases were smokers, to the observed person years.

For calculating the person/year at risk, the expected number of cases and SIR, the STATA version 10.0 software was used. The 95% CI of SIR was calculated on the assumption that the observed numbers of cases follow a Poisson distribution.

Results

Surgery and Perioperative Course

Four out of 174 patients, 2.3% (Table 3) died after the first surgical treatment, while none of the 25 that underwent 29 further surgical procedures died. Therefore, the overall postoperative mortality rate was four of 203 surgical procedures (2%). Furthermore, 113 patients actually died (Table 4), while 57 are still alive.

After surgery, 103 patients (60.6%) were able to go back to work, seven (4.1%) started a lighter job, 21 (12.3%) were unable to go back to work, 36 (21.2%) were already retired before surgery, and three (1.8%) were lost to follow-up. There was no difference among the four groups ($p=0.4999$).

The mean and median survival rate were 16.7±0.8 and 15.5 years (95% CI=13.3–18.5), first quartile 7.7, and third quartile 28.0. The death rate after 5, 10, 15, 20, 25, and 30 years was 15.3, 34.4, 48.4, 62.0, 71.9, and 76.5. The overall survival curve and expected survival curve *are given* in Fig. 1. Patients that continued drinking alcohol had a

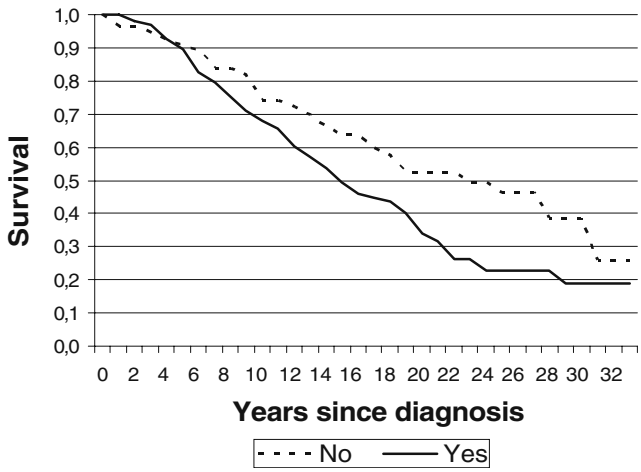

Figure 2 Observed survival of the 170 chronic pancreatitis patients that survived surgery according to the postoperative alcohol consumption (*Yes* 97, *No* 55 patients. $p=0.0314$).

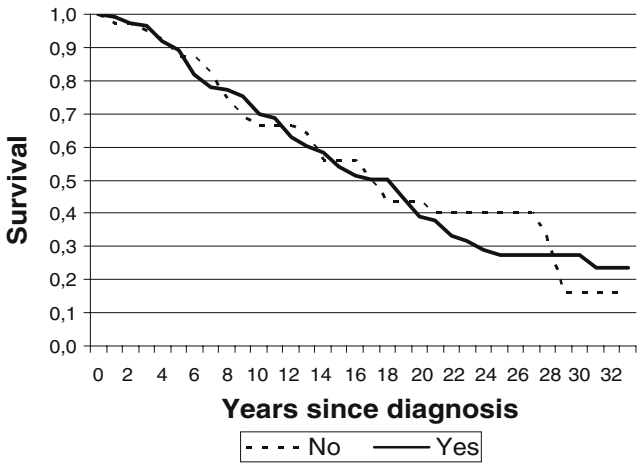

Figure 4 Observed survival of the 170 chronic pancreatitis patients that survived surgery according to the postoperative smoking habits (*Yes* 110, *No* 39, missing data 21 patients; $p=0.7780$).

significantly shorter survival than patients that stopped drinking (Fig. 2). There was no difference in survival curves for the presence (23 patients) or absence (147 patients) of preoperative diabetes (Fig. 3) *or* for patients that continued (110 patients) or stopped (39 patients) smoking (Fig. 4). The cause of death of the 113 patients that already died is reported in Table 4. Thirty-eight patients (23.3%) died of cancer; 28 of them (16.5%) died of a cancer of the smoking area. Six patients with actual or previous cancer died of an intercurrent or unknown cause. One patient underwent resection of a melanoma and another of a cancer of the vocal chords before dying of liver cirrhosis; a patient with hepatocellular adenocarcinoma in cirrhosis died of acute pancreatitis; a patient operated for squamous cancer of the auricle died of myocardial infarction (MI), and a patient operated for cancer of the kidney died of an accidental trauma. A patient with breast cancer died of unknown cause due to privacy.

Five patients are still alive after surgical treatment of their cancer: two of the lung and one each of the esophagus, colon, and kidney.

Therefore, overall, 49 of 170 patients (28.8%) surviving surgery had a cancer during their residual life, and 44 (38.9%) of the 113 deceased patients had a cancer.

For the risk of cancer of oral cavity, pharynx, esophagus, larynx, and lung, we observed 32 cases, while the expected number of cases was 85.6, yielding a SIR value of 0.37 (95% CI=0.26–0.53). *There were no* significant differences *when analyzed* by age or by years since diagnosis of chronic pancreatitis.

A small pancreatic cancer was present in the specimen taken during the first surgical procedure in three patients. One died 18 years later of pancreatic cancer, one died after 20 years and 6 months of a cause remained unknown for privacy, and one is still alive and well (Fig. 5). *One* further patient died of pancreatic cancer 18 years after a Frey's procedure. When pancreatic cancer was found only in the surgical specimen, *the patient* was excluded from further analysis. Therefore, for the risk of cancer of the pancreas, we observed two cases, while the expected number of cancer (taken from the incident rates of pancreatic cancer in Veneto Cancer Registry) was 0.68, yielding a SIR value of 2.93 (95% CI=0.36–10.60).

Discussion

In this study, we report the long-term outcome after surgical treatment for chronic pancreatitis with a postoperative

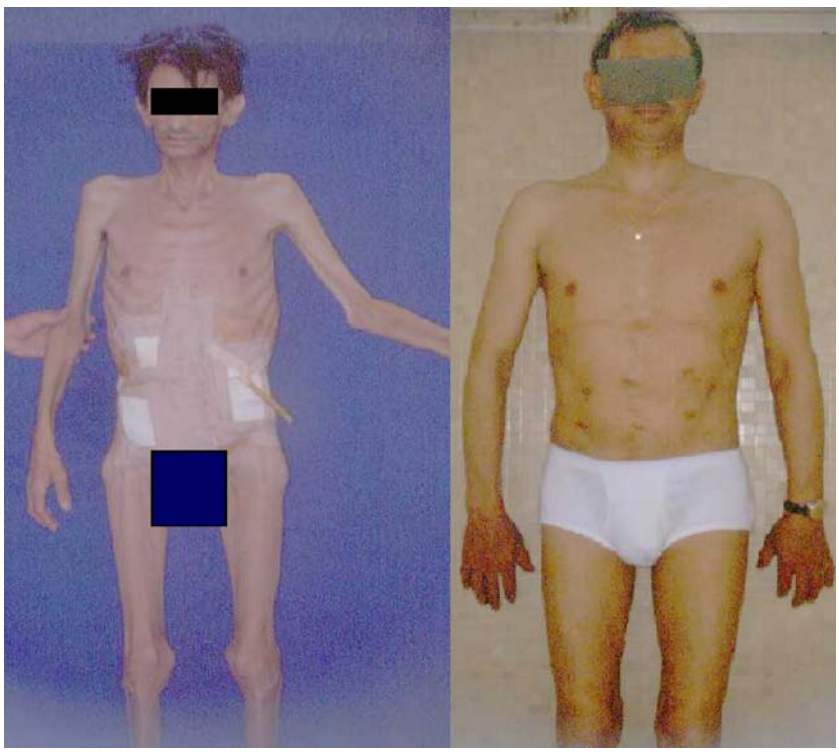

Figure 5 *On the left the picture* a 46-year-old man as soon as he was able to stand up: body weight 38 kg. He had undergone emergency surgery for bilateral subphrenic abscess and multiple pseudocysts on May 25, 1979; 3 months before the patient had undergone an explorative laparotomy elsewhere for pancreatic ascites. The abscess was drained, and a cystojejunostomy was performed. *On the right* the same patient 2 months later (body weight 48 kg), ready to undergo distal splenopancreatectomy and pancreaticojejunostomy. Histology documented a chronic pancreatitis with a small pancreatic cancer partially occluding the Wirsung duct. The patient is still alive and well.

follow-up period of 7–37 years. The follow-up was complete for all 57 still-living patients and for 107 of 113 patients who died. The cause of death of only six patients remained unknown (Table 4).

Of our 174 patients, 152 (87.4%) were men and 22 (12.6%) women.

In spite of the long period of time (1970–1999) and the relatively low number of procedures performed yearly, the surgical mortality of 2.3% compares favorably with that reported by others during the same period.[14,19,20]

Overall, 110 patients (64.7%) were able to go back to work, with seven doing a lighter work. However, if we consider only patients working before surgery, 84% (111/131) went back to work after surgery. Our results are in agreement with those reported by others.[12,13,17]

Our death rate after 5, 10, 20, and 30 years was 15.3, 34.4, 62.0, and 76.5 and is similar to that reported by others (between 4% and 14%, 8% and 35%, 20% and 77%, and 72% and 92%, respectively).[11–16] However, it is higher than expected for a similar population without chronic pancreatitis (Fig. 1). *These findings are* similar to that reported by Greenlee et al.[19] and by Lankisch[17] for patients with chronic pancreatitis that underwent surgical and/or medical treatment. The life expectancy for chronic pancreatitis patients from the time of diagnosis and/or surgical treatment is therefore significantly shorter than that of the general population without the disease.

Survival rate was similar for the different surgical treatments (data not shown). As stated by Devière et al.,[10] "at this time, we cannot provide guidelines in the treatment of this disease", as there is no difference in pain control and long-term results among the different surgical procedures.

Survival rate was not influenced by preoperative diabetes (Fig. 3), although the small number of preoperative diabetic patients (23/170) may prevent a statistically significant difference.

Survival rates were not influenced by *either* continuing or stopping smoking (Fig. 4) during follow-up. Our smoking hazard ratio was therefore different from the 1.4 reported by Lankisch[17] in 2001. Our negative result may be due to the very high percentage of patients that smoked preoperatively (161/170, 94.7%) and to the relatively small number of patients (39/149, 26.2%) stopping smoking after surgery. We must consider that the increased risk of smoke-related cancers persists for more than 10 years after cessation of smoking due to the length of the latency period of tobacco-related cancers.[21,22] In fact, the risk of most of our cancers (lung, oral cavity, pharynx, larynx, and esophagus) is lower in former smokers than in current smokers, but is still significantly higher than in non-smokers.[22] The incidence of cancer of oral cavity, pharynx, esophagus, larynx, and lung was quite high (32/170) for a general population with a normal percentage of smokers, but was lower than expected for a population of whom 94.7% smoked preoperatively. It was also lower than that reported by Talamini et al.[23] in 1999.

Survival of patients who abstain from alcohol (Fig. 2) was significantly higher than of those who continued to drink. This is a well-known phenomenon and is in accordance with other studies.[17,19]

The incidence of pancreatic cancer in our series was two of 170 patients surviving surgery. Pancreatic cancer found in the surgical specimen *at the time of original operation was excluded from analysis to prevent confounding*. Our SIR was 2.93 (95% CI=0.36–10.60) and was lower than that reported by others.[23–25]

Other important causes of death were liver cirrhosis, MI or decompensation, vascular problems, acute renal insufficiency, cerebral ictus, or subdural hematoma (Table 4). All of them *are related to the* drinking and smoking habits of our chronic pancreatitis patients.

In conclusion, surgical treatment of chronic pancreatitis can be performed safely, with a low mortality rate. The long-term survival was significantly lower than that expected for the general population of the same age and sex, and this was probably due to the high percentage of patients drinking alcohol and smoking. Eliminating drinking and smoking and increasing tests on organs at risk of cancer may prolong survival in chronic pancreatitis patients. In comparison to extrapancreatic malignancy, pancreas cancer was relatively uncommon in our series occurring in only two patients (1.1%), at least 2 years after surgery, both of whom died of the disease.

Acknowledgment The authors gratefully acknowledge Tania Lazzarin for helping with the manuscript.

References

1. DiMagno MJ, DiMagno EP. Chronic pancreatitis. Curr Opin Gastroenterol 2005;21:544–554. doi:10.1097/01.mog.0000175543.42582.55.
2. Ammann RW. Diagnosis and management of chronic pancreatitis: current knowledge. Swiss Med Wkly 2006;136:166–174.
3. Whitcomb DC, Gorry MC, Preston RA, Furey W, Sossenheimer MJ, Ulrich CD, et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. Nat Genet 1996;14:141–145. doi:10.1038/ng1096-141.
4. Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. Gastroenterology 2001;120:682–707. doi:10.1053/gast.2001.22586.
5. Lankisch PG. Chronic pancreatitis. Curr Opin Gastroenterol 2007;23:502–507. doi:10.1097/MOG.0b013e3282ba5736.
6. Fasanella KE, Davis B, Lyons J, Chen Z, Lee KK, Slivka A, et al. Pain in chronic pancreatitis and pancreatic cancer. Gastroenterol Clin North Am 2007;36:335–364. doi:10.1016/j.gtc.2007.03.011.
7. Dite P, Ruzicka M, Zboril V, Novotny I. A prospective, randomized trial comparing endoscopic and surgical therapy for

chronic pancreatitis. Endoscopy 2003;35:553–558. doi:10.1055/s-2003-40237.
8. Cahen DJ, Gouma DJ, Nio Y, Rauws EA, Boermeester MA, Busch OR, et al. Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. N Engl J Med 2007;356:676–684. doi:10.1056/NEJMoa060610.
9. Hartel M, Tempia-Caliera AA, Z'graggen K, Friess H, Büchler MW. Evidence based surgery in chronic pancreatitis. Langenbecks Arch Surg 2003;388:132–139.
10. Devière J, Bell RH Jr, Beger HG, Traverso LW. Treatment of chronic pancreatitis with endotherapy or surgery: critical review of randomized control trials. J Gastrointest Surg 2008;12:640–644. doi:10.1007/s11605-007-0448-9.
11. Ammann RW, Akovbiantz A, Largadèr F, Schueler G. Course and outcome of chronic pancreatitis: longitudinal study of a mixed medical–surgical series of 245 patients. Gastroenterology 1984;86:820–828.
12. Miyake H, Harada H, Kunichika K, Ochi K, Kimura I. Clinical course and prognosis of chronic pancreatitis. Pancreas 1987;2:378–385. doi:10.1097/00006676-198707000-00003.
13. Lankisch PG, Löhr-Happe A, Otto J, Creutzfeldt W. Natural course in chronic pancreatitis: pain, exocrine and endocrine pancreatic insufficiency and prognosis of the disease. Digestion 1993;54:148–155.
14. Russell RCG, Theis BA. Pancreaticoduodenectomy in the treatment of chronic pancreatitis. World J Surg 2003;27:1203–1210. doi:10.1007/s00268-003-7239-6.
15. Thuluvath PJ, Imperio D, Nair S, Cameron JL. Chronic pancreatitis. Long term pain relief with or without surgery, cancer risk, and mortality. J Clin Gastroenterol 2003;36:159–165. doi:10.1097/00004836-200302000-00014.
16. Riediger H, Adam U, Fischer E, Keck T, Pfeffer F, Hopt UT, et al. Long term outcome after resection for chronic pancreatitis in 224 patients. J Gastrointest Surg 2007;11:949–960. doi:10.1007/s11605-007-0155-6.
17. Lankisch PG. Natural course of chronic pancreatitis. Pancreatology 2001;1:3–14. doi:10.1159/000055786.
18. Pedrazzoli S, Sperti C, Pasquali C. Pancreaticoduodenojejunostomy for chronic pancreatitis presenting with an inflammatory mass in the head of the pancreas. Pancreas 1995;11:289–293. doi:10.1097/00006676-199510000-00012.
19. Greenlee HB, Prinz RA, Aranha GV. Long-term results of side to side pancreaticojejunostomy. World J Surg 1990;14:70–76. doi:10.1007/BF01670548.
20. Duffy JP, Reber A. Surgical treatment of chronic pancreatitis. J Hepatobiliary Pancreat Surg 2002;9:659–668. doi:10.1007/s005340200091.
21. Sasco AJ, Secretan MB, Straif K. Tobacco smoking and cancer: a brief review of recent epidemiological evidence. Lung Cancer 2004;45(Suppl.2):S3–9. doi:10.1016/j.lungcan.2004.07.998.
22. Gandini S, Botteri E, Iodice S, Boniol M, Lowenfels AB, Maisonneuve P, et al. Tobacco smoking and cancer: a meta-analysis. Int J Cancer 2008;122:155–164. doi:10.1002/ijc.23033.
23. Talamini G, Falconi M, Bassi C, Sartori N, Salvia R, Caldiron E, Frulloni L, Di Francesco V, Vaona B, Bovo P, Vantini I, Pederzoli P, Cavallini G. Incidence of cancer in the course of chronic pancreatitis. Am J Gastroenterol 1999;94:1253–1260. doi:10.1111/j.1572-0241.1999.01075.x.
24. Lowenfels AB, Maisonneuve P, Cavallini G, Ammann RW, Lankisch PG, Andersen JR, International Pancreatitis Study Group, et al. Pancreatitis and the risk of pancreatic cancer. N Engl J Med 1993;328:1433–1437. doi:10.1056/NEJM199305203282001.
25. Malka D, Hammel P, Maire F, Rufat P, Madeira I, Pessione F, et al. Risk of pancreatic adenocarcinoma in chronic pancreatitis. Gut 2002;51:849–852. doi:10.1136/gut.51.6.849.

J Gastrointest Surg (2008) 12:1938–1950
DOI 10.1007/s11605-008-0581-0

Fluorophore-conjugated anti-CEA Antibody for the Intraoperative Imaging of Pancreatic and Colorectal Cancer

Sharmeela Kaushal · Michele K. McElroy · George A. Luiken · Mark A. Talamini · A. R. Moossa · Robert M. Hoffman · Michael Bouvet

Received: 16 May 2008 / Accepted: 16 June 2008 / Published online: 30 July 2008

Abstract
Introduction Colorectal and pancreatic cancers together comprise the third and fourth most common causes of cancer-related death in the United States. In both of these cancers, complete detection of primary and metastatic lesions at the time of surgery is critical to optimal surgical resection and appropriate patient treatment.
Materials and Methods We have investigated the use of fluorophore-labeled anti-carcinoembryonic antigen (CEA) monoclonal antibody to aid in cancer visualization in nude mouse models of human colorectal and pancreatic cancer. Anti-CEA was conjugated with a green fluorophore. Subcutaneous, orthotopic primary and metastatic human pancreatic and colorectal tumors were easily visualized with fluorescence imaging after administration of conjugated anti-CEA. The fluorescence signal was detectable 30 min after systemic antibody delivery and remained present for 2 weeks, with minimal in vivo photobleaching after exposure to standard operating room lighting. Tumor resection techniques revealed improved ability to resect labeled tumor tissue under fluorescence guidance. Comparison of two different fluorophores revealed differences in dose–response and photobleaching in vivo.
Conclusion These results indicate that fluorophore-labeled anti-CEA offers a novel intraoperative imaging technique for enhanced visualization of tumors in colorectal and pancreatic cancer when CEA expression is present, and that the choice of fluorophore significantly affects the signal intensity in the labeled tumor.

Keywords Pancreatic neoplasms · Colorectal neoplasms · Carcinoembryonic antigen · Fluorescent antibody technique · Nude mouse cancer models · Fluorescence-guided surgery

Introduction

Colorectal and pancreatic cancers together comprise the third and fourth most common causes of cancer-related

These data were presented at the Society for Surgery of the Alimentary Tract meeting as part of the Digestive Diseases Week, San Diego CA, May 21 2008.

Sharmeela Kaushal and Michele K. McElroy shared authorship.

Work supported in part by: Cancer Therapeutics Training Program (T32 CA121938) National Institutes of Health (CA109949-03) American Cancer Society (RSG-05-037-01-CCE).

S. Kaushal · M. K. McElroy · M. A. Talamini · A. R. Moossa · R. M. Hoffman · M. Bouvet (✉)
Department of Surgery,
University of California San Diego, Moores Cancer Center,
3855 Health Sciences Drive #0987,
La Jolla, CA 92093-0987, USA
e-mail: mbouvet@ucsd.edu

G. A. Luiken
OncoFluor, Inc., San Diego, CA, 1211 Alameda Blvd,
Coronado, CA 92118, USA

R. M. Hoffman
AntiCancer, Inc., San Diego, CA, 7917 Ostrow St,
San Diego, CA 92111, USA

death in the United States.[1] In both of these cancers, the complete detection of primary and metastatic lesions prior to and at the time of surgery is critical to optimal surgical resection and appropriate patient treatment. For patients with pancreatic cancer, the lethality of this disease is primarily related to its aggressive biology and the often late stage at which patients are diagnosed.[2] Current chemotherapeutic regimens available offer only modest improvement in disease-related survival.[3,4] Curative resection at the time of surgery remains the most powerful determinant for patient outcomes.[5]

For colorectal cancers, the high mortality of this disease in the United States parallels a high cancer incidence.[1] These patients more often present with resectable disease[6] and have more surgical options than patients with pancreatic cancer.[7,8] Nevertheless, there remains in this patient population a clear advantage to compete resection of all primary and metastatic cancer at the time of surgery when clinically appropriate.[9,10]

The carcinoembryonic antigen (CEA) was first described following immunization of xenogenic animals with human tumor tissue.[11] Early evaluation of human tissue specimens revealed positive CEA expression in multiple cancers arising from the endodermally-derived epithelium of the digestive tract[12] as well as in human embryonic gut, pancreas, and liver tissue.[13] Although initially described with respect to adenocarcinoma of the colon,[12] CEA is often also expressed in pancreatic ductal adenocarcinoma.[14,15] In clinical medicine, CEA is most commonly utilized as a serum marker in colorectal and pancreatic cancer as a part of both preoperative staging and to follow patient response to surgery and chemotherapy.[16,17]

We report here a study evaluating the use of a fluorophore-labeled anti-CEA monoclonal antibody to aid in primary and metastatic cancer visualization in nude mouse models of human colorectal and pancreatic cancer.

Materials and Methods

Cell Culture The human pancreatic cancer cell lines MiaPaca-2, ASPC-1, BxPC-3, XPA-1, XPA-3, and XPA-4 were maintained RPMI (Gibco-BRL, Grand Island, NY) supplemented with 10% fetal calf serum (FCS; Hyclone, Logan, UT). The human pancreatic cancer cell lines CFPAC & Capan-1 were maintained in IMDM (Gibco-BRL) with 15% FCS (Hyclone). The human pancreatic cancer cell lines Panc-1 and FG and the human colorectal cancer cell lines HCT 116, HT-29, SW480, LS174T, LOVO, and SW948 were maintained in DMEM (Gibco-BRL) supplemented with 10% FCS (Hyclone). All media was supplemented with penicillin/streptomycin (Gibco-BRL), L-glutamine (Gibco-BRL), MEM nonessential amino acids (Gibco-BRL), sodium bicarbonate (Cellgro, Herndon VA), and sodium pyruvate (Gibco-BRL). All cell lines were cultured at 37°C with 5% CO_2. The Colo4104 tumors were generated from liver metastasis tissue from a human colon cancer patient which was serially passaged subcutaneously in athymic (*nu/nu*) mice. The human pancreatic cancer cell lines XPA-1, XPA-3, and XPA-4 were a gift from Dr. Anirban Maitra at Johns Hopkins University.

Conjugation of Antibody to Fluorophore Monoclonal antibody specific for CEA was purchased from Biodesign International (Saco ME, Cat # H45655M). Control IgG antibody was purchased from R&D Systems (Minneapolis MN, Cat # 6-001-A). The antibodies were labeled with the AlexaFluor 488 (Molecular Probes, Eugene, OR) or Oregon Green (Molecular Probes) fluorophores according to manufacturer's instructions. Briefly, for AlexaFluor 488 conjugation, the monoclonal antibody was reconstituted at 2 mg/mL in 0.1 M sodium bicarbonate; 500 μL of the 2 mg/mL were added to the reactive dye for each conjugation. For Oregon Green conjugation, the monoclonal antibody was reconstituted at 5 mg/mL in dH$_2$O, and 200 μL of the 5 mg/mL solution were added to the reactive dye for each conjugation. The antibody–dye mixtures were allowed to incubate for 1 h at room temperature, then overnight at 4°C. The conjugated antibody was then separated from the remaining unconjugated dye on a purification column by centrifugation. Antibody and dye concentrations in the final sample were determined using spectrophotometric absorbance. For each conjugation, the molar ratio of fluorophore to antibody was 3–4 to 1.

In Vitro Fluorescence Imaging All cell lines were plated in 96-well plates at 5×10^4 cells per well. After 48 h culture in appropriate media, the cells were incubated with 1 μg of fluorophore-conjugated anti-CEA or control-conjugated IgG antibody for 4 h at 37°C, then washed three times with phosphate-buffered saline (PBS; Gibco-BRL). Cells were imaged with an inverted Nikon DE-300 microscope and Spot camera RD. The images were then analyzed for fluorescence intensity using Image J software (National Institute of Health, Bethesda MD).

Animal Care Athymic mice were maintained in a barrier facility on high efficiency particulate air (HEPA)-filtered racks. The animals were fed with autoclaved laboratory rodent diet (Teckland LM-485; Western Research Products, Orange, CA). All surgical procedures and intravital imaging were performed with the animals anesthetized by intramuscular injection of 0.02 mL of a solution of 50% ketamine, 38% xylazine, and 12% acepromazine maleate. All animal studies were conducted in accordance with UCSD animal

care protocols and the principles and procedures outlined in the NIH Guide for the Care and Use of Animals.

Subcutaneous Tumor Cell Implantation Human pancreatic and colorectal cancer cell lines were harvested by trypsinization and washed twice with serum-free medium. Cells (1×10^6 in 100 μl of serum-free media) were injected subcutaneously within 30 min of harvesting over the right flank in female *nu/nu* mice between 4 and 6 weeks of age. Subcutaneous tumors were allowed to grow for 7–14 days until they reached a diameter of 1–2 mm prior to the delivery of conjugated antibody.

Subcutaneous Passage of Colo4104 Tumor Small (1 mm^3) fragments of the initial tumor sample obtained from the liver metastasis of a patient with stage IV colorectal cancer were implanted subcutaneously in athymic *nu/nu* mice. The tumors were maintained by serial subcutaneous passage. For passage, animals were anesthetized as described and a small 1-cm incision was made over the left flank. The harvested tumor was divided into 1-mm^3 pieces and implanted subcutaneously into the anesthetized mouse as described.

Orthotopic Tumor Implantation Orthotopic human pancreatic cancer xenografts were established in nude mice by direct injection of BxPC-3 tumor cells into the pancreas. For pancreatic tumors, a small incision was then made in the right pararectal line through the skin and peritoneum. The tail of the pancreas was exposed and 1×10^6 cells mixed 1:1 with matrigel (BD Biosciences, Bradford MA) in 30 μL final volume were injected into the pancreas using a Hamilton syringe (Hamilton Co, Reno NV). For colorectal tumors, a midline abdominal incision was made and a small segment of bowel and mesentery were exposed. A single 1-mm^3 tumor fragment from the Colo4104 tumor was sutured to the mesenteric border of the bowel wall using 8–0 nylon surgical sutures.[18] Peritoneum and skin were closed using 6–0 vicryl sutures. Orthotopic tumors were allowed to grow for 7–14 days prior to imaging.

Experimental Peritoneal and Mesenteric Metastasis Model For models of intra-abdominal metastasis, human pancreatic (ASPC-1) and primary colorectal cancer (Colo4104) cells were used. For ASPC-1 implants, the cells were harvested by trypsinization and washed three times in serum-free media. The cells were resuspended in serum-free media at 5×10^6/mL. A volume of 200 μL of the cell suspension was then injected directly into the peritoneal cavity within 30 min of harvesting. For Colo4104 implants, solid tumor was minced into small (<1 mm^3 diameter) pieces and dispersed in serum-free media; 500 μL of the tumor suspension was injected into the peritoneal cavity within 30 min of tumor harvest. The implants were allowed to grow for 7–14 days prior to imaging.

Antibody Delivery One to 2 weeks after subcutaneous, orthotopic, or intraperitoneal tumor implantation, animals were given a single intravenous (i.v.) injection of either conjugated anti-CEA or conjugated control IgG antibody diluted in PBS to a final volume of 100 μL. All i.v. injections were done via the tail vein. For the dose–response experiment, the antibody dose ranged from 12.5 to 75 μg. For the in vivo time course, photobleaching, and tumor resection experiments, the dose given was 75 μg. For the time course study, the animals were anesthetized and imaged at 30, 60 min, 2, 6, 8, 24, 48 h, and 8 and 15 days after systemic antibody delivery. For all other experiments, the animals were anesthetized and imaged 24 h after administration of the antibody.

Photobleaching In vitro tumor cells in 96-well plates were stained with conjugated anti-CEA as described, then exposed to standard OR lighting for 24 h. The cells were imaged on the Nikon inverted fluorescence microscope after 1, 2, 3, 4, 5, 6, 7, 8, 9, and 24 h of light exposure. Subcutaneous tumors were implanted as previously described. After 24 h of systemic antibody delivery, the animals were anesthetized and their subcutaneous tumor was exposed. The tumors were exposed to standard OR lighting, and the tumors were imaged on the Olympus OV100 Small Animal Imaging System over time for 8 h.

Tumor Resection Animals bearing subcutaneous BxPC3 tumors were anesthetized as described, and their right flank was sterilized. The tumor was exposed and imaged under both standard bright field illumination and fluorescence imaging. All visible tumors were removed under standard bright field illumination using a Stereo Discovery V12 dissecting microscope (Carl Zeiss IMT Corp, Maple Grove MN), and the tumor bed was then imaged again under standard bright field illumination and fluorescence imaging. All residual fluorescent tumor tissue remaining after resection was documented. The presence of tumor within the resection tissue and resection bed was confirmed by histology.

Animal Imaging Mice were imaged using the Olympus OV100 Small Animal Imaging System (Olympus Corp, Tokyo Japan),[19] containing an MT-20 light source (Olympus Biosystems, Planegg, Germany) and either the DP71 CCD camera (Olympus Corp. Tokyo, Japan) for qualitative color images of tumor implants or with the Hamamatsu monochrome camera (Hamamatsu Corp, Hamamatsu City Japan) for quantitative evaluation of fluorescence intensity. All images were processed for contrast and brightness and

analyzed with the use of Image J and Photoshop element-4 (Adobe Systems Inc, San Jose CA).

Histology Tumor samples were surgically removed en bloc with surrounding tissue following in vivo imaging. These tissue samples were then frozen in Tissue-Tek O.C.T. compound (Sakura Fintek, Torrance CA) and sectioned on a microtome. For tumors removed from conjugated CEA- or IgG-treated animals, 15-μm sections were prepared without fixation for fluorescence microscopy, and 8-μm sections were fixed and stained with H&E for standard light microscopy. The prepared slides were imaged using an inverted Nikon DE-300 fluorescent microscope and Spot camera RD. Images were processed for contrast and brightness with the use of Photoshop element-4 (Adobe Systems Inc, San Jose CA).

Human Tissue Array Evaluation The human tissue array was purchased from US Biomax, Inc (Rockwell MD). The tissue array as well as 8-μm thick sections from the positive (ASPC-1 and Colo4104 tumors) and negative (murine axillary lymph node) controls were first fixed in ice-cold acetone for 2 min. The slides were then air-dried and washed three times with PBS. The slides were next with 5% bovine serum albumin (BSA; Sigma-Aldrich, St Louis, MO) for 1 h at room temperature. The slides were again washed with PBS and then stained using 1 μg/mL AlexaFluor 488 conjugated anti-CEA or isotype-control IgG for 2 h at room temperature. The slides were then washed for a final time and imaged using the inverted Nikon DE-300 fluorescent microscope and Spot camera RD.

Results

In Vitro Expression of CEA

Of the human pancreatic cancer cell lines which were evaluated in vitro, 70% of the pancreatic cancer cell lines tested were positive for CEA-staining in culture. These cell lines included MiaPaca-2, FG, ASPC-1, BxPC-3, CFPAC, Panc-1, and Capan-1. The cell lines tested which did not express CEA included XPA-1, XPA-3, and XPA-4. Of the human colon cancer cell lines which were tested in vitro, 67% of the colon cancer cell lines expressed CEA as identified by antibody staining. These cell lines included LOVO, HCT-116, SW948, and LS174T. The cell lines which did not express CEA above background were HT-29 and SW480. For each cell line tested, the plated cells were incubated with AlexaFluor 488-labeled anti-CEA or IgG at 1 μg/well. Positive staining was indicated by fluorescence intensity above background staining with conjugated IgG (Table 1).

Table 1 CEA Expression In Vitro and In Vivo

Human pancreatic cancer cell lines		
In vitro	+	−
Mia Paca-2	x	
FG	x	
BxPC-3	x	
CFPAC	x	
Panc-1	x	
Capan-1	x	
XPA-1		x
XPA-3		x
XPA-4		x
In Vivo	+	−
ASPC-1	x	
BxPC-3	x	
CFPAC	x	
Panc-1	x	
Capan-1	x	
Human colon cancer cell lines		
In vitro	+	−
LOVO	x	
HCT-116	x	
SW948	x	
LS174T	x	
HT-29		x
SW480		x
In vivo	+	−
LS174T	x	
Colo4104	x	

Testing of human pancreatic and colon cancer cell lines for in vitro and in vivo expression. Ten human pancreatic cancer cell lines were tested for in vitro CEA expression. Of the ten lines tested seven (70%) were positive. Six human colon cancer cell lines were tested for in vitro CEA expression, of which four (67%) were positive. Seven pancreatic and one colon cancer cell line were tested in vivo, all of which were positive. In addition, the primary human colon cancer tissue Colo4104 was also positive for in vivo expression of CEA. "+"= positive CEA expression; "−"=negative CEA expression

Imaging of Subcutaneous Tumors with Fluorescent Anti-CEA Antibody

Multiple cell lines were also assayed for in vivo expression of CEA in a subcutaneous cancer model. The human pancreatic cancer cell lines ASPC-1, BxPC-3, CFPAC, Panc-1, and Capan-1 were implanted subcutaneously. In addition, one colon cancer cell line (LS174T) and a primary human colon cancer specimen (Colo4104) were also implanted subcutaneously. All tumors were allowed to grow for 7–14 days (three animals were implanted with each cell line). When the tumors had reached approximately 1–2 mm in diameter, the animals were each given a single 75-μg dose of AlexaFluor 488-conjugated anti-CEA (two animals) or IgG (one animal). All five pancreatic cancer cell lines implanted demonstrated positive in vivo binding

of CEA as did the colon cancer cell line and the primary human colon cancer specimen as determined by fluorescence intensity above background IgG (Table 1).

Immunofluorescence Staining of Tissue for Binding with Anti-CEA Antibody

Screening of normal human tissue samples for binding to conjugated anti-CEA antibody was achieved by using immunofluorescence staining of a human tissue array. This array contains two samples each of 19 different non-cancerous adult human tissues including: salivary gland, liver, small intestine, stomach, kidney, skeletal muscle, skin, heart, placenta, breast, cervix, uterus, spleen, lung, brain, thyroid, pancreas, ovary, and adrenal gland. Human tumor samples generated subcutaneously in nude mice from the pancreatic cancer cell line ASPC-1 and the primary human colon cancer specimen Colo4104 were also stained using the same protocol as positive controls, and mouse axillary lymph node tissue was included as a negative control. Both the ASPC-1 pancreatic tumor and the Colo4104 colon tumor yielded positive staining for CEA. In non-cancerous tissues, the majority of samples did not demonstrate binding of conjugated anti-CEA above our isotype-control IgG background. A low level of staining above background was present within the small intestine cervix. Notably, the pancreas did not demonstrate any binding of conjugated anti-CEA. Table 2 denotes the staining for all non-cancerous human tissue samples tested.

Table 2 CEA Expression in Adult Human Tissues

Tissue	Staining
Salivary gland	–
Liver	–
Small intestine	+/–
Stomach	–
Kidney	–
Skeletal muscle	–
Skin	–
Heart	–
Placenta	–
Breast	–
Cervix	+
Uterus	–
Spleen	–
Lung	–
Brain	–
Thyroid	–
Pancreas	–
Ovary	–
Adrenal Gland	–
ASPC-1 tumor[a]	+++
Colo4104 tumor[a]	++
Mouse axillary LN[b]	–

Staining of a tissue array of adult non-cancerous human tissues revealed a small amount of positive staining over background in cervix and small intestine tissues. In the small intestine the staining was primarily limited to cells on the mucosal surface of the bowel. In the cervix, the staining was primarily seen on the luminal surface of glandular structures. The positive controls ASPC-1 and Colo4104 revealed staining with conjugated anti-CEA both within the cytoplasm and on the cell membrane throughout the tumors.
[a] Positive control
[b] Negative control

Imaging Orthotopic Tumors with Fluorescent Anti-CEA Antibody

Tumors implanted orthotopically into the mouse pancreas and colon were evaluated for improved imaging using conjugated anti-CEA. For orthotopic tumors in the pancreas, the human pancreatic cancer cell line BxPC-3 was used. For the colon, Colo4014 was used. Orthotopic pancreatic or colon tumor-bearing animals were given a single dose of AlexaFluor 488-conjugated anti-CEA or IgG by tail vein, 7–10 days after tumor implantation, and imaged under both brightfield and fluorescence illumination using the Olympus OV100 Small Animal Imaging System. Intravital fluorescence imaging revealed what appeared to be very small pancreatic tumors which were difficult to visualize using standard brightfield illumination, even at higher magnification (Fig. 1b,c). However, under fluorescence imaging, not only was the tumor easily visible, it was clear that the extent of tumor invasion was much greater than that appreciated initially under brightfield imaging (Fig. 1e,f). The tumors in the colon cancer-bearing animals were larger and were visible under both brightfield and fluorescence imaging but more clearly by flourescence (Fig. 2b,c & e,f). The animals which received conjugated IgG showed no green fluorescence in either their pancreatic (Fig. 1d) or colon (Fig. 2d) tumors. Orthotopic tumor tissue was confirmed by H&E (data not shown).

Imaging Intraabdominal Disseminated Tumor with Fluorescent Anti-CEA Antibody

Experimental models of intraabdominal metastases of pancreatic and colorectal cancer were created to facilitate the evaluation of fluorophore-conjugated anti-CEA binding to these lesions in vivo. Animals received a single intraperitoneal injection of human pancreatic (BxPC-3) or colorectal (Colo4104 or LS174T) cancer cells and these cells were allowed to grow within the peritoneal cavity for 7 days. After 1 week, the animals were given as single 75 μg injection of AlexaFluor 488-conjugated anti-CEA or IgG by tail vein; 24 h later, the animals were imaged on the Olympus OV100 using both brightfield and fluorescence illumination. At the time of imaging these animals had developed very small peritoneal implants on the bowel

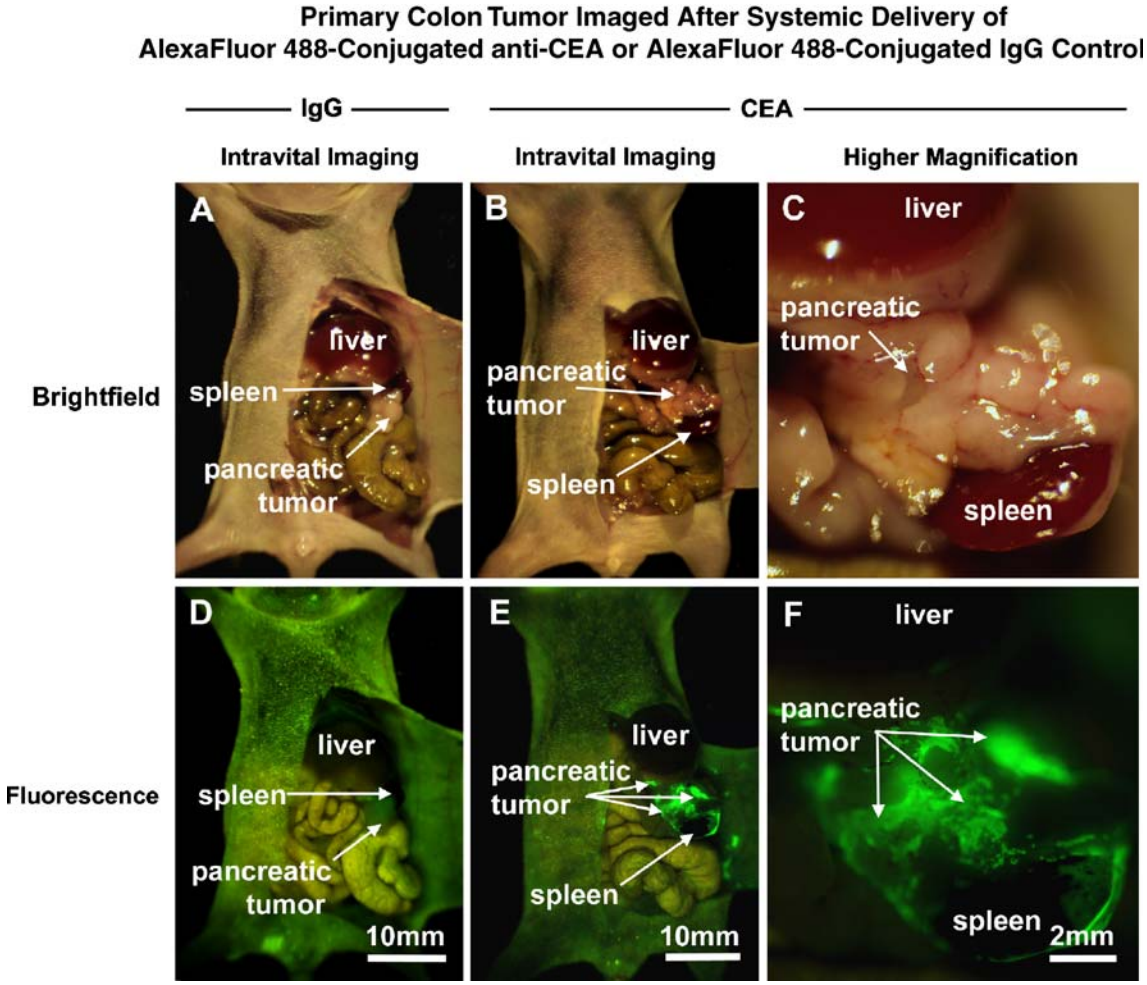

Figure 1 Imaging of orthotopic human pancreas tumors in vivo reveals greatly improved primary tumor visualization at laparotomy. Animals with orthotopically implanted BxPC-3 pancreatic tumors were imaged using both bright field (**a**–**c**) and fluorescence (**d**–**f**) illumination. Primary tumors were difficult to clearly discern under bright field imaging under both low (**a**, **b**) and high (**c**) magnification. In contrast, fluorescence illumination of anti-CEA-labeled tumors revealed easy identification of primary tumor (**e**, **f**), which was much more extensive than initially appreciated. Animals given conjugated control IgG demonstrated no fluorescence signal in the orthotopic tumor (**d**). All tumor tissue was confirmed by histology; $n=3$.

and mesentery which were difficult to visualize using brightfield imaging (Figs. 3a,b and 4a,b) but were very clearly visible under fluorescence illumination in those animals given conjugated anti-CEA (Figs. 3c,d and 4c,d). The animals who received IgG had no discernible fluorescence signal in their tumor implants (data not shown).

Time Course Imaging of Pancreatic Tumors After Injection of Fluorescent Anti-CEA Antibody

Time-course evaluation of human pancreatic tumors in nude mice labeled with conjugated anti-CEA revealed rapid binding of the antibody-fluorophore conjugate in vivo with very long signal duration. Animals bearing 1–2-mm diameter subcutaneous ASPC-1 tumors were given a single dose of 75 μg AlexaFluor 488-conjugated anti-CEA by tail vein injection. The mice were then imaged at 30 min, 1, 2, 6, 8, 24, 48, 192 (8 days), and 360 h (15 days) after delivery of a single dose of antibody. Two animals were imaged for each time point. A small amount of fluorescence signal could be seen at 30 min post-antibody injection and the signal steadily increased to peak intensity at 24 h after injection. This signal remained relatively stable over the next 24 h and then decreased over the following 6 days to yield again a very low-level signal at 8 days post-injection. By 15 days post-injection, there was minimal signal remaining within the tumor tissue (Fig. 5).

Use of Fluorescent Anti-CEA Antibody to Image Post-resection Residual Tumor

In animals bearing larger (3–10 mm diameter) subcutaneous tumors, we investigated the use of fluorophore-conjugated anti-CEA to improve our ability to perform a

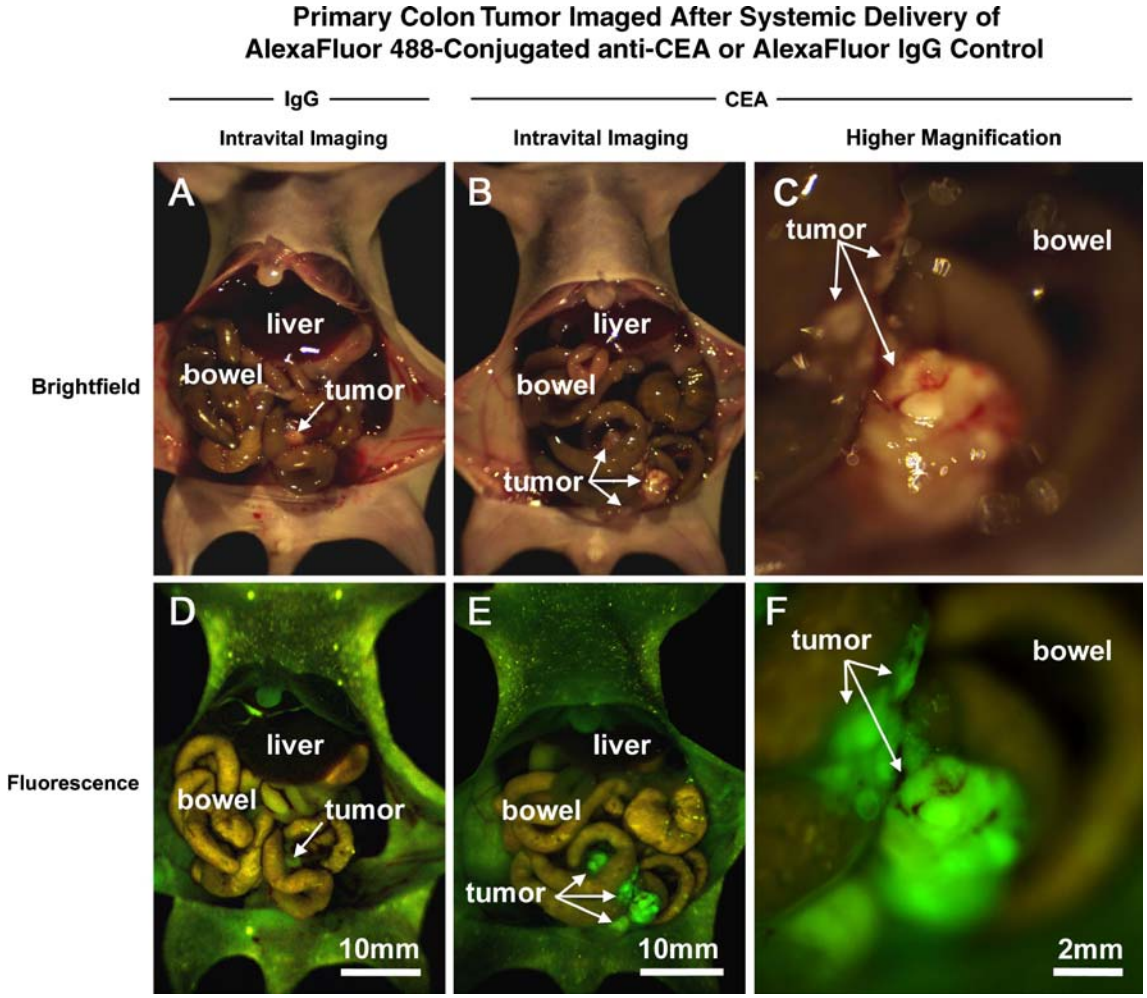

Figure 2 Imaging of orthotopic human colon tumors in vivo under fluorescence illumination improved primary tumor visualization at laparotomy. Animals with orthotopically implanted AC4104 colon tumors were imaged using both bright field (**a**–**c**) and fluorescence (**d**–**f**) illumination. Primary tumors labeled with conjugated anti-CEA appeared bright green under fluorescence illumination (**e**, **f**). Animals given conjugated control IgG demonstrated no fluorescence signal in the orthotopic tumor (**d**). All tumor tissue was confirmed by histology; $n=3$.

complete tumor resection. Animals were given a single dose of AlexaFluor 488-conjugated anti-CEA 24 h prior to attempted surgical resection. At the time of surgery, animals were anesthetized and their tumors were imaged using brightfield and fluorescence illumination (Fig. 6a,b). The tumors were then carefully resected under a dissecting microscope under brightfield illumination with careful attention paid to removing all visible tumor tissue without adjacent normal skin or muscle (Fig. 6b,c). Following resection, the operative bed was then imaged using fluorescence microscopy and all remaining areas of fluorescence (Fig. 6e,f) were documented and biopsied. Of the three animals that underwent resection in this manner, all three had residual tumor present within the tumor bed which was not visible under brightfield illumination. The presence of tumor tissue within the resected tissue as well as the presence of tumor tissue within the green fluorescent portions of the resection margin were confirmed by histology (data not shown).

Comparison of Fluorophores for Anti-CEA Antibody Conjugation

The choice of fluorophore can have a profound effect on fluorescence imaging in vitro and in vivo. For this reason, we elected to compare a commonly used green fluorophore, Oregon Green, to the AlexaFluor 488 fluorophore. We initially looked at anti-CEA conjugated with each of these fluorophores in an in vivo dosing experiment. Animals bearing 1–2-mm diameter subcutaneous ASPC-1 tumors were given a single administration of either AlexaFluor 488- or Oregon Green-conjugated anti-CEA in doses ranging from 12.5 to 75 μg by tail vein injection. 24 h after antibody delivery, the tumors were imaged using the

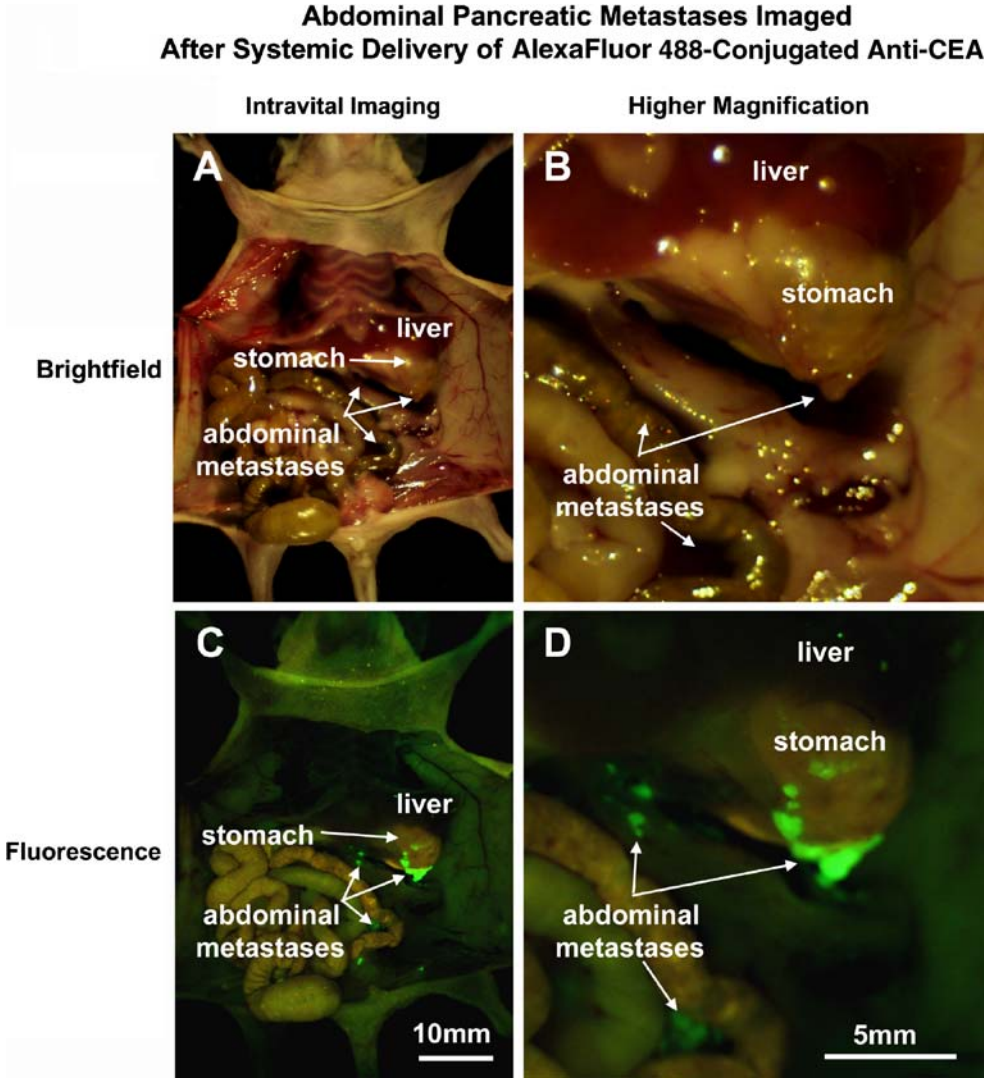

Figure 3 In vivo imaging of intraabdominal metastases from the human pancreatic cancer cell line BxPC-3 reveals greatly improved metastatic-tumor visualization at laparotomy. Animals with intraperitoneally injected BxPC-3 cells were imaged using both bright field (**a**, **b**) and fluorescence (**c**, **d**) illumination. Small metastatic implants on the bowel and mesentery were difficult to find with bright field imaging under both low (**a**) and high (**b**) magnification. In contrast, fluorescence illumination of anti-CEA-labeled tumors revealed easy identification of metastatic implants tumor (**c**, **d**); $n=3$.

Olympus OV100 Small Animal Imaging System. Three animals were evaluated at each dose for each fluorophore. Tumor fluorescence intensity increased for both fluorophores with increasing dose of fluorophore-conjugated antibody, as expected. The AlexaFluor 488-conjugated antibody showed a greater rate of in vivo fluorescence intensity increase at the three lower doses tested but demonstrated little increase from the 50 to 75 μg dose. Conversely, while the Oregon Green-conjugated antibody yielded greater in vivo fluorescence signal at the lowest dose tested, the signal remained lower than that for AlexaFluor 488 at all other doses (Fig. 7).

Photobleaching of Fluorophore-conjugated Anti-CEA Antibody

In a second comparison between AlexaFluor 488 and Oregon Green, we evaluated the propensity of these fluorophores to be affected by continuous bright-light illumination both in vitro and in vivo. Photobleaching is a well-documented phenomenon in many fluorophores but is usually caused under conditions of laser excitation. It is unclear whether exposure to bright operating room (OR) lighting would cause any significant amount of fluorescence signal loss for either of these fluorophores. To evaluate this, we first looked in vitro at a confluent monolayer of ASPC-1 cells stained with either AlexaFluor 488-conjugated or Oregon Green-conjugated anti-CEA at 1 μg per well in triplicate in a 96-well plate. The cells were exposed to bright OR lighting for 24 h and were imaged each hour for the first 9 h and again at 24 h by fluorescence microscopy. The intensity of the fluorescence signal did decrease over the first 8 h by approximately 10% in the AlexaFluor 488-stained cells and by over 50% in the Oregon Green-stained cells. After 24 h, this had progressed to a 45% loss of fluorescence signal in the AlexaFluor group and a 67% loss for Oregon Green (Fig. 8a).

In vivo photobleaching was also evaluated using a subcutaneous tumor model. Nude mice bearing 1–2-mm diameter subcutaneous ASPC-1 tumors were given a single

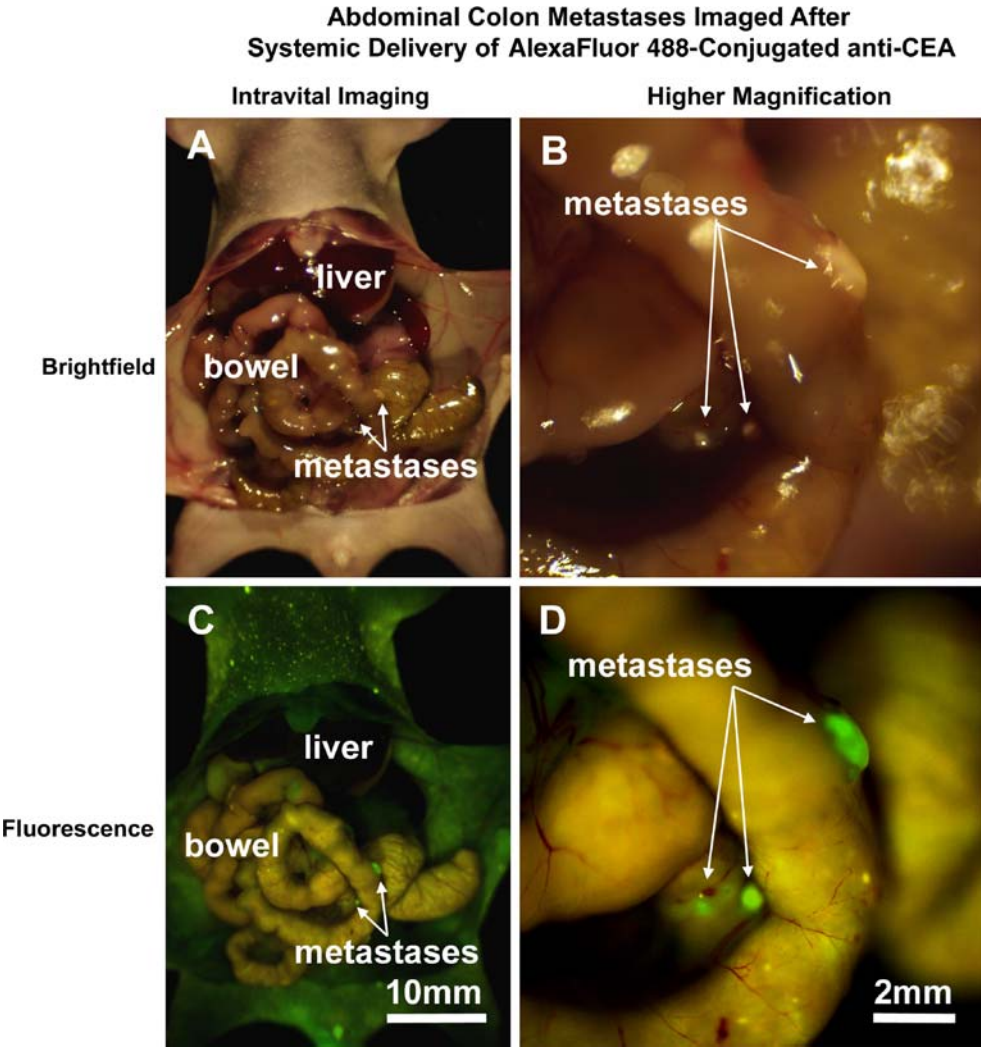

Figure 4 Imaging of metastatic human colon tumors in vivo reveals improved tumor visualization at laparotomy. Animals with intraperitoneally injected Colo4104 colon cancer cells were imaged using both brightfield (**a**, **b**) and fluorescence (**c**–**f**) illumination. The metastatic implants were small and difficult to clearly discern under brightfield imaging under both low (**a**) and high (**b**) magnification. In contrast, fluorescence illumination of anti-CEA-labeled tumors revealed facile identification of metastases (**c**, **d**); $n=3$.

dose of 75 μg AlexaFluor 488- or Oregon Green-conjugated anti-CEA by tail-vein injection (three animals were included in each group). Twenty-four hours after antibody delivery, the animals were anesthetized and their subcutaneous tumor exposed to bright OR lighting via the excision of a small patch of overlying skin. The animals were imaged on the Olympus OV100 at 0, 2, 4, 6, and 8 h after exposure of the tumors to light. The amount of signal loss in vivo was much lower than that seen in cultured cells. Over an 8-h period, the AlexaFluor 488-labeled tumors lost about 10% fluorescence signal while the Oregon Green-labeled tumors lost approximately 20% of their baseline fluorescence intensity (Fig. 8b). In both experiments, the amount of photobleaching observed was greater in the Oregon Green group.

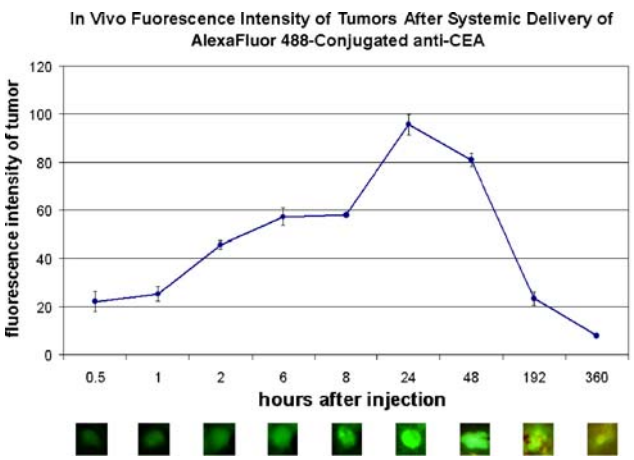

Figure 5 Evaluation of fluorescence signal duration in subcutaneous ASPC-1 tumors following a single administration of AlexaFluor 488-conjugated anti-CEA reveals a rapid onset and prolonged duration of the in vivo fluorescence signal. Animals with small subcutaneous tumors were given a single dose of conjugated antibody and imaged at 30 min, 1, 2, 6, 8, 24, and 48 h, and 8 and 15 days after antibody administration. The fluorescence signal can be seen at 30 min and reaches its peak at 24 h after injection. The signal remains high at 48 h but by 8 days (192 h) after delivery has decreased to levels comparable to that seen at 30 min and by 15 days (360 h) was comparable to background; $n=18$.

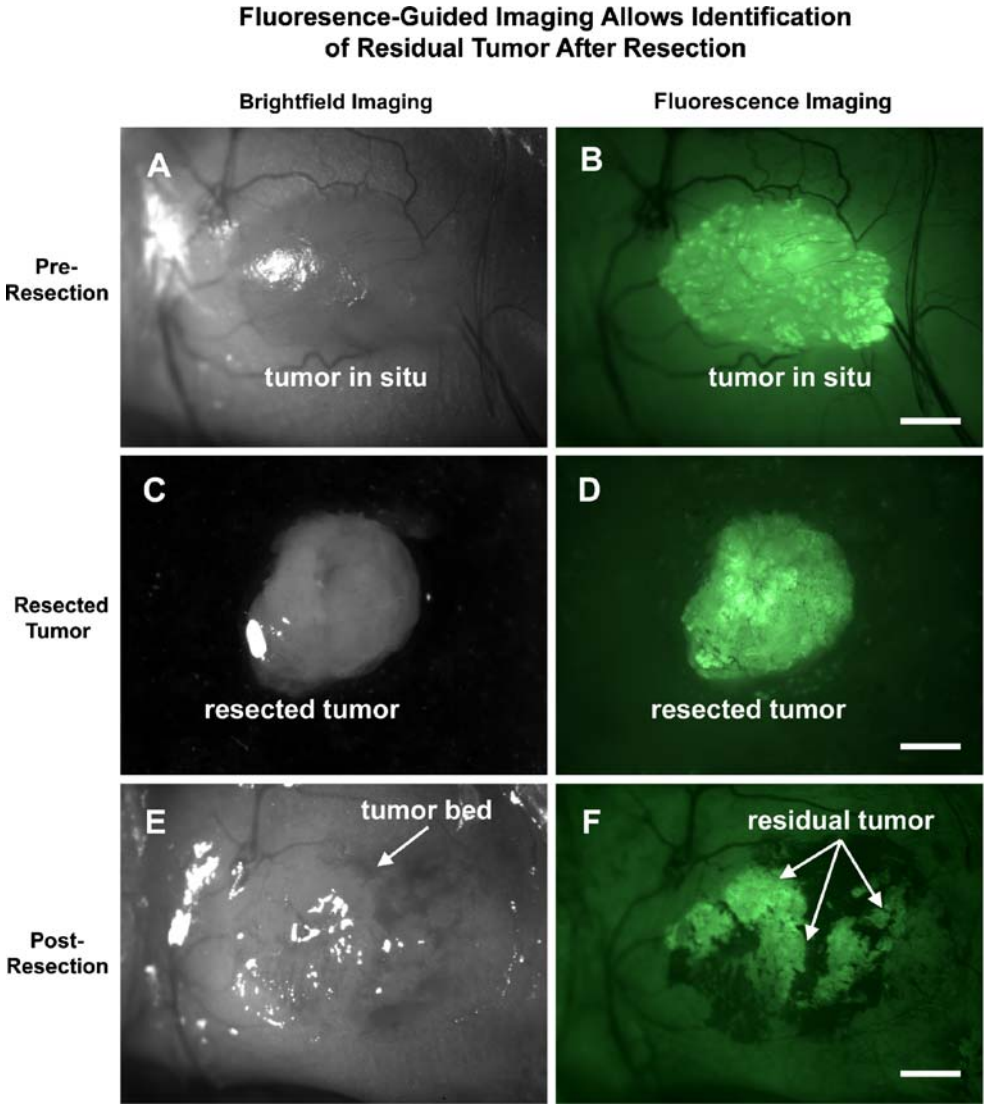

Figure 6 Tumor resection under bright-light microscopy. Larger subcutaneous AlexaFluor 488-conjugated anti-CEA-labeled BxPC-3 tumors were imaged under a dissecting microscope via both brightfield (**a**) and fluorescence (**b**) illumination. Under brightfield microscopy all visible tumor was resected, and the ex-vivo tumor was imaged under bright field (**c**) and fluorescence (**d**) microscopy. The tumor resection bed (**e**) was then imaged under fluorescence microscopy for any evidence of residual fluorescence (**f**). In all animals resected, there was residual tumor based on positive fluorescence signal within the tumor bed. Resected and residual tumor was confirmed by histology. All images taken at 20×, *scale bars*=1 mm; n=3.

Discussion

Targeted tumor imaging techniques are of great interest currently as we seek to improve our ability to localize and therefore appropriately treat the cancer burden in our patients. Fluorophore-conjugated antibodies, because they utilize technologies that have already been shown to be safe and efficacious in humans, present a unique opportunity to deliver highly specific fluorescence signals to the tissues of interest with minimal risk to patients. Monoclonal antibodies have been used safely in patients for some time,[20] as have several different fluorophores including fluorescein,[21,22] a compound very similar to Oregon Green.[23] We sought to combine the specificity of a monoclonal antibody to a tumor-associated antigen with the enhanced imaging technologies afforded by fluorescence illumination to improve cancer imaging. In our nude mouse models of human pancreatic and colon cancer, the administration of conjugated anti-CEA improved our ability to visualize both primary tumor as well as small intraabdominal lesions that were almost impossible to see under standard white light illumination even at high magnification.

In this study, we have investigated the use of fluorophore-conjugated anti-CEA for the in vivo imaging of pancreatic and colorectal cancer. The human carcinoembryonic antigen has been used clinically for many years to stage and follow patients with colorectal cancer.[16,17] This tumor-associated antigen is strongly positive in virtually all colon cancers[24,25] and up to 98% of pancreatic ductal adenocarcinomas.[14,15] The lower percentage of established colorectal and pancreatic cancer cell lines expressing CEA in vitro likely reflects changes in antigen expression after prolonged maintenance in culture. It would be expected that prior histology studies reporting the proportion of primary pancreatic and colorectal cancers with CEA expression would more accurately reflect the likelihood of CEA expression in human tumors. Several groups have looked at the use of CEA expression for the identification of occult tumor cells in distant sites including

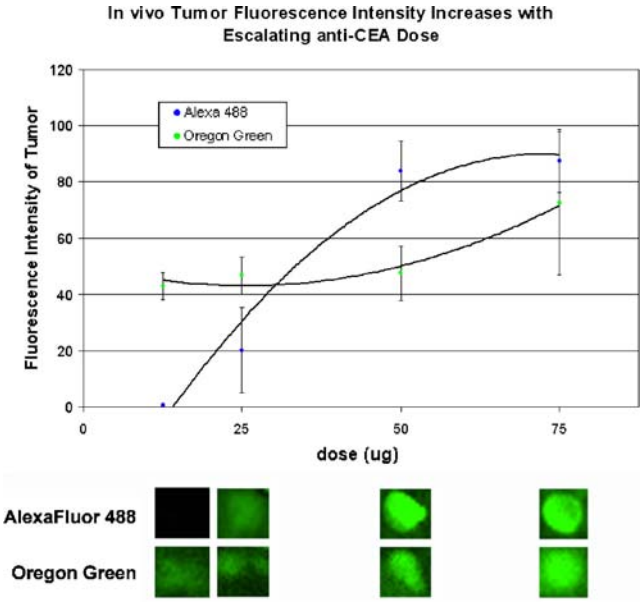

Figure 7 Dose response in vivo was compared for AlexaFluor 488-conjugated anti-CEA versus Oregon Green-conjugated anti-CEA. Animals bearing small subcutaneous ASPC-1 tumors were given doses of either AlexaFluor 488- (*blue circles*, *upper pictures*) or Oregon Green (*green circles*, *lower pictures*)-conjugated anti-CEA ranging from 12.5 μg to 75 μg per animal; 24 h after antibody delivery, the animals were imaged on the OV100. Although the Oregon Green-labeled tumors showed greater in vivo fluorescence intensity at the lowest dose (12.5 μg), the AlexaFluor 488-labeled tumors were brighter at the remaining doses (25, 50, and 75 μg); n=12 AlexaFuor 488, n=12 Oregon Green.

bone marrow, peripheral blood, and lymph nodes.[26] Kim et al. used CEA expression in liver metastases from primary colorectal cancer and found 100% of the metastatic implants tested expressed CEA.[27] Based on these data, we would expect a high proportion of metastatic lesions in patients with CEA-expressing primary tumors to also express this tumor-associated antigen.

Although there are some adult tissues which express a small amount of anti-CEA, including the colon, stomach, tongue, esophagus, and cervix,[28,29] the level of expression in normal adult tissue is very low.[14,30] In the case of intestinal expression of CEA, the signal is predominantly present on the luminal surface,[14,30] and this non-tumor staining is unlikely to be great enough to obscure the signal from a CEA-expressing tumor. Our findings of weakly positive CEA staining only within the cervix and small intestine in our non-cancerous adult human tissue array parallels this previously published work. Although the tissue array used in our study did not contain a colon specimen, we expect that the CEA expression in colonic mucosa would also parallel historic reports. Given these findings, we expect that the use of this fluorophore-conjugated antibody would have relatively low non-tumor binding and thus low background fluorescence staining in patients.

One potential issue in the use of fluorescence imaging intraoperatively is the propensity of certain fluorophores to lose their fluorescence intensity with prolonged exposure to bright light, a phenomenon known as photobleaching.[31] Due to differences between fluorophores in their signal intensity, photobleaching, and signal duration, it is of vital

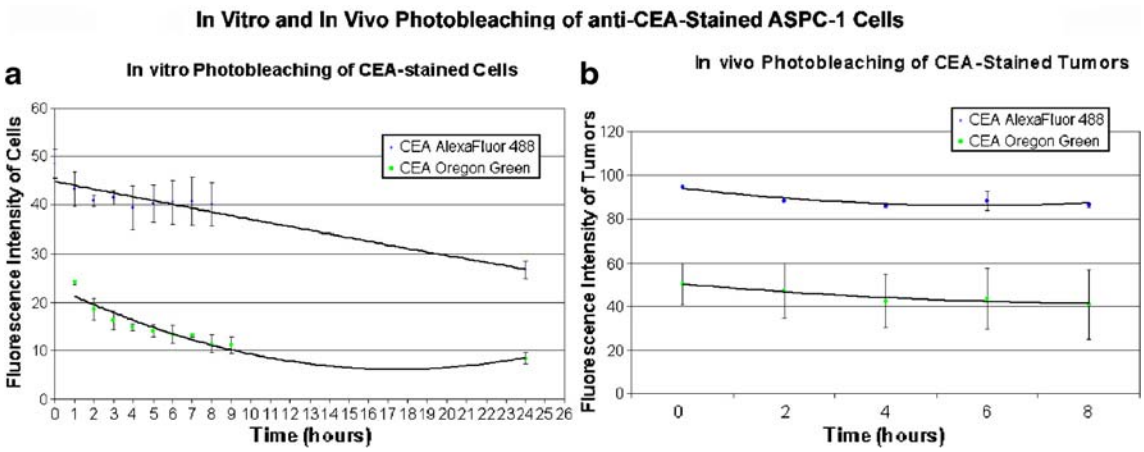

Figure 8 Both in vitro and in vivo photobleaching were compared for AlexaFluor 488- versus Oregon Green-labeled cells. In vitro AlexaFluor 488- and Oregon Green-stained ASPC-1 cells (**a**) were exposed to bright OR lighting for 24 h. The cells were imaged on a fluorescence microscope at 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 24 h. The in vitro fluorescence signal in Oregon Green-labeled cells decreased by 50% and 67% at 9 and 24 h, respectively. AlexaFluor 488-stained cells lost only 10% and 45% of their signal at 9 and 24 h. In vivo AlexaFluor 488- and Oregon Green-stained subcutaneous ASPC-1 tumors (**b**) were exposed to bright OR lighting for 8 h. The tumors were imaged on the OV100 at 0, 2, 4, 6, and 8 h. The in vivo fluorescence signal in Oregon Green-labeled tumors decreased by about 20% over 8 h, whereas that of the AlexaFluor 488-labeled tumors decreased by only 10%; n=3 AlexaFluor 488, n=3 Oregon Green.

importance to choose a stable fluorophore with appropriate signal intensity for in vivo use. We have compared two fluorophores, AlexaFluor 488 and Oregon Green, for their in vivo signal intensity and photobleaching kinetics under standard bright lighting compatible with OR lights. In our model, the AlexaFluor compound appeared to offer both a stronger and a more stable in vivo signal when compared to Oregon Green.

Several groups have recently looked at the use of fluorophore-conjugated monoclonal antibodies for the detection of tumor in animal models.[32–35] Kulbersh and Withrow evaluated fluorescent-conjugated anti-EGFR and anti-VEGF respectively, in mouse models of head and neck cancer. Both groups found that the use of fluorophore-conjugated antibodies improved the sensitivity of tumor resection at surgery.[33,34] Koyama et al. showed improved ability to image lung metastases using a rhodamine-conjugated antibody specific for Her2.[35] Hama et al. used a secondary antibody system in which the primary antibody, specific for Her1, was biotinlyated. Mice bearing Her1-overexpressing intraabdominal tumors were given the biotinylated Her1 followed by a neutravidin-fluorescent conjugate to facilitate imaging of peritoneal tumor implants.[32] We have previously described the use of fluorophore-conjugated CA19-9 in the evaluation of pancreatic cancer in a murine model system and found that the use of this antibody–fluorophore conjugate improved our ability to image orthotopic and metastatic pancreatic cancer.[36] CEA offers the advantage of being widely expressed in many gastrointestinal cancers and is frequently strongly positive in both pancreatic and colon cancer, with minimal expression in normal adult human tissues.

Limited studies have been done to date utilizing fluorescence technology to image tumor implants in human subjects. Fluorescence imaging has the potential for use in both laparoscopic and open surgery via either fluorescence laparoscopy or with the use of simple handheld LED lights and appropriate emission filters.[37] Fluorophore emissions can be affected by overlying tissue, with tissue absorption and scatter causing loss of the fluorescence signal. With respect to deep tumor deposits within solid organs such as the liver, the absorption and scatter of the fluorescence signal by the overlying tissue may hamper visualization of small lesions. For this reason, fluorescence-imaging techniques would best be paired with another method for evaluating deep tissue deposits such as intraoperative or laparoscopic ultrasound. Fluorescence laparoscopy following the pretreatment of tumor implants with sensitizing agents such as 5-aminolevulinic acid have been described in a small number of patients with encouraging improvements in the intraoperative localization of tumor implants.[38] The technology described here could easily be used intraoperatively either at staging laparoscopy, laparoscopic-assisted surgical resection, or even at laparotomy to improve not only detection of tumor metastases but also to facilitate the complete resection of the primary tumor.

Conclusions

In this study, we have used a fluorophore-antibody conjugate specific for the oncofetal antigen CEA to image both primary and metastatic colon and pancreatic tumors in mouse model systems. Our approach offers the advantage of a single antibody delivery and is very effective for imaging of primary and disseminated tumor. Fluorophore-conjugated anti-CEA improved visualization of primary and metastatic pancreatic and colorectal cancer and improved the identification of residual tumor tissue at the time of resection in a murine model. Fluorophore-conjugated anti-CEA has the potential to improve intraoperative visualization of both primary and metastatic pancreatic and colorectal cancer when CEA expression is present.

References

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C et al. Cancer statistics, 2006. CA Cancer J Clin 2006;56:106–30.
2. Wray CJ, Ahmad SA, Matthews JB, Lowy AM. Surgery for pancreatic cancer: recent controversies and current practice. Gastroenterology 2005;128:1626–41. doi:10.1053/j.gastro.2005.03.035.
3. Bria E, Milella M, Gelibter A, Cuppone F, Pino MS, Ruggeri EM et al. Gemcitabine-based combinations for inoperable pancreatic cancer: have we made real progress? A meta-analysis of 20 phase 3 trials. Cancer 2007;110:525–33. doi:10.1002/cncr.22809.
4. Boeck S, Ankerst DP, Heinemann V. The role of adjuvant chemotherapy for patients with resected pancreatic cancer: systematic review of randomized controlled trials and meta-analysis. Oncology 2007;72:314–21. doi:10.1159/000113054.
5. Wagner M, Redaelli C, Lietz M, Seiler CA, Friess H, Buchler MW. Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma. Br J Surg 2004;91:586–94. doi:10.1002/bjs.4484.
6. Robinson MH, Thomas WM, Hardcastle JD, Chamberlain J, Mangham CM. Change towards earlier stage at presentation of colorectal cancer. Br J Surg 1993;80:1610–2. doi:10.1002/bjs.1800801241.
7. Pawlik TM, Schulick RD, Choti MA. Expanding criteria for resectability of colorectal liver metastases. Oncologist 2008;13:51–64. doi:10.1634/theoncologist.2007-0142.
8. Bonjer HJ, Hop WC, Nelson H, Sargent DJ, Lacy AM, Castells A et al. Laparoscopically assisted vs open colectomy for colon cancer: a meta-analysis. Arch Surg 2007;142:298–303. doi:10.1001/archsurg.142.3.298.
9. Turrini O, Viret F, Guiramand J, Lelong B, Bege T, Delpero JR. Strategies for the treatment of synchronous liver metastasis. Eur J Surg Oncol 2007;33:735–40. doi:10.1016/j.ejso.2007.02.025.
10. Andreoni B, Chiappa A, Bertani E, Bellomi M, Orecchia R, Zampino M et al. Surgical outcomes for colon and rectal cancer over a decade: results from a consecutive monocentric experience

in 902 unselected patients. World J Surg Oncol 2007;5:73. doi:10.1186/1477-7819-5-73.
11. Gold P, Freedman SO. Demonstration of tumor-specific antigens in human colonic carcinomata by immunological tolerance and absorption techniques. J Exp Med 1965;121:439–62. doi:10.1084/jem.121.3.439.
12. Gold P, Shuster J, Freedman SO. Carcinoembryonic antigen (CEA) in clinical medicine: historical perspectives, pitfalls and projections. Cancer 1978;42:1399–405. doi:10.1002/1097-0142(197809)42:3+<1399::AID-CNCR2820420803>3.0.CO;2-P.
13. Gold P, Freedman SO. Specific carcinoembryonic antigens of the human digestive system. J Exp Med 1965;122:467–81. doi:10.1084/jem.122.3.467.
14. Albers GH, Fleuren G, Escribano MJ, Nap M. Immunohistochemistry of CEA in the human pancreas during development, in the adult, chronic pancreatitis, and pancreatic adenocarcinoma. Am J Clin Pathol 1988;90:17–22.
15. Yamaguchi K, Enjoji M, Tsuneyoshi M. Pancreatoduodenal carcinoma: a clinicopathologic study of 304 patients and immunohistochemical observation for CEA and CA19-9. J Surg Oncol 1991;47:148–54. doi:10.1002/jso.2930470303.
16. Locker GY, Hamilton S, Harris J, Jessup JM, Kemeny N, Macdonald JS et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. J Clin Oncol 2006;24:5313–27. doi:10.1200/JCO.2006.08.2644.
17. Goldstein MJ, Mitchell EP. Carcinoembryonic antigen in the staging and follow-up of patients with colorectal cancer. Cancer Invest 2005;23:338–51.
18. Fu XY, Besterman JM, Monosov A, Hoffman RM. Models of human metastatic colon cancer in nude mice orthotopically constructed by using histologically intact patient specimens. Proc Natl Acad Sci USA 1991;88:9345–9. doi:10.1073/pnas.88.20.9345.
19. Yamauchi K, Yang M, Jiang P, Xu M, Yamamoto N, Tsuchiya H et al. Development of real-time subcellular dynamic multicolor imaging of cancer-cell trafficking in live mice with a variable-magnification whole-mouse imaging system. Cancer Res 2006;66:4208–14. doi:10.1158/0008-5472.CAN-05-3927.
20. Reichert JM, Valge-Archer VE. Development trends for monoclonal antibody cancer therapeutics. Nat Rev Drug Discov 2007;6:349–56. doi:10.1038/nrd2241.
21. Suzuki K, Kodama N, Sasaki T, Matsumoto M, Ichikawa T, Munakata R et al. Confirmation of blood flow in perforating arteries using fluorescein cerebral angiography during aneurysm surgery. J Neurosurg 2007;107:68–73. doi:10.3171/JNS-07/07/0068.
22. Bartlett H, Eperjesi F. use of fundus imaging in quantification of age-related macular change. Surv Ophthalmol 2007;52:655–71. doi:10.1016/j.survophthal.2007.08.022.
23. Hama Y, Urano Y, Koyama Y, Bernardo M, Choyke PL, Kobayashi H. A comparison of the emission efficiency of four common green fluorescence dyes after internalization into cancer cells. Bioconjug Chem 2006;17:1426–31. doi:10.1021/bc0601626.
24. Itzkowitz SH, Shi ZR, Kim YS. Heterogeneous expression of two oncodevelopmental antigens, CEA and SSEA-1, in colorectal cancer. Histochem J 1986;18:155–63. doi:10.1007/BF01676115.
25. Pihl E, McNaughtan J, Ward HA, Nairn RC. Immunohistological patterns of carcinoembryonic antigen in colorectal carcinoma. Correlation with staging and blood levels. Pathology 1980;12:7–13. doi:10.3109/00313028009060048.
26. Tsavellas G, Patel H, Allen-Mersh TG. Detection and clinical significance of occult tumour cells in colorectal cancer. Br J Surg 2001;88:1307–20. doi:10.1046/j.0007-1323.2001.01863.x.
27. Kim JC, Gong G, Roh SA, Park KC. Carcinoembryonic antigen gene and carcinoembryonic antigen expression in the liver metastasis of colorectal carcinoma. Mol Cells 1999;9:133–7.
28. Prall F, Nollau P, Neumaier M, Haubeck HD, Drzeniek Z, Helmchen U et al. CD66a (BGP), an adhesion molecule of the carcinoembryonic antigen family, is expressed in epithelium, endothelium, and myeloid cells in a wide range of normal human tissues. J Histochem Cytochem 1996;44:35–41.
29. Nap M, Mollgard K, Burtin P, Fleuren GJ. Immunohistochemistry of carcino-embryonic antigen in the embryo, fetus and adult. Tumour Biol 1988;9:145–53.
30. Hammarstrom S. The carcinoembryonic antigen (CEA) family: structures, suggested functions and expression in normal and malignant tissues. Semin Cancer Biol 1999;9:67–81. doi:10.1006/scbi.1998.0119.
31. Song L, Hennink EJ, Young IT, Tanke HJ. Photobleaching kinetics of fluorescein in quantitative fluorescence microscopy. Biophys J 1995;68:2588–600.
32. Hama Y, Urano Y, Koyama Y, Choyke PL, Kobayashi H. Activatable fluorescent molecular imaging of peritoneal metastases following pretargeting with a biotinylated monoclonal antibody. Cancer Res 2007;67:3809–17. doi:10.1158/0008-5472.CAN-06-3794.
33. Withrow KP, Newman JR, Skipper JB, Gleysteen JP, Magnuson JS, Zinn K et al. Assessment of bevacizumab conjugated to Cy5.5 for detection of head and neck cancer xenografts. Technol Cancer Res Treat 2008;7:61–6.
34. Kulbersh BD, Duncan RD, Magnuson JS, Skipper JB, Zinn K, Rosenthal EL. Sensitivity and specificity of fluorescent immunoguided neoplasm detection in head and neck cancer xenografts. Arch Otolaryngol Head Neck Surg 2007;133:511–5. doi:10.1001/archotol.133.5.511.
35. Koyama Y, Hama Y, Urano Y, Nguyen DM, Choyke PL, Kobayashi H. Spectral fluorescence molecular imaging of lung metastases targeting HER2/neu. Clin Cancer Res 2007;13:2936–45. doi:10.1158/1078-0432.CCR-06-2240.
36. McElroy M, Kaushal S, Luiken GA, Talamini MA, Moossa AR, Hoffman RM, Bouvet M. Imaging of primary and metastatic pancreatic cancer using a fluorophore–conjugated anti-CA19-9 antibody for surgical navigation. World J Surg 2008;32:1057–1066.
37. Yang M, Luiken G, Baranov E, Hoffman RM. Facile whole-body imaging of internal fluorescent tumors in mice with an LED flashlight. Biotechniques 2005;39:170–172.
38. Zopf T, Schneider AR, Weickert U, Riemann JF, Arnold JC. Improved preoperative tumor staging by 5-aminolevulinic acid induced fluorescence laparoscopy. Gastrointest Endosc 2005;62:763–7. doi:10.1016/j.gie.2005.05.020.

J Gastrointest Surg (2008) 12:1951–1960
DOI 10.1007/s11605-008-0640-6

Hepatic Neuroendocrine Metastases: Chemo- or Bland Embolization?

Susan C. Pitt · Jaime Knuth · James M. Keily · John C. McDermott · Sharon M. Weber · Hebert Chen · William S. Rilling · Edward J. Quebbeman · David M. Agarwal · Henry A. Pitt

Received: 9 July 2008 / Accepted: 22 July 2008 / Published online: 16 August 2008

Abstract
Introduction Aggressive management of hepatic neuroendocrine (NE) metastases improves symptoms and prolongs survival. Because of the rarity of these tumors, however, the best method for hepatic artery embolization has not been established. We hypothesized that in patients with hepatic NE metastases, hepatic artery chemoembolization (HACE) would result in better symptom improvement and survival compared to bland embolization (HAE).
Methods Retrospective review identified all patients with NE hepatic metastases managed by HACE or HAE at three institutions from January 1996 through December 2007.
Results We identified 100 patients managed by HACE (n=49) or HAE (n=51) that were similar with respect to age, gender, and primary tumor type. The percentage of patients experiencing morbidity, 30-day mortality, and symptom improvement were similar between the two groups (HACE vs. HAE: 2.4% vs. 6.6%; 0.8% vs. 1.8%; and 88% vs. 83%, respectively.) No differences in the median overall survival were observed between HACE and HAE from the time of the first embolization procedure (25.5 vs. 25.7 months, p=0.79). Multivariate analysis revealed that resection of the primary tumor predicted survival (73.8 vs. 19.4 months, p<0.04).
Conclusions These data suggest that morbidity, mortality, symptom improvement, and overall survival are similar in patients with hepatic neuroendocrine metastases managed by chemo- or bland hepatic artery embolization.

Keywords Chemoembolization · Embolization · Hepatic artery · Metastasis · Neuroendocrine tumor · Liver

Grant Support American College of Surgeons Resident Research Scholarship, National Institutes of Health Grant T32 CA009614 Physician Scientist Training in Cancer Medicine.

Presented at Society for Surgery of the Alimentary Tract, May 21, 2008, San Diego, CA, USA.

S. C. Pitt · J. Knuth · H. A. Pitt (✉)
Department of Surgery, Indiana University,
535 Barnhill Dr., RT103D,
Indianapolis, IN 46, USA
e-mail: hapitt@iupui.edu

S. C. Pitt · S. M. Weber · H. Chen
Department of Surgery, University of Wisconsin,
Madison, WI, USA

J. M. Keily · E. J. Quebbeman
Department of Surgery, Medical College of Wisconsin,
Milwaukee, WI, USA

J. C. McDermott
Department of Radiology, University of Wisconsin,
Madison, WI, USA

W. S. Rilling
Department of Radiology, Medical College of Wisconsin,
Milwaukee, WI, USA

D. M. Agarwal
Department of Radiology, Indiana University,
535 Barnhill Dr., RT103D,
Indianapolis, IN 46, USA

Introduction

Neuroendocrine (NE) tumors comprise a heterogeneous group of similarly behaving cancers that include gastrointestinal carcinoid and pancreatic islet cell tumors. Due to the indolent nature of NE tumors, patients frequently present late in the disease course once metastases have spread to regional lymph nodes, the liver, and/or bone. Accordingly, NE tumors are the second most common cause of isolated hepatic metastases after colorectal adenocarcinoma.[1] The treatment of hepatic NE metastases frequently involves a multidisciplinary approach because aggressive management has been shown to improve symptoms and prolong survival.[2–4] Medical treatments including somatostatin analogs, chemotherapy, and external beam radiation have limited effectiveness on slowing disease progression but have been shown to reduce symptoms and improve quality of life, particularly the somatostatin analogs.[5–7] More invasive treatments for patients with advanced disease include surgical resection, cryo- and radiofrequency ablation, transplantation, and various forms of hepatic arterial embolization.[8–10]

Over the past several years, a number of controversies have developed over the optimal treatment for patients with this disease due, in part, to the rare nature of NE tumors and the resultant lack of level I evidence. One particular debate that has emerged is whether hepatic arterial embolization should be performed with or without localized, intra-arterial chemotherapy. Many practitioners believe that hepatic artery chemoembolization (HACE) is superior to bland embolization (HAE) in terms of symptom control and survival, but no study to date fully supports this belief. Only two reports have directly addressed this question; but both have failed to show a statistically significant difference between HACE and HAE in patients with NE hepatic metastases.[11–12] Therefore, we designed a multi-institutional study to test the hypothesis that HACE would result in better symptom improvement and overall survival than HAE with equivalent morbidity and mortality in patients with hepatic NE metastases.

Materials and Methods

Patient Population

Retrospective review identified all patients with NE hepatic metastases treated by HACE or HAE at three institutions from January 1996 to December 2007. The participating institutions were Indiana University (IU), the University of Wisconsin (UW), and the Medical College of Wisconsin (MCW). Prospective cancer registries, interventional radiology databases, and hospital records at each organization were utilized to identify eligible patients. At all three institutions, electronic medical records, clinic charts, radiological studies, and pathology reports were reviewed to gather patient demographics, symptom reporting, tumor characteristics, and treatment information. The diagnosis of NE tumor was confirmed by pathologic review of tissue samples. Standard cross-sectional imaging techniques were used to verify the presence of liver metastases. Approval for this study was obtained from the respective institutional review boards at IU, UW, and MCW.

Treatment Groups

Patients were grouped with respect to the treatment modality received: HACE or HAE. At each institution, the attending interventional radiologist selected which method of embolization to perform: HACE or HAE. Four patients who underwent both procedures during their care were excluded from the analyses. In addition, three recent patients who were treated by yttrium-90 radioembolization were excluded. The procedures were performed with particle embolization with or without iodized oil using either polyvinyl alcohol, gel foam, or embospheres (Fig. 1). The chemotherapies administered varied among institutions and included cisplatin, adriamycin, and mitomycin C. The timing between treatments, total number of embolizations performed, and extent of each procedure was at the discretion of the attending physicians, surgeons, and interventional radiologists. Factors considered in these decisions were multiple, such as presence of symptoms, performance status, and response to prior treatments. If patients underwent two separate procedures to address bilobar metastases (i.e., one right and one left hepatic artery procedure), these procedures were classified separately in our analyses. At all three institutions, protocols in compliance with hospital and national standards of care were used to obtain informed consent and screen laboratory values and to administer post-procedure intravenous fluids, analgesics, antibiotics, steroids, and antiemetics.

Outcomes

Our primary outcome measurement was overall survival which was calculated both from the time of diagnosis of metastatic disease and the time of first hepatic artery embolization until the time of death or date of last follow-up. In all patients, survival and follow-up data were obtained from respective hospital records including electronic medical records, clinic notes, cancer registries, and the Social Security Death Index database.

Improvement in symptoms was a secondary outcome measure in this study. We evaluated symptoms due to

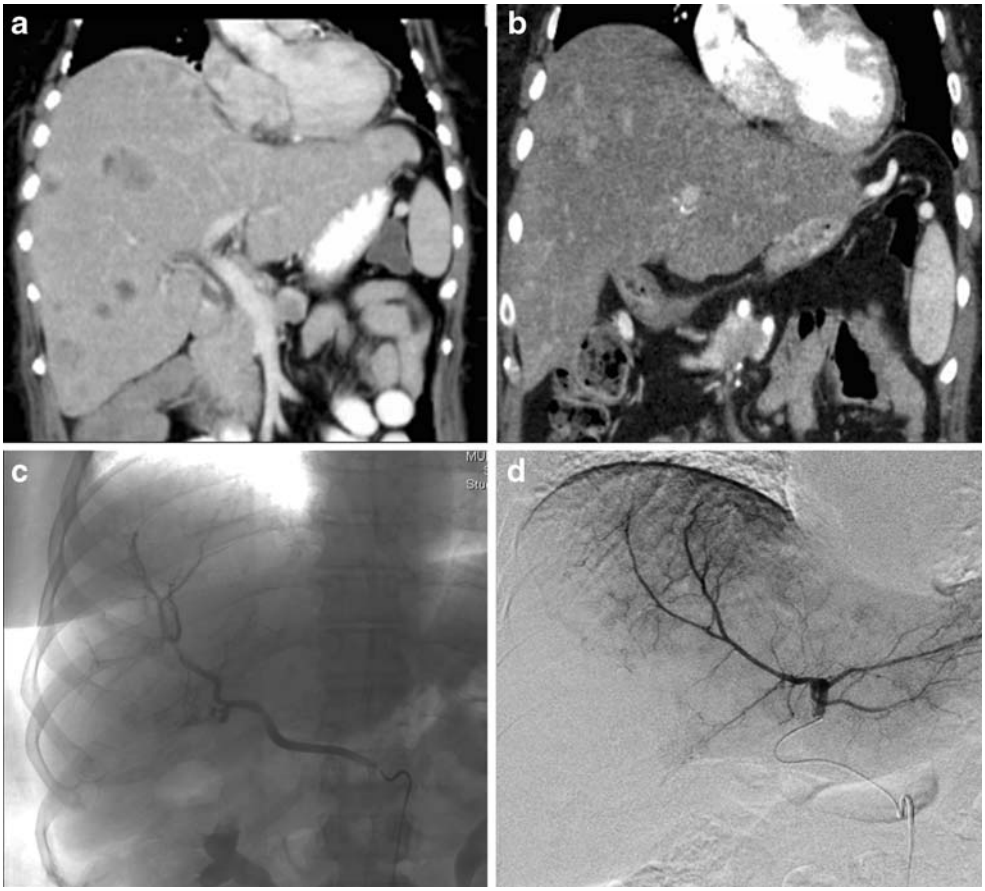

Figure 1 CT imaging of a patient with multiple, bilobar NE hepatic metastases before (**a**) and after (**b**) bland HAE. This patient underwent sequential embolizations of her replaced right (**c**) and left (**d**) hepatic arteries with subsequent symptom improvement.

systemic hormone release, locoregional invasion, and mass effect. Therefore, symptoms were considered present if the patient reported flushing, diarrhea, or abdominal pain. Patients who reported complete alleviation or significant sustained relief of their symptoms were regarded as improved.

In addition, we analyzed procedure-related morbidity and mortality as secondary outcome measurements. Any complication that occurred during or within 30 days following an embolization procedure was considered morbidity. Patients who experienced "post-embolization syndrome" were not included in the morbidity analysis as symptoms were mild, common, and difficult to quantify retrospectively. Similarly, mortality was defined as a death by any cause within 30 days of an embolization.

Statistical Analysis

Groups were compared by Fisher's exact or χ^2 analysis where appropriate. Statistical significance was reached at $p < 0.05$. Statistical Package for Social Sciences (SPSS) software version 11.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the survival data by the Kaplan–Meier actuarial method with statistical significance ascertained by log-rank analysis as well as to perform univariate and multivariate analyses.

Results

Demographics

One hundred patients (43 females and 57 males) with hepatic NE metastases managed by either HACE or HAE were identified at IU, UW, and MCW (Table 1). Mean age was 56 years (age range, 26–82 years). No significant differences in age or gender were found between the HACE and HAE treatment groups. The primary tumor type was carcinoid in 56 patients and islet cell in 44 patients. The two treatment groups, HACE and HAE, were similar with respect to the primary tumor type (% carcinoid 63 vs. 55, respectively) and location (% small bowel 61 and 51, respectively).

We also found no differences between the groups with respect to tumor burden within the liver (% bilobar involvement for HACE vs. HAE, 90 vs. 94, respectively) or the disease presentation (% synchronous 80 vs. 78, respectively; Table 1). The size of the largest metastatic lesion was also comparable between the HACE and HAE groups [mean ± standard error of the mean (SEM), 5.1±0.5 and 6.1±0.7, respectively]. With respect to number of hepatic metastases, we limited the total to a maximum of eight lesions to improve reporting accuracy in those patients with "innumerable" metastases. The percentage of patients with eight or

Table 1 Patient Demographics and Characteristics

	HACE	HAE	*p* Value
Number	49	51	
Age, years	58±2	54±2	0.14
Female, %	47	37	0.33
Tumor type			
Carcinoid, %	63	55	0.40
Small bowel, %	61	51	
Colorectal, %	2	0	
Other, %	0	4	
Pancreatic islet cell, %	37	45	0.31
Extent of hepatic metastases			
Bilobar, %	90	94	0.43
Tumor size, cm	5.1±0.5	6.2±0.8	0.24
Metastases number	6.7±0.3	6.4±0.3	0.42
>8 metastases, %	61	53	0.43
Synchronous, %	80	78	0.84
Treatments			
Number of embolizations	2.9±0.3	2.1±0.1	**0.015**
Primary tumor resected, %	67	49	0.07
Liver resection or ablation, %	41	4	**0.0001**
Octreotide, %	45	66	0.052
Chemotherapy, %	14	61	**0.0001**

Results reported as mean ± SEM where appropriate; Significant values in bold type.

greater lesions in the HACE and HAE groups was 63 and 53, respectively (p=0.43). The mean number of metastatic liver lesions was similar between the HACE and HAE groups (mean ± SEM, 6.7±0.3 and 6.4±0.3, respectively).

Treatments

The 49 patients in the HACE group underwent a total of 123 chemoembolization procedures (mean ± SEM, 2.9± 0.3; Table 1). Compared to the 51 patients in the HAE group who underwent 106 bland embolizations (mean ± SEM, 2.1±0.1), the HACE group was treated with a statistically significant greater number of embolization procedures (p<0.02). While the percentage of patients who underwent surgical resection of their primary tumor was similar between the two groups (HACE vs. HAE, 67 and 49, respectively, p=0.07), the HACE group was more likely to undergo resection and/or ablation of their hepatic metastases (HACE vs. HAE, 41% and 4%, respectively, p<0.0001). In addition, the HACE group, when compared to the HAE group, was less likely to receive additional therapies, such as chemotherapy or octreotide (14% vs. 61%, p<0.0001 and 45% vs. 66%, p=0.052, respectively). The finding that patients in the HACE group underwent a greater number of surgical procedures addressing their hepatic metastases, but the fact that they received fewer chemotherapy or octreotide treatments, probably reflects differences in treatment algorithms among the three institutions (see Table 2).

Table 2 Patient Treatments by Institution

	MCW	UW	IU
Number	45	21	34
HACE, %	100*	13	3
HAE, %	0*	87	97
Primary tumor resected, %	67	38	60
Liver resection or ablation, %	38*	19	3
Octreotide, %	42	57	76*
Chemotherapy, %	11	76*	36

*p<0.05 vs. others by chi square analysis

Because of the varying treatment philosophies for patients with significant hepatic NE metastases among the three participating hospitals, we analyzed the results by institution. Table 2 shows the differences in therapies at MCW, UW, and IU where patients are treated largely by HACE ± liver resection and/or ablation, HAE ± chemotherapy, and HAE alone, respectively. Therefore, patients at MCW were treated more aggressively with respect to their hepatic NE metastases. These patients were more likely to undergo potentially curative liver resection and/or ablation in addition to HACE and less likely to receive chemotherapy or octreotide in an attempt to slow tumor progression. At both UW and IU, patients were treated with HAE primarily for palliation of symptoms as opposed to tumor progression. Figure 2 depicts the Kaplan–Meier curve for overall survival from the time of metastases diagnosis and reveals no differences among the institutions involved in this study (p=0.23).

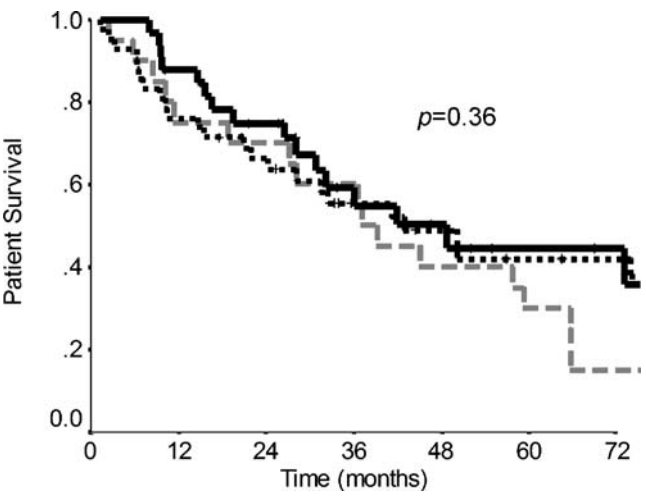

Figure 2 Overall survival calculated from the time of metastases diagnosis reveals no differences among the three institutions involved in this study: IU (*solid line*—median survival 48.7 months), UW (*dashed grey line*—median survival 37.0 months), and MCW (*dotted line*—median survival 42.9 months; p=0.23).

Morbidity and Mortality

The morbidity and mortality between the two treatment groups were comparable (Table 3). In the HACE group, three complications occurred after 123 chemoembolization procedures (2.4%): a groin hematoma, acute renal failure, and a biloma. Seven patients in the HAE group experienced complications after 106 bland embolizations (6.6% per procedure, p=0.19 compared to HACE). These complications included three liver abscesses, two patients with ileus, one groin hematoma, and one patient with hypotension. One patient in the HACE group and two patients in the HAE group died within 30 days of a procedure (0.8% vs. 1.8%, respectively, p=0.60). The patient in the HACE group had widespread metastatic disease, and her death was not thought to be directly related to the procedure. One of the patients in the HAE group died within 30 days after choosing to go on hospice care. The other patient in the HAE group developed liver failure (thought to be secondary to tumor burden), pneumonia, and acute lung injury after his embolization and was unable to be resuscitated when he went into a dysrhythmia.

Symptom Control

The HACE and HAE groups were similar with respect to both the presence of symptoms and improvement of symptoms after embolization (Table 3). Of the 49 patients in the HACE group and the 51 patients in the HAE group, 37 and 35 patients in each group, respectively, had tumor-related symptoms (76% and 69%, respectively, p=NS). Eighty-six percent of patients in the HACE group (32/37) improved after therapy compared to 83% of HAE patients (29/35, p=NS).

Survival

Median survival for the entire cohort was 32.4 months (range 1.3–177). Overall survival from the time of diagnosis of hepatic NE metastases was not statistically significantly different in the HACE group compared to the HAE group (Table 3, Fig. 3a). The median survival calculated from the time of metastasis diagnosis was slightly longer in the HACE group at 50.1 compared to 39.1 months for the HAE group, but this difference was not statistically different (p=0.62). The probability of 1-, 2-, and 5-year survival for HACE patients from the time of diagnosis of metastases was 78%, 69%, and 45%, respectively, while HAE patients' survival was 82%, 71%, and 33%.

When analyzed from the time of first embolization procedure, the overall survival for the two treatment groups was also similar (Table 3, Fig. 3b). The median survival for the HACE and HAE groups from first embolization was 25.5 and 25.7 months, respectively (p=0.79). The HACE and HAE groups had 1-, 2-, and 5-year survival probabil-

Table 3 Tumor Response and Outcomes

	HACE	HAE	p Value
Morbidity, %	2.4	6.6	0.19
30-day mortality, %	0.8	1.8	0.60
Symptomatic, %	76	69	0.34
Symptoms improved, %	86	83	0.70
Survival—metastases dx			0.64
Median, months	50.1	39.1	
5-year, %	43	35	
Survival—1st embolization			0.79
Median, months	25.5	25.7	
5-year, %	19	13	

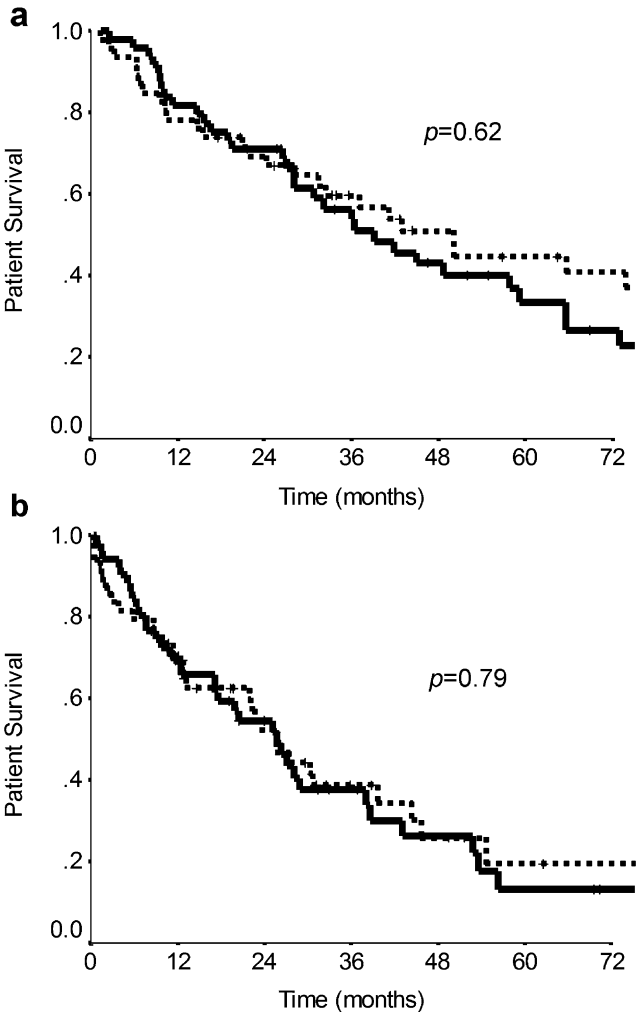

Figure 3 Kaplan–Meier curves comparing overall survival from **a** the time of diagnosis of metastases (median survival 50.1 vs. 39.1 months, respectively, p=0.62) and **b** the time of first embolization procedure (median survival 25.5 vs. 25.7 months, respectively, p=0.79) between patients treated by HACE (*dotted line*) or HAE (*solid line*).

ities of 69%, 52%, and 19% and 70%, 54%, and 13%, respectively. Comparison of the median overall survivals from the time of diagnosis of metastases to the time of first embolization procedure revealed a similar delay of 24.6 and 19.3 months for the HACE and HAE groups, respectively. This delay likely represents the time elapsed during surgical resection of the primary lesion and/or hepatic metastases with an associated recovery period(s) as well as the time to development of symptoms from the metastatic lesions.

Further univariate analysis of the entire cohort examining factors predictive of overall survival found that only resection of the primary tumor significantly increased survival. The median survival for patients undergoing resection of their primary tumor versus those tumors left intact revealed 73.1 versus 28.0 months (p=0.0002; Table 4). The cumulative overall survival rates at 1, 2, and 5 years were 89%, 80%, and 55% for patients whose primary tumor was resected as opposed to 67%, 53%, and 16% for patients who did not undergo surgery. Figure 4 depicts the Kaplan–Meier curve for overall survival plotted as a function of primary tumor resection. Additional factors that were examined for predictive effects on overall survival but were not significant included age, gender, tumor type (carcinoid vs. islet cell), disease presentation (synchronous vs. metachronous), extent of liver involvement (unilobar vs. bilobar), resection and/or ablation of liver metastases, octreotide, chemotherapy, and embolization type (HACE vs. HAE; Table 4). Only resection or ablation of liver metastases (p=0.11) trended toward significance and was included in a multivariate analysis. Resection of the primary tumor was not predictive of poor survival in the multivariate model (p=0.08).

Table 4 Univariate Analysis for Factors Predictive of Overall Survival

Factor	Number	Median survival, months	p Value
Age (continuous)[a]	95		0.42
Gender			
Male	53	41.7	0.30
Female	42	50.1	
Tumor type			
Carcinoid	57	45.0	0.84
Islet cell	38	32.0	
Disease presentation			
Synchronous	77	37.0	0.53
Metachronous	18	48.7	
Liver involvement			
Unilobar	8	81.6	0.47
Bilobar	87	41.8	
Primary tumor resection			
Yes	55	73.1	**0.0002**
No	39	28.0	
Resection/ablation mets			
Yes	22	65.6	0.11
No	73	36.5	
Octreotide			
Yes	46	48.6	0.85
No	37	37.0	
Chemotherapy			
Yes	25	39.1	0.71
No	50	43.0	
Embolization type			
HACE	46	50.1	0.62
HAE	49	39.1	

Significant values in **bold** type.
[a] Log transformation

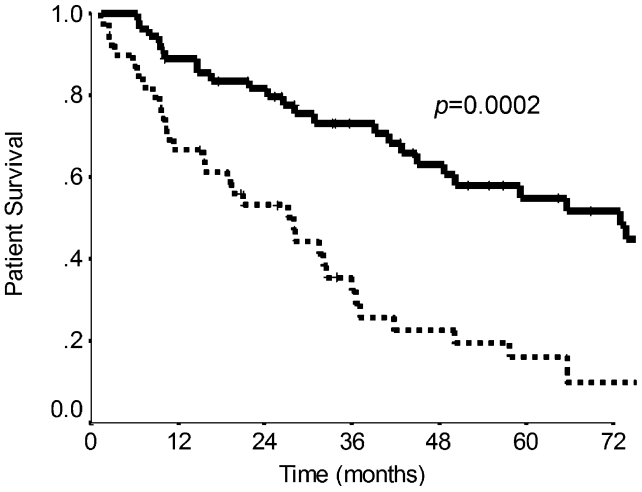

Figure 4 Overall survival in patients who underwent resection of their primary tumor (*solid line*) was significantly longer compared to those whose primary tumors remained intact (*dotted line*) (median survival 73.1 vs. 28.0 months, respectively, p=0.0002). Survival was calculated from the time of diagnosis of metastatic disease.

Discussion

As a result of the rarity and often unpredictable biologic behavior of NE tumors with hepatic metastases, the appropriate treatment algorithm for these patients has yet to be defined. The majority of patients with this disease undergo a wide variety of treatments ranging from somatostatin analogs to hepatic artery embolization to liver transplantation. In this series, we reviewed 100 patients from three institutions with hepatic NE metastases who were similar with respect to age, gender, primary tumor type, and extent of hepatic tumor burden (Table 1). We compared these patients based on the type of hepatic artery embolization procedure they received: chemoembolization-HACE (n=49) or bland embolization-HAE (n=51). The morbidity and 30-day mortality were similar between the two groups (Table 3). We observed no differences in the rate of symptoms at presentation or symptom relief after either procedure (Table 3). Overall survival from the time

of diagnosis of hepatic metastases and the time of first embolization procedure was also comparable between HACE and HAE (Table 3, Fig. 3A and B). The only factor found to be predictive of survival for all patients in a univariate analysis was resection of the primary tumor ($p=0.002$, Table 4, Fig. 4). However, in multivariate analysis that included those factors with a $p\leq0.15$ (resection and/or ablation of hepatic metastases and resection of the primary tumor), resection of the primary tumor was no longer an independent predictor of a better prognosis ($p=0.08$). Further analysis of the patients revealed that differences in treatment philosophies of patients with NE hepatic metastases exist among the institutions involved; however, despite these differences, overall survival was similar at all three institutions (Table 2, Fig. 2).

Treatment of hepatic NE metastases with bland HAE has been reported since the early to mid-1980s in multiple case series.[13–16] However, the last 25 years has seen tremendous improvements in techniques, technologies, and aggressiveness of treatment strategies in this patient population. More recent studies examining the efficacy of HAE alone report morbidity (major complications) in the range of 0% to 17% and mortality ranging from 0% to 6%.[17–23] Our results of 6% morbidity and 1.8% 30-day mortality after HAE are consistent with these previous reports. Some of these same analyses also revealed symptomatic improvement after HAE ranging from 64% to 91%, which is consistent with the 83% observed in this study.[3,20–22] Likewise, for patients receiving HAE, we found the median overall survival from the time of first embolization procedure (25.7 months) to be similar to that reported in the literature (range 20–80 months).[3,17,19,21,22]

Studies examining the effectiveness and safety of adding intra-arterial chemotherapy to hepatic artery embolization began to appear in the literature about 10 years later in the early 1990s.[24–26] The morbidity, mortality, symptomatic control, and survival with HACE were similar to HAE in these reports; but, until recently, the largest case series was a single institution report of 23 patients.[24,27,28] In 2003, Gupta et al., then, reported 81 patients who underwent either HAE or HACE demonstrating a 63% reduction in tumor-related symptoms and 31-month median overall survival from the time of first embolization procedure. However, in this report, the two treatment types were examined together.[29] More recently, Ho et al. described a cohort of 46 patients who underwent primarily HACE (93% of procedures) of whom 78% had improved symptoms and median survival was 32 months.[30] The morbidity and mortality reported in this cohort were 9.7% and 4.3%, respectively.[30] In the current study, we found a 25.5-month median overall survival for patients treated by HACE, which is slightly shorter but still comparable to these previous reports. Similarly, our 2.4% morbidity and 0.8% 30-day mortality rates per procedure after HACE are somewhat improved over these same studies.

Most recently, two larger series have been reported that directly compare HACE and HAE.[11,12] The largest of these studies from Gupta et al. examined 69 patients with carcinoids and 54 patients with islet cell tumors who were examined separately because the overall survival for patients with carcinoids was significantly longer (33.8 vs. 23.2 months, $p=0.012$).[11] Whether or not these heterogeneous NE tumors should be considered as a single cohort or separately is unclear. Other studies have shown differences in survival between carcinoid and islet cell tumors similar to Gupta et al., all of which reveal a more favorable prognosis for patients with carcinoids.[12, 17, 31–34] However, our analyses and others have found no significant differences in overall survival for these two types of NE tumors (carcinoid vs. islet cell: 45.0 vs. 32.0 months, $p=0.83$, Fig. 5).[2, 30] Consequently, we chose to analyze carcinoids and islet cell tumors together.

The literature comparing HACE to HAE shows similar toxicity profiles, morbidity, and mortality for these two procedures.[11,12] The results we reported here confirm these findings of previous authors. Ruutiainen et al. also described similar rates of symptom improvement after HACE and HAE, 92% vs. 93%, respectively, which is comparable to our data (Table 3).[12] The only two other series that have examined overall survival comparing HACE to HAE in patients with hepatic NE metastases (including carcinoid and islet cell tumors) both reported prolonged overall survival for patients treated with HACE (31.5 and 44 months) compared to those treated with HAE (18.2 and 39 months).[11,12] However, these differences did not reach statistical significance in either study due, in part,

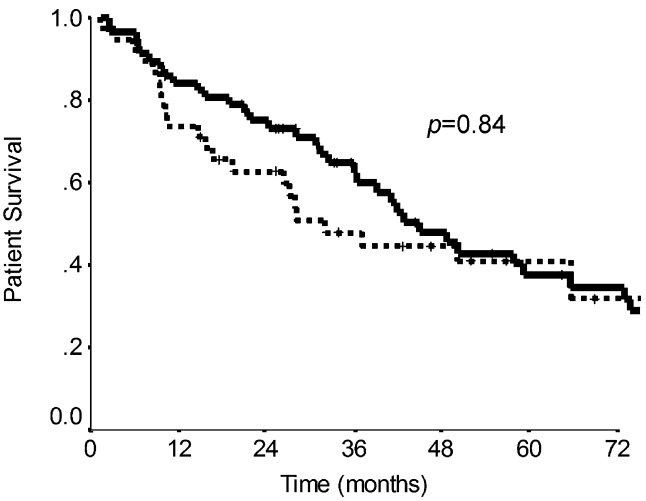

Figure 5 Patient overall survivals by primary tumor type: median survival for carcinoids (*solid line*) was 45.0 months while islet cell tumors (*dotted line*) had a median survival of 32.0 months. This difference was not statistically significant ($p=0.84$).

to the small number of patients. In our cohort, the median survival from first embolization was nearly identical for patients treated by HACE and HAE (25.5 vs. 25.7 months, $p=0.79$, Fig. 3b). These results taken together suggest that the addition of intra-arterial chemotherapy to embolization does not provide a survival benefit over bland HAE. On the other hand, HACE does not confer increased risks to the patient since morbidity and mortality are comparable to HAE, and HACE offers equal expectations of symptom control.

The efficacy of systemic chemotherapy, including streptozotocin, fluorouracil, doxorubicin, irinotecan, interferon-α, oxaliplatin, capcitabine, and others, has been extensively examined in patients with hepatic NE metastases. Both single and multi-agent regimens have limited effectiveness in patients with unresectable disease due to poor response rates coupled with significant toxicity.[35] Reported median overall survival for patients with metastatic NE tumors treated with chemotherapy ranges from 15 to 23 months.[36,37] Longer median overall survivals of up to 40 months in a subset patients with well-differentiated NE tumors or up to 37 months in patients with pancreatic islet cell tumors also have been reported.[38,39] In addition, newer agents, including anti-angiogenic drugs such as vascular endothelial growth factor monoclonal antibodies, tyrosine kinase inhibitors, epidermal growth factor receptor inhibitors, and mammalian target of rapamycin inhibitors are currently under investigation and show promising initial results especially in patients with islet cell tumors.[40–42] In 1994, Moertel et al. demonstrated that the addition of systemic chemotherapy in patients undergoing HAE improved the rate and duration of tumor response.[31] Therefore, some authors have supported a theoretical advantage of HACE in patients with islet cell tumors, which tend to respond better to systemic chemotherapy.[11] In the current study, we found no differences in survival in patients who received systemic chemotherapy in addition to either type of embolization procedure compared to patients who did not undergo chemotherapy, even when carcinoid and islet cell tumors were analyzed separately (carcinoid only: 57.8 vs. 41.1 months, respectively, $p=0.84$; islet cell only: 28.0 vs. 50.1 months, respectively, $p=0.62$). However, the administration of systemic chemotherapy was not standardized in this study. Furthermore, when islet cell tumors were analyzed alone, no significant differences in overall survival were found between patients treated with HACE and HAE, though HACE-treated patients did tend to live longer (50.1 vs. 27.1 months, respectively, $p=0.45$).

While either method of embolic therapy appears to provide a survival benefit over no treatment or systemic chemotherapy alone, surgical resection of the primary and any associated metastatic disease, even if incomplete, remains the recommended approach. Our study found that resection of the primary tumor significantly prolonged survival, 73.1 vs. 28.0 months ($p=0.0002$; Table 4, Fig. 4). Other studies also have revealed that primary tumor resection is a favorable prognostic variable;[11,43] however, the predictive value of primary tumor resection on survival may reflect a selection bias towards healthier patients that are able to undergo surgery.

Correspondingly, several authors have shown that surgical debulking or cytoreduction with either hepatic resection or ablation results in improved symptom control and survival when compared to embolization alone.[2–4,22] While our data were not statistically significant, resection or ablation of the hepatic metastases did provide a survival advantage over no surgical debulking (65.6 vs. 36.5 months, respectively, $p=0.11$). Despite a greater number of liver resections and/or ablations in the HACE group (Table 1), we found no significant survival benefit in these patients. Studies comparing curative and palliative resection of hepatic NE metastases show a clear survival benefit when curative resection is achieved (85% vs. 63% 5-year survival in one study).[4] Analyses that have not distinguished the curative intent of the liver resection still report 5-year survivals of at least 70%.[2,4,22] Meanwhile, reports of HACE and cytoreduction used in combination reveal 5-year survivals in the range of 40% to 50%.[2,4] Theses rates are better than what we observed with a 19% 5-year survival in patients undergoing HACE; however, only 41% of these patients underwent hepatic resection and/or ablation in addition to HACE (Table 1). In addition, survival was calculated from the time of first embolization procedure and not the time of hepatic resection as in the other studies. Therefore, we continue to recommend an aggressive treatment strategy with resection of the primary tumor and surgical debulking of hepatic NE metastases when possible, combined with either HAE or HACE.[2,22,44]

Our study has several limitations including nonrandomized retrospective design, inherent selection bias, changes in technology over the 11-year study period, and lack of standardized treatment protocols at the three institutions. Additionally, reporting of symptoms and symptom improvement were subjective and not collected with a validated assessment tool. Biochemical markers were also not routinely measured and, therefore, could not be analyzed as part of this study. Because whole-body octreotide or bone scans were not performed on all patients, we were unable to collect reliable data with respect to the presence of extrahepatic metastases; therefore, we did not analyze whether the presence of extrahepatic disease influenced survival. In addition, the quality, availability, and reporting of CT scans precluded our ability to stratify patients accurately with respect to the percentage of liver involvement. The presence of extrahepatic metastases and greater than 50% liver involvement are both factors that have been shown to predict survival in other studies.[2,11]

The addition of HACE to HAE in patients with hepatic NE metastases did not prolong survival or improve symptoms. However, the morbidity and mortality associated with HACE were similar to HAE and did not pose additional risks to the patient. As with any rare disease, the design of a prospective, randomized trial examining these therapies will be difficult but should be undertaken. Our results support resection of the primary carcinoid or islet cell tumor, when possible, even in the presence of metastatic disease. In conclusion, we continue to support an aggressive approach in patients with NE hepatic metastases including HACE or HAE in addition to surgical resection and somatostatin analogs.

Acknowledgement This work was supported by the American College of Surgeons Resident Research Scholarship and National Institutes of Health Grant T32 CA009614 Physician Scientist Training in Cancer Medicine.

References

1. Chen H, Hardacre J, Uzar A, Cameron J, Choti M. Isolated liver metastases from neuroendocrine tumors: does resection prolong survival? J Am Coll Surg 1998;187:88–93. doi:10.1016/S1072-7515(98)00099-4.
2. Touzios JG, Kiely JM, Pitt SC, Rilling WS, Quebbeman EJ, Wilson SD et al. Neuroendocrine hepatic meastases: does aggressive management improve survival? Ann Surg 2005;241:776–785. doi:10.1097/01.sla.0000161981.58631.ab.
3. Musunuru S, Chen H, Rajpal S, Stephani N, McDermott JC, Holen K et al. Metastatic neuroendocrine hepatic tumors: resection improves survival. Arch Surg 2006;141:1000–1004. doi:10.1001/archsurg.141.10.1000.
4. Yoa KA, Talamonti MS, Nemeck A, Angelos P, Chrisman H, Skarda J et al. Indications and results of liver resection and hepatic chemoembolization for metastastic gastrointestinal neuroendocrine tumors. Surgery 2001;130:677–685. doi:10.1067/msy.2001.117377.
5. Woodside KJ, Townsend CM Jr, Evers MB. Current management of gastrointestinal carcinoid tumors. J Gastrointest Surg 2004;8:742–756. doi:10.1016/j.gassur.2004.04.010.
6. Schupak KD, Wallner KE. The role of radiation therapy in the treatment of locally unresectable or metastatic carcinoid tumors. Int J Radiol Oncol Biol Phys 1991;20:489–495.
7. Townsend CM Jr, Thompson JC. The clinical use of gastrointestinal hormones for alimentary tract disease. Adv Surg 1996;29:79–92.
8. Que FG, Nagorney DM, Batts KP et al. Hepatic resection for metastatic neuroendocrine carcinomas. Am J Surg 1995;169:36–42. doi:10.1016/S0002–9610(99)80107-X.
9. O'Toole D, Maire F, Ruszniewski P. Ablative therapies for liver metastases of digestive endocrine tumors. Endocr Relat Cancer 2003;10:463–468. doi:10.1677/erc.0.0100463.
10. Le Treut YP, Delpero JR, Dousset B et al. Results of liver transplantation in the treatment of metastatic neuroendocrine tumors: a 31-case French multicentric report. Ann Surg 1997;225:355–364. doi:10.1097/00000658-199704000-00003.
11. Gupta S, Johnson MM, Murthy R, Ahrar K, Wallace MJ, Madhoff DC et al. Hepatic arterial embolization and chemoembolization for the treatment of patients with metastatic neuroendocrine tumors: variables affecting response rate and survival. Cancer 2005;104:1590–1602. doi:10.1002/cncr.21389.
12. Ruutiainen AT, Soulen MC, Tuite CM, Clark TWI, Mandschein JI, Stavropoulos SW et al. Chemoembolization and bland embolization of neuroendocrine tumor metastases to the liver. J Vasc Interv Radiol 2007;18:847–855. doi:10.1016/j.jvir.2007.04.018.
13. Lunderquist A, Ericsson M, Nobin A, Sandén G. Gelfoam powder embolization of the hepatic artery in liver metastases of carcinoid tumors. Radiologe 1982;22:65–70.
14. Mårtensson H, Nobin A, Bengmark S, Lunderquist A, Owman T, Sandén G. Embolization of the liver in the management of metastatic carcinoid tumors. J Surg Oncol 1984;27:152–158. doi:10.1002/jso.2930270305.
15. Stöckman F, Von Romatowski HJ, Reimold WV, Schuster R, Cruetzfeldt W. Hepatic artery embolization for the treatment of endocrine gastrointestinal tumors with liver metastases. Z Gastroenterol 1984;22:652–660.
16. Odurny A, Birsch SJ. Hepatic arterial embolisation in patients with metastatic carcinoid tumours. Clin Radiol 1985;36:597–602. doi:10.1016/S0009-9260(85)80241-5.
17. Eriksson BK, Larsson EG, Skogseid BM, Löfberg Am, Lörelius LE, Oberg KE. Liver embolizations of patients with malignant neuroendocrine gastrointestinal tumors. Cancer 1998;83:2293–2301. doi:10.1002/(SICI)1097-0142(19981201)83:11<2293::AID-CNCR8>3.0.CO;2-E.
18. Brown KT, Koh BY, Brody LA, Getrajdman GI, Susman J, Fong Y et al. Particle embolization of hepatic neuroendocrine metastases for control of pain and hormonal symptoms. J Vasc Interv Radiol 1999;10:397–403.
19. Chamberlain RS, Canes D, Brown KT, Saltz L, Jarnagin W, Fong Y et al. Hepatic neuroendocrine metastases: does intervention alter outcomes? J Am Coll 2000;190:432–435. doi:10.1016/S1072-7515(00)00222-2.
20. Schell SR, Camp ER, Caridi JG, Hawkins IF Jr. Hepatic artery embolization for control of symptoms, octreotide requirements, and tumor progression in metastatic carcinoid tumors. J Gastrointest Surg 2002;6:664–670. doi:10.1016/S1091-255X(02)00044-6.
21. Strosberg JR, Choi J, Cantor AB, Kvols LK. Selective hepatic artery embolization for treatment of patients with metastatic carcinoid and pancreatic endocrine tumors. Cancer Control 2006;13:72–78.
22. Osborne DA, Zervos EE, Strosberg J, Boe BA, Malafa M, Rosemurgy AS et al. Improved outcome with cytoreduction versus embolization for symptomatic hepatic metastases of carcinoid and neuroendocrine tumors. Ann Surg Oncol 2006;13:572–581. doi:10.1245/ASO.2006.03.071.
23. Granberg D, Eriksson LG, Welin S, Kindmark H, Janson ET, Skogseid B et al. Liver embolization with trisacryl gelatin microshperes (embosphere) in patients with neuroendocrine tumors. Acta Radiol 2007;48:180–185. doi:10.1080/02841850601080440.
24. Stokes KR, Stuart K, Clouse ME. Hepatic arterial chemoembolization for metastatic endocrine tumors. J Vasc Interv Radiol 1993;4:341–345.
25. Therasse E, Breittmayer F, Roche A, DeBaere T, Indushekar S, Ducreux M et al. Transcatheter chemoembolization of progressive carcinoid liver metastases. Radiology 1993;189:541–7.
26. Clouse ME, Perry L, Stuart K, Stokes KR. Hepatic arterial chemoembolization for metastatic neuroendocrine tumors. Digestion 1994;199(55):92–97.
27. Drougas JG, Anthony LB, Blair TK, Lopez RR, Wright JK Jr, Chapman WC et al. Hepatic arterial chemoembolization for management of patients with advanced metastatic carcinoid tumors. Am J Surg 1998;175:408–412. doi:10.1016/S0002-9610(98)00042-7.
28. Dominguez S, Denys A, Madiera I, Hammel P, Vilgrain V, Menu Y et al. Hepatic arterial chemoembolization with streptozocin in patients with metastatic digestive endocrine tumors. Eur J Gastroenterol Hepatol 2000;12:151–157.

29. Gupta S, Yao JC, Ahrar K, Wallace MJ, Morello FA, Madoff DC et al. Hepatic arterial embolizationand chemoembolization for treatment of patients with metastatic carcinoid tumors: the M.D. Anderson experience. Cancer J 2003;9:261–267. doi:10.1097/00130404-200307000-00008.
30. Ho AS, Picus J, Darcy MD, Tan B, Gould JE, Pilgram TK et al. Long-term outcome after chemoembolization and embolization of hepatic metastatic lesions from neuroendocrine tumors. AJR Am J Roentgenol 2007;188:1201–1207. doi:10.2214/AJR.06.0933.
31. Moertel CG, Johnson CM, McKusick MA, Martin JK Jr, Nagorney DM, Kvols LK et al. The management of patients with advanced carcinoid tumors and islet cell carcinomas. Ann Intern Med 1994;120:302–309.
32. McDermott EW, Guduric B, Brennan MF. Prognostic variables in patients with gastrointestinal carcinoid tumours. Br J Surg 1994;81:1007–1009. doi:10.1002/bjs.1800810725.
33. Shabani KO, Souba WW, Finkelstein DM, Stark PC, Elgadi KM, Tenabe KK et al. Prognosis and survival in patients with gastrointestinal tract carcinoid tumors. Ann Surg 1999;229:815–823. doi:10.1097/00000658-199906000-00008.
34. Caprotti R, Angelini C, Mussi C et al. Gastrointestinal carinoids. Prognosis and survival. Minerva Chir 2003;58:523–532.
35. Woodside KJ, Townsend CM Jr, Evers MB. Current management of gastrointestinal carcinoid tumors. J Gastrointest Surg 2004;8:742–756. doi:10.1016/j.gassur.2004.04.010.
36. Andreyev HJ, Scott-Mackie P, Cunningham D, Nicolson V, Norman AR, Badve SS et al. Phase II study of continuous infusion fluorouracil and interferon alpha-2b in the palliation of malignant neuroendocrine tumors. J Clin Oncol 1995;13:1486–1492.
37. Ducreux MP, Boige V, Leboulleux S et al. A phase II study irinotecan with 5-fluorouracil and leucovorin in patients with pretreated gastroenteropancreatic well-differentiated endocrine carcinomas. Oncology 2006;70:134–140. doi:10.1159/000093004.
38. Kouvaraki MA, Anjani JA, Hoff P, Wolff R, Evans DB, Lozano R et al. Fuorouracil, doxorubicin, and streptozosin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. J Clin Oncol 2004;22:4762–4771. doi:10.1200/JCO.2004.04.024.
39. Bajetta E, Catena L, Procopio G, De Dosso S, Bichisao E, Ferrari L et al. Are capecitabine and oxaliplatin (XELOX) suitable treatment for progressing low-grade and high-grade neuroendocrine tumours? Cancer Chemother Pharmacol 2007;59:637–642. doi:10.1007/s00280-006-0306-6.
40. Durán I, Salazar R, Casanovas O, Arruzubi V, Vilar E, Siu LL et al. New drug development in digestive neuroendocrine tumors. Ann Oncol 2007;18:1307–1313. doi:10.1093/annonc/mdm009.
41. Modlin IM, Oberg K, Chung DC, Jensen RT, de Herder WW, Thakker RV et al. Gastroenteropancreatic neuroendocrine tumors. Lancet Oncol 2008;9:61–72. doi:10.1016/S1470-2045(07)70410-2.
42. Pinchot SN, Pitt SC, Sippel RS, Kunnimalaiyaan M, Chen H. Novel target for the treatment and palliation of gastrointestinal neuroendocrine tumors. Curr Opin Investig Drugs 2008;9:576–582.
43. Chu QD, Hill HC, Douglass HO Jr, Driscoll D, Smith JL, Nava HR et al. Predictive factors associated with long-term survival in patients with neuroendocrine tumors of the pancreas. Ann Surg Oncol 2002;9:855–862. doi:10.1007/BF02557521.
44. Sarmiento JM, Heywood G, Rubin J et al. Surgical treatment of neuroendocrine metastases to the liver: a plea for resction to increase survival. J Am Coll Surg 2003;197:29–37. doi:10.1016/S1072-7515(03)00230-8.

J Gastrointest Surg (2008) 12:1961–1966
DOI 10.1007/s11605-008-0663-z

Monopolar Floating Ball Versus Bipolar Forceps for Hepatic Resection: A Prospective Randomized Clinical Trial

Guido Torzilli · Matteo Donadon · Matteo Marconi · Fabio Procopio · Angela Palmisano · Daniele Del Fabbro · Florin Botea · Antonino Spinelli · Marco Montorsi

Received: 29 May 2008 / Accepted: 8 August 2008 / Published online: 3 September 2008

Abstract
Background Hepatic transection by Pean-clasia is the mainstream technique that can be used with different coagulators. Monopolar floating ball (MFB) is proposed for liver transection. Whether its value for liver transection is unclear, its efficiency as a coagulator only seems high. We compared in a prospective randomized study the standard Pean-clasia with bipolar forceps (BF) versus Pean-clasia with MFB in patients undergoing hepatic resection.
Methods Seventy-six patients scheduled for hepatectomy were randomized in two groups, according to the coagulator device: group A (MFB, $n=38$) and group B (BF, $n=38$). The two groups were homogeneous in terms of tumor presentation and background liver features. Blood loss, blood transfusions, transection time, number of ligatures, drain discharge, drain bilirubin levels at third, fifth, and seventh postoperative day, and postoperative morbidity and mortality were prospectively evaluated.
Results No significant differences between groups A and B were seen in terms of blood transfusions (11.5% versus 16.5%; $p=0.450$), blood loss/cm^2 (mean 7.2 versus 7.6 ml; $p=0.450$), transection time/cm^2 (mean 2.1 versus 2.3; $p=0.070$), number of ligatures/cm^2 (mean 0.7 versus 0.7; $p=1$), drain discharge (mean 55 versus 66.7 ml; $p=0.451$), and drain bilirubin levels (mean 1.9 versus 2.1 mg/dl; $p=0.664$). No mortality or major morbidity was recorded in both groups.
Conclusions This study showed that association of Pean-clasia with MFB was safe and minimized the blood loss during hepatic resection. However, MFB did not offer significant benefits over BF, while its cost is not negligible.

Keywords Liver surgery · Liver dissection · Liver tumors · Blood transfusion

Introduction

Several different surgical devices for hepatic transection and coagulation are nowadays proposed with the aim to minimize intraoperative blood loss and blood transfusions, which are two of the most important outcome predictors after hepatic resection. In fact, intraoperative blood loss and perioperative blood transfusions have already been reported to worsen the short- and long-term prognosis of patients submitted to liver surgery.[1–5] Few randomized studies investigated the role of such different surgical devices for hepatic transection, reporting no significant benefits of technological instruments compared with the traditional Pean-clasia.[6–8] Indeed, hepatic transection by Pean-clasia is a safe, simple, and low-cost technique that can be used with different coagulators. Monopolar floating ball (MFB—Tissuelink™) is a relatively new device proposed for liver transection, which seems able to provide an effective coagulation. However, it seems less efficient in disclosing the vascular structures encountered during dissection, and it may produce necrosis on the cut-surface, which may be a source of morbidity. On the other hand, its efficiency as a coagulator still needs to be investigated, in spite of this effect being its best feature. Bipolar forceps (BF) seem to

G. Torzilli (✉) · M. Donadon · M. Marconi · F. Procopio · A. Palmisano · D. Del Fabbro · F. Botea · A. Spinelli · M. Montorsi
Third Department of Surgery, University of Milan, School of Medicine, IRCCS Istituto Clinico Humanitas, Via Manzoni 56, 20089 Rozzano, Milan, Italy
e-mail: guido.torzilli@unimi.it

be one of the most widely used and a more economic coagulation device in liver surgery. The aim of this study was to compare in a prospective randomized fashion the Pean-clasia with MFB versus Pean-clasia with BF in patients undergoing hepatic resection.

Material and Methods

Terminology

The terminology used for liver anatomy and liver resections was based on the Brisbane classification.[9] Liver resections were considered major when at least three adjacent segments were removed. Postoperative major morbidity was considered as any adverse event that required additional surgery or any invasive, corrective procedure. Postoperative bile leakage was considered when bilirubin concentration in the drain discharge was higher than 10 mg/dl for at least 3 days starting from the fifth postoperative day. Postoperative death was analyzed at 30 and 90 days.

Population

All patients scheduled for hepatic resection at our unit were considered eligible for this study. Our selection criteria for hepatic resection for hepatocellular carcinoma (HCC)[10,11] or colorectal liver metastases (CLM)[12] were previously described. Written informed consent was obtained from all patients. All the patients received the same and well-established preoperative work-up and postoperative care.[4]

Sample Size

In our experience, a mean blood loss of 320 ml with a standard deviation (SD) of 280 ml was expected; according with these results, we hypothesized to find a difference of 200 ml in blood loss using the MFB coagulator. Taking a two-tailed *T*-test with a type I error of 0.05 and a statistical power of 85%, 38 patients were required to verify that hypothesis. Therefore, 38 patients had hepatic resection by Pean-clasia and MFB (group A), and 38 had resection by Pean-clasia and BF (group B).

Outcome Measures

The outcome measures were the amount of overall blood loss and per squared centimeter of hepatic resection area; rate of blood transfusions, transection time per squared centimeter of hepatic resection area; number of ligatures per squared centimeter of hepatic resection area; drain discharge; drain bilirubin levels at third, fifth, and seventh postoperative day; rate of postoperative morbidity and mortality; tumor-free margins width; and rate of cut-edge tumor recurrences.

Surgical Procedures

The same surgeon (G.T.) performed all the operations. J-shaped or inverted-T laparotomies were routinely carried out. In case of tumors involving segments 1, 4 cranial, 7 and 8 close to the hepato-caval confluence, a J-shaped thoracophrenolaparotomy was performed. Intraoperative ultrasound (IOUS) was systematically performed both to stage the disease and to guide the resection. Contrast-enhanced IOUS (CEIOUS) was performed for any new lesion detected at IOUS for HCC and, in every case, for CLM as previously reported by us.[13,14] IOUS was performed in all cases using the Aloka SDD 5500 machine (Aloka Ltd, Tokyo, Japan) equipped with a standard 3- to 6-MHz frequency convex probe and with a 7.5- to 10-MHz frequency microconvex probe. CEIOUS was carried out using the standard 3- to 6-MHz frequency convex probe working at 1.88- to 3.76-MHz harmonic frequency. The surgical strategy was based on the IOUS-, CEIOUS-, and color-Doppler IOUS-findings following the criteria previously reported.[15,16] Hepatic dissection was accomplished with the intermittent Pringle maneuver (15 min of clamping and 5 min of declamping) without preconditioning in all patients. The transection was carried out by the Pean-clasia and the vessel coagulation by the MFB or BF according to the randomization process, which was blinded to the surgeon. However, vessels thicker than 2 mm were ligated with thin (2/3–0) sutures in both groups. Absorbable or nonabsorbable clips were not used.

The cut surface of the liver was secured by 2/3–0 sutures, electrocautery, and fibrin glue (Quixil, Ethicon, USA). To rule out bile leakage, a careful examination of the resection area was done. For this purpose, we did not usually perform intraoperative cholangiography.[17] Conventionally, we did not close the laparotomy until at least 50 min passed from the end of the liver transection. Closed 19-French suction drains were always inserted, and they were removed not before the seventh postoperative day after the evidence that the bilirubin level was less than the level recorded on the fifth postoperative day and anyway <10 mg/dl.[18]

Statistical Analysis

Continuous variables were presented as mean and SD. Discrete variables were presented as number and percentage. Statistical significant differences were searched with the Fisher, the *T* test, or the χ^2 test when appropriate. All analyses were performed on an intention-to-treat basis. A p value<0.05 was considered statistically significant.

Table 1 Demographic, Clinical and Pathological Characteristics

	Monopolar floating ball (n=38)	Bipolar forceps (n=38)	p[a]
Age (years)			
Mean±SD	62.2±12.1	67.2±11.4	0.068
Gender			
Male	29 (76%)	28 (74%)	
Female	9 (24%)	10 (26%)	1.000
Pathology			
CLM	13 (34%)	10 (27%)	
HCC	20 (53%)	21 (55%)	
Other	5 (13%)	7 (18%)	0.688
Liver background			
Non-cirrhosis	21 (55%)	16 (42%)	
Cirrhosis	17 (45%)	22 (58%)	0.359
Platelets count ($\times 10^3/mm^3$)			
Mean±SD	178±75.1	176.9±73.3	0.949
Previous local treatment			
PAT	2 (5%)	3 (8%)	1.000
TACE	1 (3%)	1 (3%)	
Combined treatment	2 (5%)	1 (3%)	
None	33 (87%)	33 (87%)	
Type of resection			
Minor	30 (79%)	34 (90%)	0.346
Major	8 (21%)	4 (10%)	
Tumors size (cm)			
Mean±SD	5.5±3.2	5.1±3.6	0.610
Tumors number			
Mean±SD	3.3±3.8	2.5±2.5	0.282

CLM colorectal liver metastasis; *HCC* hepatocellular carcinoma; *PAT* percutaneous ablation therapy; *TACE* trans-arterial chemo-embolization
[a] Performed with the Fisher or two-tailed *T* test when appropriate

Patients

Between October 2005 and January 2007, 76 patients underwent hepatic resection at our unit and were considered eligible for this study. Among these patients, 38 were randomized to MFB and 38 to BF. Demographic, clinical, and pathological characteristics were homogenous in the two groups as described in Table 1.

Results

Overall mean resection area, Pringle time, blood loss, and rate of blood transfusion were 86.8 cm^2, 101.6 min, 494.7 ml, and 12%, respectively.

There were no statistically significant differences between the two groups in the transection time, operation time, resection area, blood transfusions, and number of ligatures. No differences were also found in the abdominal drain discharge and in their sampled bilirubin levels. No biliary fistula or septic collections after hepatectomy were seen. Tumor-free margin width was not significantly different too: in both groups, there were a significant number of patients with a 0-cm tumor-free margin (12 in the BP group versus nine in the MFB group; p=0.442). Postoperative mortality and major morbidity were nil in both groups. Thereby, there were no differences in the overall operative morbidity, which consisted of 10.5% and 13% in groups A and B, respectively. These results are reported in Table 2.

MFB costs 1,105 € per piece, and 38 pieces were used (one per patient) for a global cost of 41,990 €. Adopted BF was a multiuse piece adapted for irrigation and costs 216 €: the same instrument was used for the 38 patients operated using the BF, for a total cost of 216 €.

Table 2 also shows that there were no differences in terms of costs for the surgical theaters.

In both groups, there were no cut-edge local recurrences at a mean follow-up of 18 (median 19; range 1–31) in the BF group and 18 (median 19; range 1–31) in the MFB group.

Discussion

Three main aspects of the liver transection should be highlighted as worthy of particular care by the surgeon: skeletonization of the intrahepatic vascular structures,

Table 2 Surgical Outcomes

	Mean±SD		p[c]
	Monopolar floating ball (n=38)	Bipolar forceps (n=38)	
Resection area (cm^2)	93.9±48.3	79.8±48.4	0.208
Transection time (min)	173±61.5	185±49	0.258
Transection time per cm^2 (min)	2.1±0.6	2.3±0.3	0.070
Operation time (min)	451.5±111.2	421.6±136.8	0.299
Costs for surgical theater (€)	2519±1076	2124±708.96	0.063
Total blood loss (ml)	527.6±472	461.8±380.7	0.871
Blood transfusions	4 (10.5%)	5 (16%)	0.450
Blood loss per cm^2 (ml)	7.6±14.5	7.2±6.9	0.878
Number of ligatures per cm^2	0.7±0.4	0.7±0.3	1.000
Drains discharge (ml)	55±33	66.7±41	0.451
Drains bilirubin level (mg/dl)[a]	1.9±0.9	2.1±1.1	0.664
Tumor-free margins width (cm)	0.4±0.4	0.3±0.3	0.764
Overall operative morbidity	4 (10.5%)	5 (13%)	1.000
Major operative morbidity	0 (0%)	0 (0%)	–
Operative mortality[b]	0 (0%)	0 (0%)	–

[a] Calculated at the third, fifth, and seventh postoperative day
[b] Calculated at 30- and 90-days after surgery
[c] Performed with the Fisher or two-tailed *T* test when appropriate

hemostasis, and biliostasis. For that, the ideal division method of the liver parenchyma during hepatectomy should allow the surgeon to get an early and clear disclosure of the major vascular structures encountered during the transection to prevent their accidental damage, provide an adequate hemostasis, and prevent the occurrence of bile leaks. The clamp crushing and ligatures under warm ischemia obtained by intermittent clamping of the hepatic hilum is the mainstream technique to which any method should be compared. In fact, this technique was associated with such good results in terms of safety, which are still the standard for any reference.[10,19,20] In this sense, many are the available and proposed alternative devices, but poor are the evidences that among them there should be one to be preferred and, most importantly, which could substitute the standard of the reference technique.

Some authors aimed to analyze new devices in complete substitution of the clamp crushing and ligature techniques. Lesurtel et al.[6] made a prospective randomized study on 100 consecutive noncirrhotic and noncholestatic patients comparing four different surgical devices: the clamp crushing technique with Pringle maneuver versus CUSA versus Hydrojet versus MFB without Pringle maneuver. In this study, the authors found that the crushing technique was the most efficient device for liver resection. Arita et al.[7] recently made a randomized clinical trial studying the effect of the MFB versus the traditional clamp crushing technique focusing on blood loss. These authors failed to find any statistically significant difference between the two devices. Furthermore, Sakamoto et al.[21] reported that using the MFB in spite of the clamp crushing technique resulted in specimens with more than 5 mm of necrotized area around the transection plane. This might be a source of postoperative morbidity such as biliary fistula because of accidental injury of undisclosed bile ducts or septic collection in relation to the larger amount of necrotic tissue. Moreover, such scalded area, if close to the surgical margins, may reduce the accuracy of the pathologist to assess the status of the margins, giving to this device a disadvantage rather than an advantage in terms of margin control as reported by others.[22,23] Necrotized layer of liver parenchyma represented also the main drawback of the technique proposed by Weber et al.,[24] who introduced the blunt division of the liver parenchyma after tissue heating using radiofrequency needles. Inhomogeneous results from more recent studies reported by the same authors did not clearly rule out the impression that this technique may increase the risks of postoperative bile leakage and septic collection.[25,26] This impression is strengthened by the study of Lupo et al.,[27] who showed how the clamp crushing technique resulted in a lower rate of postoperative morbidity: in particular, the authors showed a significantly higher rate of abscesses and biliary fistula in those operated using the radiofrequency-assisted technique. Aloia et al.[23] reported in a nonrandomized setting that the combination of ultrasonic dissector with the MFB was an efficient technique for liver resection in comparison to ultrasonic dissector alone. However, considering the costs of the proposed technique, their conclusions seemed not that strong to show a clear benefit of their approach and, furthermore, that technique was referred to the use of ultrasonic dissector as standard for reference, which, inversely, was not proven to be superior to the clamp crushing method. Indeed, Takayama et al.[8] compared in a randomized study the ultrasonic dissector versus the clamp crushing technique, concluding that the ultrasonic dissector offered no significant advantages and, more importantly, that the quality of hepatic resection was superior by clamp crushing. Certainly, the literature is replete by other contradicting studies. Indeed, Aldrighetti et al.[28] compared the ultrasonic dissector with the harmonic scalpel versus the clamp crushing technique, showing statistically significant benefits of the technological approach versus the traditional approach in reducing blood loss, blood transfusions, length of hospital stay, and operative morbidity. However, the comparison was not accomplished in a randomized setting and, moreover, was referred to a historical cohort of patients operated with the crushing technique, which may have affected their results.

Contradictions among the various studies, partially explained by the methodological biases of some of them, suggest that the level of confidence of the surgical methods analyzed by the different teams may be bias per se. However, the fact that all those studies performed in a randomized fashion did not show any significant benefit for the new techniques versus the clamp crushing technique should suggest that there are no devices able to clearly substitute the traditional clamp crushing as the standard for reference while also considering its low cost.

Therefore, rather than substituting the Pean-clasia, the identification of the optimal device for hemostasis and biliostasis should be the target worthy to be achieved. In this sense, the BF represents the device most frequently utilized. However, one of the main drawbacks is the need of continually cleaning the tips of the instrument; otherwise, the instrument does not work properly. For this reason, some surgeons operate using two BFs to always have an available, clean and properly working instrument. MFB offers undoubtedly a higher coagulative power and does not need the same meticulous caring. Furthermore, if just used for thin vessel coagulation, it does not create a thickened layer of necrotic tissue, which is, as described above, a possible source of morbidity.

Therefore, we analyzed the role of MFB versus the BF only for vessel coagulation in combination with the Pean-clasia. In detail, the only aspect that was close to the

significance was the transection time, which was shorter in the group treated using the MFB (Table 2). This finding reflects the aforementioned advantage of MFB providing a stronger coagulative effect and the need for a simpler care for its functionalities than BF. On the other hand, the use of BF was associated with shorter overall operation time, which was not significant but resulted in an almost significantly higher cost for the surgical theater in the group of patients operated using the MFB. Furthermore, the BF group had a lower amount of blood loss although not significantly. Substantially, this study failed to find any significant difference between the MFB and BF among the variables considered. These results might be explained by the meticulous technique we adopted during the transection of the liver. In fact, limiting the use of both devices only for coagulation of small intrahepatic vessels (<2–3 mm), previously identified with the crushing technique by Pean-clasia, while each vessel larger than 2–3 mm was isolated, ligated, and then dissected, could have limited the disclosure of significant difference in the coagulative power of the compared devices. However, the randomization was secured from major biases, which could mask effective differences. The only drawbacks of the present study could be in the sample size, which was calculated to disclose at least 200 ml of difference in mean blood loss between the two methods. Probably, a larger number of patients may help in disclosing differences that were not apparent at the time of the study. However, considering the absence of a significant difference between the two devices herein compared, in the selection of the most proper technique, we could not neglect the cost of each device, especially in this era of cost control. In this sense, MFB, which cost us 1,105 € per disposable handpiece, a total cost of more than 40,000 €, is certainly less appealing than BF that cost just 216 €, and with one reusable instrument, it was possible to treat all the patients included in that arm. On the other hand, the cost of MFB we had was not that higher than the approximately 900 € reported by Lesurtel et al.[6]

Oncologically, the choice of a device did not influence the results, as we had no cut-edge recurrences in either group. Furthermore, the technique utilized did not influence our policy to get closer to the tumor using meticulous IOUS guidance to maximize the parenchymal sparing surgical approach;[15,16] indeed, Table 2 shows the lack of any significant difference between the two groups in terms of mean tumor-free margin width. The relatively high rate of 0-cm tumor-free margins in both groups followed an already extensively reported policy.[15,16] Indeed, in specific conditions ruled by precise classification of tumor vessel relations at IOUS, even in the presence of HCC or CLM in contact or close adjacency with intrahepatic major vessels, the vessel itself can be spared.

Conclusions

In conclusion, this study showed that the use of Pean-clasia with MFB was safe and minimized the blood loss during hepatic resection. However, its use offered no significant benefits over the standard BF technique, to justify the higher costs. Therefore, the crush clamping technique with BF confirmed to be an adequate and low-cost technique for liver dissection. Conversely, the role of MFB in liver surgery, considering also the nonunivocal results of other reports about its use in the conventionally proposed manner[6] or in association with other devices,[21,23] needs to be at least further clarified.

Acknowledgments This work was supported by a grant from the "C. Bannò Foundation for Cancer Research".

References

1. Makuuchi M, Takayama T, Gunvén P, et al. Restrictive versus liberal blood transfusion policy for hepatectomies in cirrhotic patients. World J Surg. 1989;13:644–648. doi:10.1007/BF01658893.
2. Okano T, Ohwada S, Nakasone Y, et al. Blood transfusion causes deterioration in liver regeneration after partial hepatectomy in rats. J Surg Res. 2001;101:157–165. doi:10.1006/jsre.2001.6284.
3. Kooby DA, Stockman J, Ben-Porat L, et al. Influence of transfusions on perioperative and long-term outcome in patients following hepatic resection for colorectal metastases. Ann Surg. 2003;237:860–869. doi:10.1097/00000658-200306000-00015.
4. Torzilli G, Gambetti A, Del Fabbro D, et al. Techniques for hepatectomies without blood transfusion, focusing on interpretation of postoperative anemia. Arch Surg. 2004;139:1061–1065. doi:10.1001/archsurg.139.10.1061.
5. Ibrahim S, Chen CL, Lin CC, et al. Intraoperative blood loss is a risk factor for complications in donors after living donor hepatectomy. Liver Transpl. 2006;12:950–957. doi:10.1002/lt.20746.
6. Lesurtel M, Selzner M, Petrowsky H, et al. How should transection of the liver be performed? A prospective randomized study in 100 consecutive patients comparing four different transection strategies. Ann Surg. 2005;242:814–822. doi:10.1097/01.sla.0000189121. 35617.d7.
7. Arita J, Hasegawa K, Kokudo N. Randomized clinical trial of the effect of a saline-linked radiofrequency coagulator on blood loss during hepatic resection. Br J Surg. 2005;92:954–959. doi:10.1002/bjs.5108.
8. Takayama T, Makuuchi M, Kubota K, et al. Randomized comparison of ultrasonic vs clamp transection of the liver. Arch Surg. 2001;136:922–928. doi:10.1001/archsurg.136.8.922.
9. Terminology Committee of the IHPBA. Terminology of liver anatomy and resections. HPB Surg. 2000;2:333–339.
10. Torzilli G, Makuuchi M, Inoue K, et al. No-mortality liver resection for hepatocellular carcinoma in cirrhotic and noncirrhotic patients: is there a way? A prospective analysis of our approach. Arch Surg. 1999;134:984–992. doi:10.1001/archsurg.134.9.984.
11. Torzilli G, Donadon M, Marconi M, et al. Hepatectomy for hepatocellular carcinoma in stage B and C of BCLC classification: a prospective analysis of our approach. Arch Surg. in press.
12. Donadon M, Torzilli G. Surgical treatment of liver metastases from colorectal carcinoma. Minerva Chir. 2007;62:257–267.

13. Torzilli G, Palmisano A, Del Fabbro D, et al. Contrast-enhanced intraoperative ultrasonography during surgery for hepatocellular carcinoma in liver cirrhosis: is it useful or useless? A prospective cohort study of our experience. Ann Surg Oncol. 2007;14:1347–1355. doi:10.1245/s10434-006-9278-3.
14. Torzilli G, Del Fabbro D, Palmisano A, et al. Contrast-enhanced intraoperative ultrasonography during hepatectomies for colorectal cancer liver metastases. J Gastrointest Surg. 2005;9:1148–1153. doi:10.1016/j.gassur.2005.08.016.
15. Torzilli G, Montorsi M, Donadon M, et al. "Radical but conservative" is the main goal for ultrasonography-guided liver resection: prospective validation of this approach. J Am Coll Surg. 2005;201:517–528. doi:10.1016/j.jamcollsurg.2005.04.026.
16. Torzilli G, Montorsi M, Del Fabbro D, et al. Ultrasonographically-guided surgical approach to liver tumours involving the hepatic veins close to the caval confluence. Br J Surg. 2006;93:1238–1246. doi:10.1002/bjs.5321.
17. Ijichi M, Takayama T, Toyoda H, et al. Randomized trial of the usefulness of a bile leakage test during hepatic resection. Arch Surg. 2000;135:1395–1400. doi:10.1001/archsurg.135.12.1395.
18. Torzilli G, Olivari N, Del Fabbro D, et al. Bilirubin level fluctuation in drain discharge after hepatectomies justifies long-term drain maintenance. Hepatogastroenterology. 2005;52:1206–1210.
19. Miyagawa M, Makuuchi M, Kawasaki S, et al. Criteria for safe hepatic resection. Am J Surg. 1995;169:589–594. doi:10.1016/S0002-9610(99)80227-X.
20. Imamura H, Seyama Y, Kokudo N, et al. One thousand fifty-six hepatectomies without mortality in 8 years. Arch Surg. 2003;138:1198–1206. doi:10.1001/archsurg.138.11.1198.
21. Sakamoto Y, Yamamoto J, Kokudo N, et al. Bloodless liver resection using the monopolar floating ball plus ligasure diathermy: preliminary results of 16 liver resections. World J Surg. 2004;28:166–172. doi:10.1007/s00268-003-7167-5.
22. Topp SA, McClurken M, Lipson D, et al. Saline-linked surface radiofrequency ablation: factors affecting steam popping and depth of injury in the pig liver. Ann Surg. 2004;239:518–527. doi:10.1097/01.sla.0000118927.83650.a4.
23. Aloia TA, Zorzi D, Abdalla EK, et al. Two-surgeon technique for hepatic parenchymal transection of the noncirrhotic liver using saline-linked cautery and ultrasonic dissection. Ann Surg. 2005;242:172–177. doi:10.1097/01.sla.0000171300.62318.f4.
24. Weber JC, Navarra G, Jiao LR, et al. New technique for liver resection using heat coagulative necrosis. Ann Surg. 2002;236:560–563. doi:10.1097/00000658-200211000-00004.
25. Ayav A, Jiao L, Dickinson R, et al. Liver resection with a new multiprobe bipolar radiofrequency device. Arch Surg. 2008;143:396–401. doi:10.1001/archsurg.143.4.396.
26. Ayav A, Bachellier P, Habib NA, et al. Impact of radiofrequency assisted hepatectomy for reduction of transfusion requirements. Am J Surg. 2007;193:143–148. doi:10.1016/j.amjsurg.2006.04.008.
27. Lupo L, Gallerani A, Panzera P, et al. Randomized clinical trial of radiofrequency-assisted versus clamp-crushing liver resection. Br J Surg. 2007;94:287–291.
28. Aldrighetti L, Pulitanò C, Arru M, et al. "Technological" approach versus clamp crushing technique for hepatic parenchymal transection: a comparative study. J Gastrointest Surg. 2006;10:974–979. doi:10.1016/j.gassur.2006.02.002.

J Gastrointest Surg (2008) 12:1967–1972
DOI 10.1007/s11605-008-0622-8

Resection Versus Laparoscopic Radiofrequency Thermal Ablation Of Solitary Colorectal Liver Metastasis

Eren Berber · Michael Tsinberg · Gurkan Tellioglu · Conrad H. Simpfendorfer · Allan E. Siperstein

Received: 27 May 2008 / Accepted: 15 July 2008 / Published online: 8 August 2008

Abstract
Purpose There is scant data in the literature regarding radiofrequency thermal ablation (RFA) versus resection of colorectal liver metastases. The aim of this study is to compare the clinical profile and survival of patients with solitary colorectal liver metastasis undergoing resection versus laparoscopic RFA.
Methods Between 1996 and 2007, 158 patients underwent RFA (n=68) and open liver resection (n=90) of solitary liver metastasis from colorectal cancer. Patients were evaluated in a multidisciplinary fashion and allocated to a treatment type. Data were collected prospectively for the RFA patients and retrospectively for the resection patients.
Results Although the groups were matched for age, gender, chemotherapy exposure and tumor size, RFA patients tended to have a higher ASA score and presence of extra-hepatic disease (EHD) at the time of treatment. The main indication for referral to RFA included technical reasons (n=25), patient comorbidities (n=24), extra-hepatic disease (n=10) and patient decision (n=9). There were no peri-operative mortalities in either group. The complication rate was 2.9% (n=2) for RFA and 31.1% (n=28) for resection. The overall Kaplan–Meier median actuarial survival from the date of surgery was 24 months for RFA patients with EHD, 34 months for RFA patients without EHD and 57 months for resection patients (p<0.0001). The 5-year actual survival was 30% for RFA patients and 40% for resection patients (p=0.35).
Conclusions This study shows that, although patients in both groups had a solitary liver metastasis, other factors including medical comorbidities, technically challenging tumor locations and extra-hepatic disease were different, prompting selection of therapy. With a simultaneous ablation program, higher risk patients have been channeled to RFA, leaving a highly selected group of patients for resection with a very favorable survival. RFA still achieved long-term survival in patients who were otherwise not candidates for resection.

Keywords Colorectal cancer · Liver metastasis · Radiofrequency ablation · Laparoscopic

E. Berber · M. Tsinberg · G. Tellioglu · C. H. Simpfendorfer · A. E. Siperstein
Department of General Surgery, Cleveland Clinic, Cleveland, OH, USA

E. Berber (✉)
9500 Euclid Avenue/A 80,
Cleveland, OH 44195, USA
e-mail: berbere@ccf.org

Introduction

Liver resection is the treatment of choice with the best chance for long-term cure in patients with colorectal liver metastases.[1–4] Radiofrequency ablation (RFA) is a newer modality introduced in late 1990s. With accumulating data and experience, it has established its role in the treatment algorithm of patients with unresectable colorectal liver metastases as a minimally invasive modality with low morbidity and short hospital stay.[5–7] However, it is unknown if RFA is equivalent to liver resection regarding survival in patients with resectable liver disease. The data in the literature is scant.[1,2,3,8–11]

Our group offers a multimodality treatment to patients with colorectal liver metastasis with adjunctive laparoscopic RFA and resection programs. In the present study, our aim was to compare the clinical and oncological profiles and survival of patients with solitary liver metastasis who were channeled to RFA versus liver resection at a single institution.

Methods

Between December 1996 and February 2008, 68 patients underwent RFA and 90 patients resection of solitary liver metastasis from colorectal cancer. These patients were registered in an IRB-approved database. All RFA patients were followed under a protocol with quarterly liver CT scans and blood work including CEA levels at the Cleveland Clinic. The follow up for the resection patients were less uniform as most of these patients were followed up by referring oncologists. Therefore, data for the RFA patients was entered to the database in a prospective manner while the data for the resection patients were collected retrospectively from the medical records. Additional follow up regarding deaths was acquired using the Social Security Death Index and letters to referring physicians. Median follow up was 23 months (mean 27, range 2–86 months) for RFA and 33 months (mean 41, range 2–132 months) for the resection group. Kaplan–Meier curves were used to determine survival and the logrank test was used for comparison between groups. Multivariate analysis was performed using the Cox Proportional Hazards Model. A p level <0.05 was accepted for statistical significance.

A potential statistical error when interpreting the survival numbers of the current study could arise when only the Kaplan–Meier actuarial survival estimates are taken into account, as the two groups have different lengths of median follow up. In order to prevent this error, the actual 3- and 5-year survival numbers were calculated by including those patients who were at least 3 or 5 years out, respectively, from their liver procedures at the time of this analysis. All data are expressed as mean±SEM

Results

Although the groups were matched for age, gender, chemotherapy exposure, and tumor size, RFA patients tended to have a higher ASA score and presence of extra-hepatic disease (EHD) at the time of treatment (Table 1). extra-hepatic disease included limited amounts of pulmonary metastases, and/or periportal lymphadenopathy in most patients. One patient had small bowel metastasis that was resected after the RFA procedure.

The main indication for referral to RFA included technical factors (n=25), patient comorbidities (n=24), extra-hepatic disease (n=10) and patient decision (n=9). The technical factors included various combinations of the presence of fatty liver risking adequate remnant liver function, obesity, vessel (inferior vena cava) contiguity, concomitant colorectal resection precluding a major liver resection at the same time, religious factors against blood transfusion rendering a major liver resection risky, and multiple prior lesions responding to chemotherapy with a high risk for recurrent liver disease after resection (Fig. 1). Mean operative time was 118.3±8.4 min for the RFA and 199±7.3 min for the resection group (p<0.0001). Mean length of hospitalization was 1.3±0.3 days for the RFA group and 6.8±0.3 days for the resection group (p< 0.0001). The complication rate was 2.9% (n=2) for RFA and 31.1% (n=28) for resection. Complications in the RFA group included urinary retention and nausea requiring readmission in one patient each. The complications in the resection group included pulmonary (n=7), wound infection (n=5), bile leak (4), ileus (n=4), cardiac (n=3), colitis (n=2), pancreatitis (n=1), urinary retention (n=1), and post-operative hemorrhage (n=1).

The overall Kaplan–Meier median actuarial survival from the date of surgery was 24 months for RFA patients

Table 1 Clinical Profile of Patients in the RFA (n=68) and Resection (n=90) Groups

	RFA	Resection	p
Gender	43 men (63%) 25 women (37%)	57 men (63%) 33 women (37%)	NS
Age	67±1.4 years	63.7±1.3 years	0.08
Tumor size	3.7±0.2 cm	3.8±0.2 cm	0.9
ASA score	1–2 23 patients (34%) 3–4 45 patients (66%)	1–2 47 patients (52%) 3–4 43 patients (48%)	0.003
Preoperative extra-hepatic disease	26 patients	0 patients	<0.0001
Preoperative chemotherapy	56 (82%)	63 (72%)	0.6
Type of metastasis	Synchronous 5 Metachronous 63	Synchronous 15 Metachronous 75	

ASA American Society of Anesthesiologists score

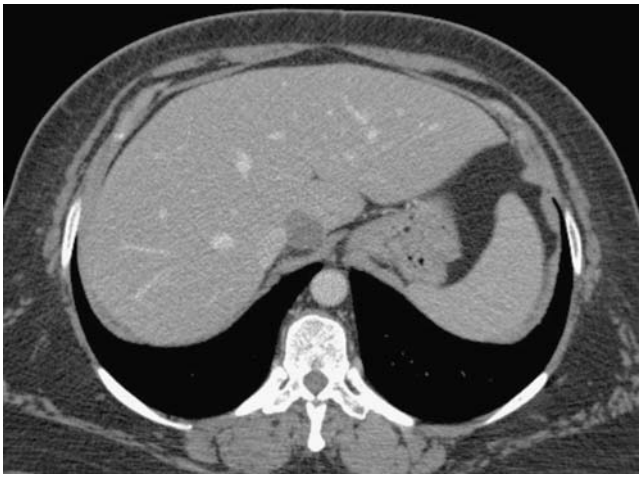

Figure 1 CT scan of a patient who was initially channeled to the RFA arm of the study due to obesity, and challenging tumor location at the caudate lobe and around the inferior vena cava. After RFA, the patient developed local recurrence at 6 months and then underwent left hepatectomy, caudate lobe resection, and resection and reconstruction of the inferior vena cava with a tubular graft.

with EHD, 34 months for RFA patients without EHD and 57 months for resection patients ($p<0.0001$; Fig. 2). Three-year actual survival rates were 26%, 35% and 70%, for RFA with EHD, RFA without EHD, and resection groups, respectively. Median Kaplan–Meier actuarial survival after diagnosis of liver metastasis was 33 months for RFA with EHD ($n=26$), 40 months for RFA without EHD ($n=42$), and 59 months for resection ($n=90$; $p=0.005$; Fig. 3). After excluding RFA patients with EHD, the Kaplan–Meier actuarial median disease-free survival was 9 months for the RFA group ($n=42$) and 30 months for the resection group ($p<0.0001$; Fig. 4). ASA I–II patients without EHD had the best prognosis in the RFA group, as the median

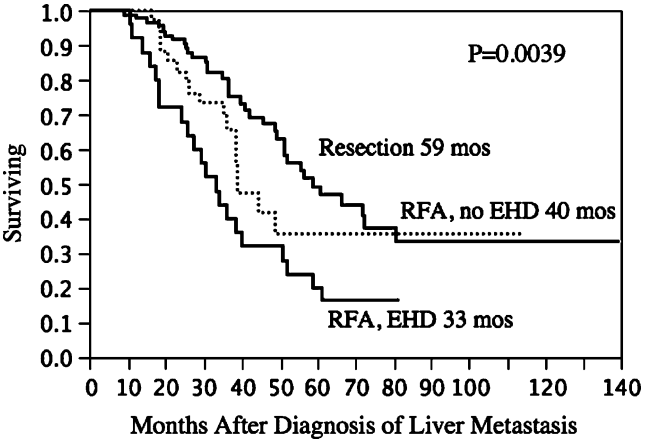

Figure 3 Kaplan–Meier survival curves after diagnosis of liver metastasis. Median survival after diagnosis of liver metastasis was 33 months for RFA with EHD, 40 months for RFA without EHD, and 59 months for resection ($p=0.005$).

survival of these patients ($n=11$) was 49 months after diagnosis of liver metastasis versus 59 months of the similar patients in the resection group ($n=26$; $p=0.9$; Fig. 5).

The 5-year actual survival, obtained by including only those patients operated on prior to April 2003, was 30% for RFA patients ($n=27$) and 40% for resection patients ($n=30$; $p=0.35$; Fig. 6).

Four patients in the resection group subsequently underwent laparoscopic RFA and three patients in the RFA group liver resection for recurrent liver disease in follow up.

Forty-nine percent of patients in the RFA group developed extra-hepatic disease, 16% had local liver recurrence and 57% had new liver recurrence in follow up. In the resection group, 30% developed extra-hepatic disease, 2% local liver recurrence and 24% new liver

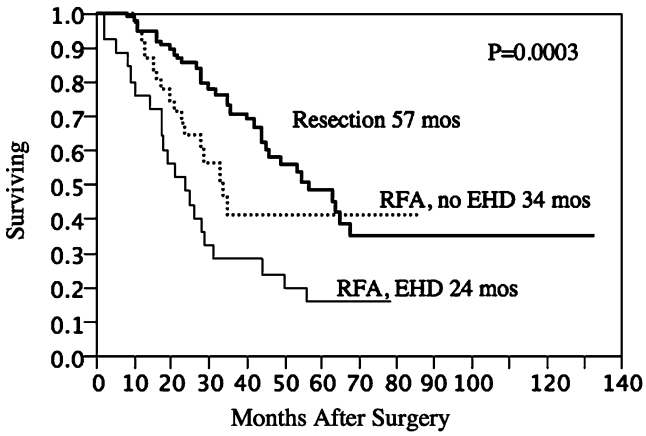

Figure 2 Kaplan–Meier survival curves after date of surgical treatment for liver metastasis. The overall Kaplan–Meier median survival was 24 months for RFA patients with EHD, 34 months for RFA patients without EHD and 57 months for resection patients ($p<0.0001$).

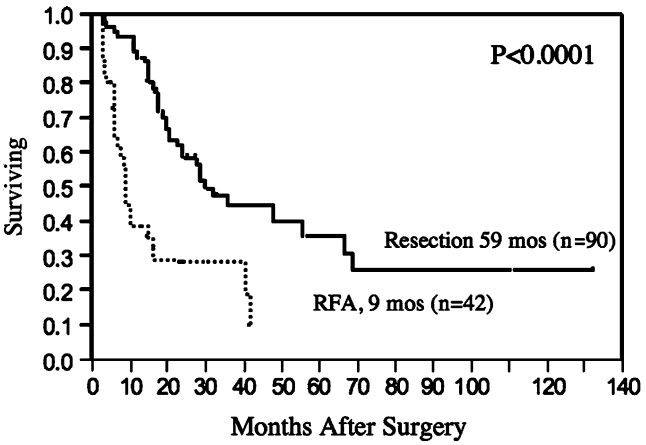

Figure 4 Disease-free survival after excluding RFA patients with EHD. The Kaplan–Meier median disease-free survival was 9 months for the RFA group ($n=42$) and 30 months for the resection group.

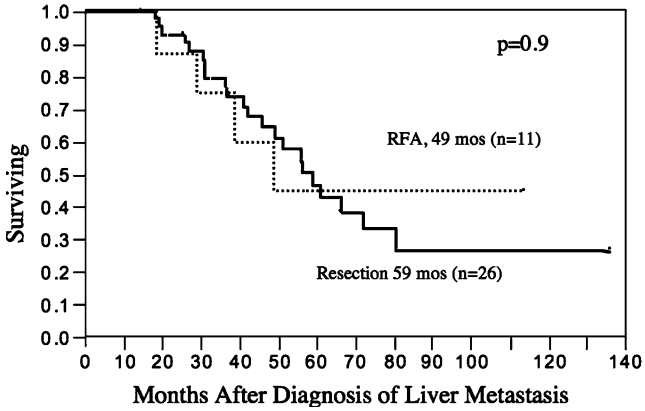

Figure 5 Kaplan–Meier survival comparing ASA I–II patients without EHD undergoing RFA versus resection. These patients were the subgroup with the best prognosis in the RFA group, as the median survival of these patients (n=11) was 49 months after diagnosis of liver metastasis versus 59 months of the similar patients in the resection group (n=26; p=0.9).

recurrence in follow up. Cause of death was known in 21 patients in the RFA group and in 24 patients in the resection group. In the RFA group, death was due to progression of liver metastasis in 29%, extra-hepatic disease in 27%, and unknown in 44% patients. In the resection group, death was due to liver disease progression in 26%, extra-hepatic disease in 42% progression, and unknown in 32%.

In the RFA group, repeat RFA was performed in three patients and liver resection in three patients for local recurrence in follow up. In five other patients with local recurrence after RFA, neither RFA nor resection was performed due to multifocal liver recurrence and/or progression of extra-hepatic disease.

On multivariate analysis, the independent factor affecting survival was tumor size. The presence of extra-hepatic disease approached statistical significance (p=0.06; Table 2). Treatment type was not an independent predictor of survival.

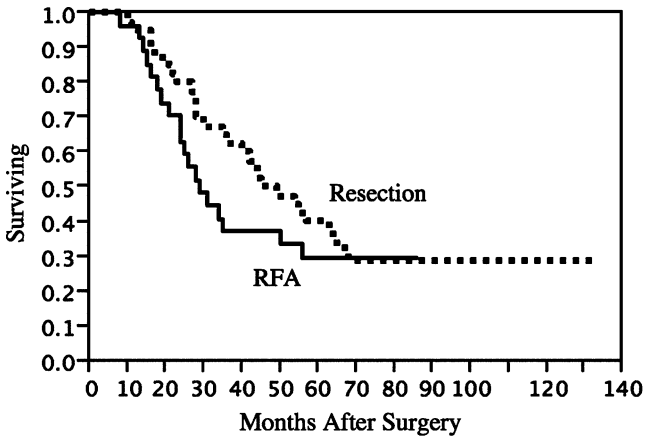

Figure 6 Kaplan–Meier survival curves of those patients who underwent their liver procedure before April 2003 (RFA 27, resection 30 patients), revealing an actual 5-year survival of 30% for RFA and 40% for resection.

Discussion

Over the last decade, RFA has been incorporated into the treatment of patients with unresectable colorectal liver metastases. These patients form the largest pool of patients with colorectal liver metastases. Despite the advances in systemic chemotherapy, persistence of liver involvement has made regional therapies an indispensable option for these patients. This need was initially fulfilled using cryotherapy, but RFA has replaced cryotherapy due to its better patient tolerance and tumor control with a lower morbidity. With local tumor rates below 30%,[12–15] studies have also suggested increased survival compared to chemotherapy patients alone.[16–18] In the largest study to-date, the 5-year actuarial survival of patients with unresectable liver disease who have failed chemotherapy was 18.4%; whereas, there are no long-term survivors in patients who have undergone salvage chemotherapy.[16]

The success of RFA in this setting has led to the question of whether it can be used in patients who have resectable liver metastases. Unfortunately, there has been no randomized or prospective comparison study to answer this question, but there are a number of retrospective studies in the literature. Only one of these studies[8] showed equivalent median (41 vs 37 months) and 3-year survival rates (55.4% vs 52.6%) between resection and RFA groups, whereas the others reported better 5-year (71% vs 27%)[3] and overall median survival (56 vs 36 months),[2,10] as well as disease-free survival (15 vs 8 months)[10] for resection versus RFA. In these studies, indications for RFA included extra-hepatic disease,[8] vessel contiguity,[8] comorbidities,[3,8,10] and inadequate liver remnant after resection.[3] RFA patients also were more likely to have undergone prior liver resection and higher serum CEA levels.[2] In summary, despite the intent,

Table 2 Cox Proportional Hazards Model Identified Tumor Size as an Independent Predictor of Poor Survival

Parameter	Hazard ratio	95% Confidence interval	p
Age	1.01	0.99–1.04	0.2163
RFA vs resection	1.24	0.91–1.66	0.1603
Preop EHD vs no EHD	1.35	0.98–1.88	0.0650
Tumor >3 cm vs <3 cm	1.60	1.21–2.21	0.0008
ASA III–IV vs I–II	0.97	0.76–1.24	0.7775

Preoperative EHD approached significance

these studies have compared apples with oranges. The RFA patients in these studies were more likely to have extra-hepatic disease, higher tumor burden evidenced by higher CEA levels, and more comorbidities. Moreover, most of these studies compared resection to percutaneous RFA,[2,10] which is known to have higher local recurrence rates compared to open or laparoscopic RFA and also an inherent weakness of understaging the tumor since the abdominal cavity would not be explored. Another issue is related to the technique of ablation as some of these studies used 3-cm ablation catheters which require overlapping cycles for larger tumors, increasing the risk of local recurrence. In addition, the follow-up protocol was not uniform and clear in most of these studies. Finally, the cause of death as due to progression of liver versus extra-hepatic disease or comorbities was not analyzed. Our study, by retrospective design, suffers from some of these limitations as well.

RFA via laparoscopic, open or percutaneous methods is a much easier procedure compared to liver resection. In addition, there is a striking difference regarding patient tolerance and morbidity compared to open liver resection. Therefore, there is a danger that it may be over-utilized when performed outside a protocol. In our program, we are strictly adhering to IRB-approved criteria when selecting unresectable patients for RFA. It is important to follow these patients under a protocol with liver CT scans every 3 months for the first 2 years. By doing so, we were able to identify recurrent disease early to provide additional treatment.

In accordance with the literature, our study confirms the difference in patient profile with the RFA patients having more comorbidities, higher likelihood for extra-hepatic disease, and presenting with more challenging tumors due to technical factors despite both groups having a solitary liver metastasis. Therefore, the patients in the resection group had a better disease-free and overall survival, similar to other reports.[3,10] Nevertheless, this was not related to the type of procedure in a given patient, as in the multivariate analysis RFA was not a predictor of poor survival, but larger tumor size and extra-hepatic disease were. In fact, healthier patients (ASA I–II) without extra-hepatic disease undergoing RFA had a similar overall survival compared to those undergoing resection, though limited by small sample size. Moreover, the difference between RFA and resections groups decreased when actual 5-year overall survival rates were calculated.

We did not find the presence of extra-hepatic disease to affect survival in our previous analyses of all patients with unresectable colorectal liver metastases undergoing laparoscopic RFA,[16,17] but in the current study demonstrated that in patients with a limited amount of liver involvement, the presence of extra-hepatic disease is a predictor of poor survival.

There are limitations of this study due to its retrospective nature. There was a difference in data collection and uniformity of follow up between the two groups. Since most of the resection patients were followed without a uniform protocol outside our institution, it was not possible to do a detailed analysis regarding the patterns of recurrence and cause of death between the study groups. The relevant question to ask when critically assessing RFA is what the patterns of recurrence were in patients undergoing this treatment and whether local recurrence was a significant issue to play a role in the decreased survival of these patients compared to the resection patients. About half of the RFA patients developed new extra-hepatic disease and three-fourths recurrent liver disease (mostly new) in follow up. Local recurrence was present in 16%. On the other hand, one-third of the resection patients developed new liver disease and another one-third extra-hepatic disease in follow up. These differences in recurrence patterns suggest a more aggressive and larger tumor burden in RFA patients.

A common scenario for a technical indication for laparoscopic RFA was concomitant colorectal resection of the primary in this study. In these cases, a major liver resection might not be possible at the same setting. We previously reported on the safety of performing concomitant RFA in 16 patients.[19] The performance of RFA in this scenario does not preclude those patients from getting a liver resection after a period of chemotherapy. Livraghi[20] reported that when the "test-of-time" approach was used to perform RFA in 88 patients with resectable colorectal liver metastases, RFA decreased the number of resections performed by providing complete tumor necrosis in some patients and an interval for others who ultimately developed new intrahepatic and/or extra-hepatic metastases to do so.

In conclusion, this study underscores the fact that there are no data in the literature to objectively comment if RFA is equivalent to liver resection in patients with resectable liver disease since patients are not comparable regarding their clinical and oncological profiles. Since sicker patients with more aggressive tumors are included in the RFA series, their survival was shown to be inferior to the resection series. Our study shows that the difference might diminish for patients with less comorbidities without extra-hepatic disease, although it was not powered for this analysis. This has two implications: the first is that a randomized study could be possible by including patients with small (<3 cm) solitary colorectal liver metastasis between a resection or RFA arm. The second is that, until those data are available, RFA and resection should be used in adjunction to each other and not as a replacement for each other. The patients with resectable disease should be offered resection while RFA is reserved for unresectable cases. With a simultaneous RFA and resection program, high-risk patients were

channeled to RFA, resulting in a group of patients enjoying a very favorable long-term survival after resection, whereas a lower long-term survival was still achieved in sicker patients with more aggressive tumors. Moreover, each modality was also used to salvage patients who developed recurrent liver disease after treatment with the other modality in the past.

References

1. Abdalla EK, Vauthey JN, Ellis LM, Ellis V, Pollock R, Broglio KR, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg 2004;239:818–825. discussion 825–7doi:10.1097/01.sla.0000128305.90650.71.
2. White RR, Avital I, Sofocleous CT, Brown KT, Brody LA, Covey A, et al. Rates and patterns of recurrence for percutaneous radiofrequency ablation and open wedge resection for solitary colorectal liver metastasis. J Gastrointest Surg 2007;11:256–263. doi:10.1007/s11605-007-0100-8.
3. Aloia TA, Vauthey JN, Loyer EM, Ribero D, Pawlik TM, Wei SH, Curley SA, Zorzi D, Abdalla EK. Solitary colorectal liver metastasis: resection determines outcome. Arch Surg 2006;141: 460–466. discussion 466–7.
4. Belghiti J, Hiramatsu K, Benoist S, Massault P, Sauvanet A, Farges O. Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. J Am Coll Surg 2000;191:38–46. doi:10.1016/S1072-7515(00)00261-1.
5. Berber E, Rogers S, Siperstein A. Predictors of survival after laparoscopic radiofrequency thermal ablation of hepatocellular cancer: a prospective study. Surg Endosc 2005;19(5):710–714. doi:10.1007/s00464-004-8815-z.
6. Machi J, Oishi AJ, Sumida K, Sakamato K, Furumoto NL, Oishi RH, et al. Long-term outcome of radiofrequency ablation for unresectable liver metastases from colorectal cancer: evaluation of prognostic factors and effectiveness in first- and second-line management. Cancer J 2006;12:318–326. doi:10.1097/00130404-200607000-00011.
7. Amersi FF, McElrath-Garza A, Ahmad A, Zogakis T, Allegra DP, Krasne R, et al. Long-term survival after radiofrequency ablation of complex unresectable liver tumors. Arch Surg 2006;141:318–326.
8. Oshowo A, Gillams A, Harrison E, Lees WR, Taylor I. Comparison of resection and radiofrequency ablation for treatment of solitary colorectal liver metastases. Br J Surg 2003;90:1240–1243. doi:10.1002/bjs.4264.
9. Mulier S, Ni Y, Jamart J, Ruers T, Marchal G, Michel L. Local recurrence after hepatic radiofrequency coagulation: multivariate meta-analysis and review of contributing factors. Ann Surg 2005;242(2):158–171. doi:10.1097/01.sla.0000171032.99149.fe.
10. Park IJ, Kim HC, Yu CS, Kim PN, Won HJ, Kim JC. Radiofrequency ablation for metachronous liver metastasis from colorectal cancer after curative surgery. Ann Surg Oncol 2007;15:227–232.
11. Mulier S, Ni Y, Jamart J, Michel L, Marchal G, Ruers T. Radiofrequency ablation versus resection for resectable colorectal liver metastases: time for a randomized trial? Ann Surg Oncol 2008;15:144–157. Epub 2007 Sep 29.
12. Curley SA, Izzo F, Ellis LM, Nicolas Vauthey J, Vallone P. Radiofrequency ablation of hepatocellular cancer in 110 patients with cirrhosis. Ann Surg 2000;232:381–391.
13. Wood TF, Rose DM, Chung M, Allegra DP, Foshag LJ, Bilchik AJ. Radiofrequency ablation of 231 unresectable hepatic tumors: indications, limitations, and complications. Ann Surg Oncol 2000;7:593–600.
14. Curley SA, Izzo F, Delrio P, Ellis LM, Granchi J, Vallone P, Fiore F, Pignata S, Daniele B, Cremona F. Radiofrequency ablation of unresectable primary and metastatic hepatic malignancies: results in 123 patients. Ann Surg 1999;230:1–8.
15. Siperstein A, Garland A, Engle K, Rogers S, Berber E, Foroutani A, String A, Ryan T, Ituarte P. Local recurrence after laparoscopic radiofrequency thermal ablation of hepatic tumors. Ann Surg Oncol 2000;7:106–113.
16. Siperstein AE, Berber E, Ballem N, Parikh RT. Survival after radiofrequency ablation of colorectal liver metastases: 10-year experience. Ann Surg 2007;246:559–565. discussion 565–7.
17. Berber E, Pelley R, Siperstein AE. Predictors of survival after radiofrequency thermal ablation of colorectal cancer metastases to the liver: a prospective study. J Clin Oncol 2005;23:1358–1364.
18. Machi J, Oishi AJ, Sumida K, Sakamoto K, Furumoto NL, Oishi RH, Kylstra JW. Long-term outcome of radiofrequency ablation for unresectable liver metastases from colorectal cancer: evaluation of prognostic factors and effectiveness in first- and second-line management. Cancer J 2006;12:318–326.
19. Berber E, Senagore A, Remzi F, Rogers S, Herceg N, Casto K, Siperstein A. Laparoscopic radiofrequency ablation of liver tumors combined with colorectal procedures. Surg Laparosc Endosc Percutan Tech 2004;14:186–190..
20. Livraghi T, Solbiati L, Meloni F, Ierace T, Goldberg SN, Gazelle GS. Percutaneous radiofrequency ablation of liver metastases in potential candidates for resection: the “test-of-time approach”. Cancer 2003;97:3027–3035.

J Gastrointest Surg (2008) 12:1973–1980
DOI 10.1007/s11605-008-0624-6

Management of Preoperatively Suspected Choledocholithiasis: A Decision Analysis

Bilal Kharbutli · Vic Velanovich

Received: 19 June 2008 / Accepted: 15 July 2008 / Published online: 6 August 2008

Abstract
Background The management of symptomatic or incidentally discovered common bile duct (CBD) stones is still controversial. Of patients undergoing elective cholecystectomy for symptomatic cholelithiasis, 5–15% will also harbor CBD stones, and those with symptoms suggestive of choledocholithiasis will have an even higher incidence. Options for treatment include preoperative endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy (ERCP/ES) followed by laparoscopic cholecystectomy, laparoscopic cholecystectomy with intraoperative cholangiogram (LC/IOC), followed by either laparoscopic common bile duct exploration (LCBDE) or placement of a common bile duct double-lumen catheter with postoperative management. The purpose of this analysis was to determine the optimal management of such patients.
Methods A decision analysis was performed to analyze the management of patients with suspected common bile duct stones. The basic choice was between preoperative ERCP/ES followed by LC, LC/IOC followed by LCBDE, or common duct double-lumen catheter (Fitzgibbons tube) placement with either expectant management or postoperative ERCP/ES. Data on morbidity and mortality was obtained from the literature. Sensitivity analysis was done varying the incidence of positive CBD stones on IOC with associated morbidity and mortality.
Results One-stage management of symptomatic CBD stones with LC/LCBDE is associated with less morbidity and mortality (7% and 0.19%) than two-stage management utilizing preoperative ERCP/ES (13.5% and 0.5%). Sensitivity analysis shows that there is an increase in morbidity and mortality for LC/LCBDE as the incidence of positive IOC increases but are still less than two-stage management even with a 100% positive IOC (9.4%, 0.5%). If a double-lumen catheter is to be used for positive IOC, the morbidity would be higher than two-stage management only if the positive IOC incidence is more than 65% but still with no mortality.
Conclusion LCBDE has lower morbidity and mortality rates compared to preoperative ERCP/ES in the management of patients with suspected CBD stones even if the chance of CBD stones reaches 100%. Using a common duct double-lumen catheter may be considered if LCBDE is not feasible and the chance of CBD stone is less than 65%.

Keywords Choledocholithiasis · Laparoscopic cholecystectomy · Intraoperative cholangiography · Common bile duct exploration · Endoscopic retrograde cholangiopancreatiography · Decision analysis

Presented in part at the 49th Annual Meeting of the Society for Surgery of the Alimentary Tract [Poster Session], San Diego, CA, May 17–21, 2008

B. Kharbutli · V. Velanovich (✉)
Division of General Surgery, K-8, Henry Ford Hospital,
2799 West Grand Blvd.,
Detroit, MI 48202, USA
e-mail: vvelano1@hfhs.org

The controversy on the optimal management of symptomatic or suspected common bile duct stone continues. The incidence of common bile duct (CBD) stones varies depending on patients' presentations (obstructive jaundice, gallstone pancreatitis, cholangitis, or biliary colic only) and laboratory and imaging studies. The incidence of CBD stones in patients undergoing elective cholecystectomy is 5–15%,[1–5] while it is higher and more variable in patients with suspected CBD stones on ultrasonography or with abnormal laboratory findings.[6–9] Under these circumstances, some studies report a positive cholangiography incidence of 94%.[6,10]

The main options for management were either a two-stage approach with preoperative endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (ES) followed by laparoscopic cholecystectomy (LC) or one-stage approach with laparoscopic cholecystectomy with laparoscopic common bile duct exploration (LC/LCBDE).[1,3,4,7,11–13] There have been many studies reporting success rates, morbidity, mortality, length of stay, and cost for each of these management options.[1,3–5,7,8,10–26] The purpose of this study was to use decision analysis to determine the optimal management of patients harboring suspected common bile duct stones.

Methods

Decision Analysis Decision analysis is a method to order all the relevant factors involved in a clinical decision.[27] The mechanics and theory of decision analysis have been described in detail elsewhere. Briefly, any clinical problem is amenable to decision analysis once it is appropriately identified and bound. Starting with a problem in need of a decision, a decision tree is constructed consisting of choice nodes and chance nodes. A choice node is where the decision-maker must make a decision, such as to observe or operate. A chance node is the possible outcomes of that decision, for example, the patient recovers uneventfully or has a complication. By convention, choice nodes are represented as squares, while chance nodes are represented as circles; and the decision tree is written left to right (Fig. 1).

This decision analysis attempts to address the problem of the patient with suspected choledocholithiasis. This includes patients who are asymptomatic, undergoing elective cholecystectomy, and patients with recent episodes of jaundice or gallstone pancreatitis. The basic decision includes one of two

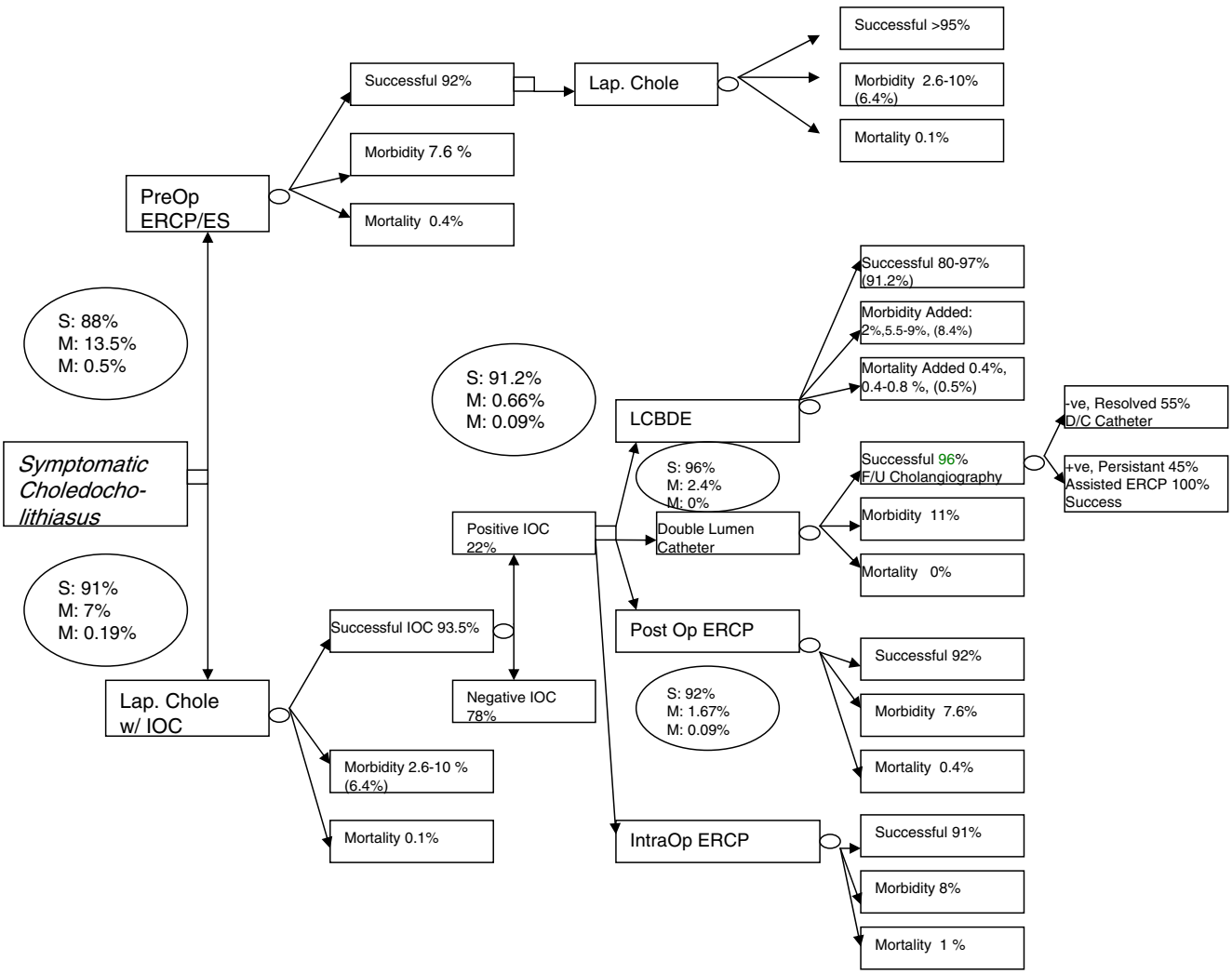

Figure 1 Decision tree for treatment of choledocholithiasis.

choices: (1) laparoscopic cholecystectomy with intraoperative cholangiogram, then address choledocholithiasis if found, or (2) preoperative ERCP to diagnosis and remove choledocholithiasis, followed by laparoscopic cholecystectomy. For choice (1), four additional choices are possible for a positive intraoperative cholangiogram (IOC): (1) laparoscopic common bile duct exploration, (2) Placement of a double-lumen Fitzgibbons tube, (3) postoperative ERCP, and (4) intraoperative ERCP (Fig. 1). The possible outcomes and the probabilities of these outcomes were obtained from the literature.[1,3–8,11–23,25,26,28–32]

Sensitivity Analysis As there are ranges of probabilities of postoperative events occurring, sensitivity analysis is the process of varying the chances of different outcomes occurring in order to determine the effects of different probabilities on the decision. For this decision analysis, we varied the incidence of common bile duct stones. We also performed sensitivity analysis based on morbidity and mortality rates of LC/LCBDE.

Decision Tree The basic decision in a patient with suspected choledocholithiasis is immediate laparoscopic cholecystectomy with intraoperative cholangiogram versus preoperative ERCP followed by laparoscopic cholecystectomy. The choices when an IOC confirms the diagnosis of common bile duct stones include LCBDE, placement of a double-lumen biliary stent (Fitzgibbons tube), or postoperative ERCP (Fig. 1). An assumption is made that the stones will require extraction by some method. CBD stones which are so small that the surgeon can be confident that they will pass without intervention will not be considered in the decision analysis.

Outcome Probabilities Preoperative ERCP/ES for CBD stones has a >90% success rate in extracting all stones from the CBD but also has a reported morbidity rate of >7% and mortality rate of >0.4% (Table 1).[1,3,10–12,14,16–18,20,21,33] The positive IOC incidence varies and is approximately 22% and a reported incidence of negative ERCP of 55%, 80%, 84%, and 93% in patients presenting with jaundice, pancreatitis, colic, and cholecystitis, respectively, and others reporting incidence of 50–72%.[4,7–9,20,21,24,30]

Table 1 ERCP Complications

ERCP/ES Complications	Percent
Pancreatitis	1–19 (3)
Bleeding	1–6 (2)
Perforation	1–2 (1)
Cholangitis	1–4
Recurrent stones	2–16
Stenosis	1–7

Table 2 Laparoscopic Cholecystectomy Complications

Laparoscopic cholecystectomy complications	Percent
Wound infection	0.5–1.45
Bleeding	0.15–1
Abscess	0.15
Postoperative bile leak	0.4–1.5
Pulmonary embolism	0.02–0.1
Pneumonia, pulmonary	0.01–0.4
Urinary	0.5–0.9
Cardiac	0.05–0.55
Retained stones	0.2–0.7

Laparoscopic cholecystectomy with IOC carries a morbidity of more than 6% and a mortality of 0.1% (Table 2).[1,3–5,8,11–14,23,29,34] Performing IOC in selective patients with symptomatic or suspected CBD stones carries no significant morbidity or mortality. In the 22% of patients with choledocholithiasis by IOC, LC/LCBDE increased both the morbidity and mortality of laparoscopic cholecystectomy/LCBDE to 8% and 0.8%, respectively.

Alternative to LCBDE is either placement of the Fitzgibbons common duct double-lumen catheter, postoperative ERCP/ES, or even intraoperative ERCP/ES. The Fitzgibbons tube is placed intraoperatively in a transcystic fashion and allows for the possibility that most stones will pass with no further intervention in >50% of patients. A study by Fitzgibbons et al.[7] described a success rate of over 96%, failed cannulation rate of 3.4%, and a complication rate of 10% with no mortality (Table 3).

Results

The decision tree with average probabilities is presented in Fig. 1.

The choice of preoperative ERCP applies only to those patients with suspected common bile duct stones, such as patients with gallstone pancreatitis or recent jaundice. The overall success rate for treatment of both the chronic calculus cholecystitis and choledocholithiasis is 88%. Combining the morbidity and mortality of ERCP/ES with

Table 3 Transcystic Double-Lumen Catheter Complications

Transcystic catheter complications	Percent
Sepsis/cholangitis	1.7
Wound infection	3.4
Subhepatic collection	1.7
Cystic duct injury	1.7
Pancreatic abscess	1.7

the next step of management with laparoscopic cholecystectomy, the overall morbidity and mortality rates for the two-stage management are 13.5% and 0.5%, respectively.

For the choice of LC with IOC; performing LC/LCBDE for a positive IOC produces an overall success rate of 91% and a morbidity of 8.4% and mortality rate of 0.5%. Performing LCBDE only when IOC is positive will yield success rate for this choice of 91%, morbidity and mortality rates of 7% and 0.2%, respectively, if the assumed incidence of positive IOC is 22%.

For the choice of LC/IOC, placement of a Fitzgibbons tube for a positive IOC; the success rate is 96%, with a morbidity of 10% and mortality of 0%. Placement of this catheter, only for those with positive IOC, assumed at 22%, yields a combined success rate of 92%, total morbidity of 8.8%, and mortality of 0.1% for this choice.

For the choice of LC/IOC, postoperative ERCP/ES yields a success rate of 92%, with a morbidity of 7.6% and mortality 0.0.4%. Performing this only when IOC is positive, assumed at 22%, and combining this with the morbidity and mortality of a LC yields success rate of 91%, morbidity of 8%, and mortality rate of 0.2%.

Sensitivity Analysis

Figure 2 shows the sensitivity analysis for morbidity rate by the rate of finding choledocholithiasis by IOC for the one-stage and two-stage treatment strategies. All other assumptions in the decision tree were kept the same as for the baseline decision analysis. We see that there is never a rate of positive IOC which resulted in the one-stage approach having a higher morbidity than the two-stage approach. It also shows the sensitivity analysis for mortality rate by the rate of finding choledocholithiasis by positive IOC for the one-stage and two-stage treatment strategies. All other assumptions in the decision tree were kept the same as for the baseline decision analysis. We see that one-stage management always has less mortality than two-stage approach except when the incidence of positive IOC is 100%, then the mortality will be equal at 0.5%.

Figure 3 shows the sensitivity analysis of the LCBDE added mortality to the overall mortality of LC/LCBDE compared to the overall combined mortality for the two-stage approach with preoperative ERCP and LC. The threshold value for the one-stage approach having a lower mortality rate compared to the two-stage approach is when the added mortality of performing LCBDE is 1.8% or less. This figure also shows the sensitivity analysis for the added morbidity of LCBDE to overall morbidity of LC/LCBDE compared to the overall combined morbidity of the two-stage approach. The threshold value for the one-stage approach having a lower morbidity rate compared to the two-stage approach is when the added morbidity rate of performing LCBDE is 32% or less.

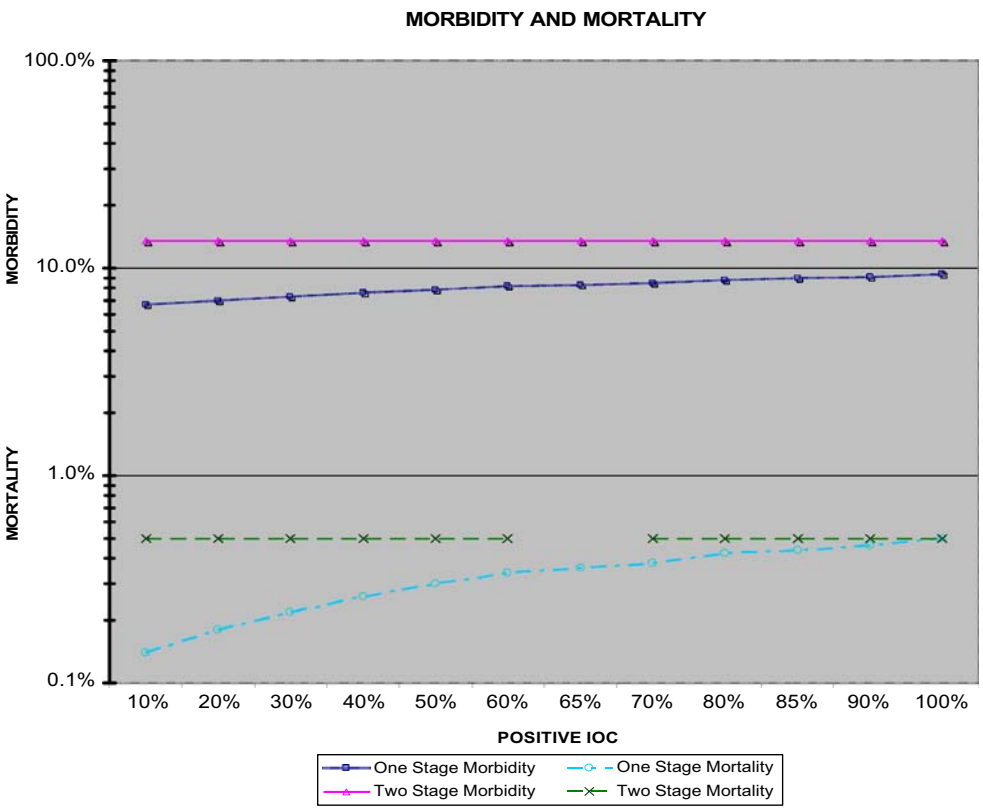

Figure 2 Sensitivity Analysis with Variable incidence of positive IOC and the 1- Morbidity outcome for one and two stage management approach. It shows that even with 100% incidence of a positive IOC the Morbidity of One-Stage management would still be less than Two-stage Management. 2- Mortality outcome for one and two stage management approach. It shows that even with 100% incidence of positive IOC the Mortality of One-Stage management would be equal to that of the Two-stage Management.

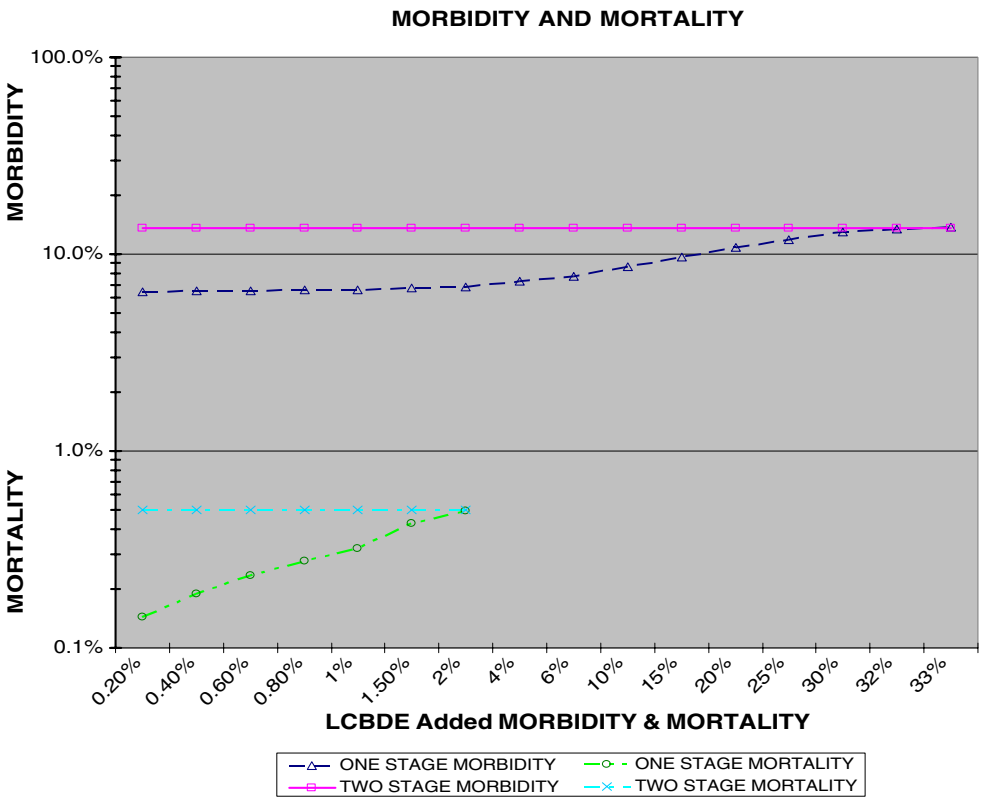

Figure 3 Sensitivity Analysis with Variable incidence of positive IOC and the 1- Morbidity outcome for one and two stage management approach. It shows that even with 100% incidence of a positive IOC the Morbidity of One-Stage management would still be less than Two-stage Management. 2- Mortality outcome for one and two stage management approach. It shows that even with 100% incidence of positive IOC the Mortality of One-Stage management would be equal to that of the Two-stage Management.

Figure 4 shows the sensitivity analysis by the rate of finding choledocholithiasis by IOC for the transcystic double-lumen tube and the two-stage treatment strategy. Once again, the other assumptions are the same as the baseline decision analysis. The threshold value for when the two-stage approach has less morbidity than the Fitzgibbons tube approach is 65%. That is, when the chance of finding common bile duct stones is greater that

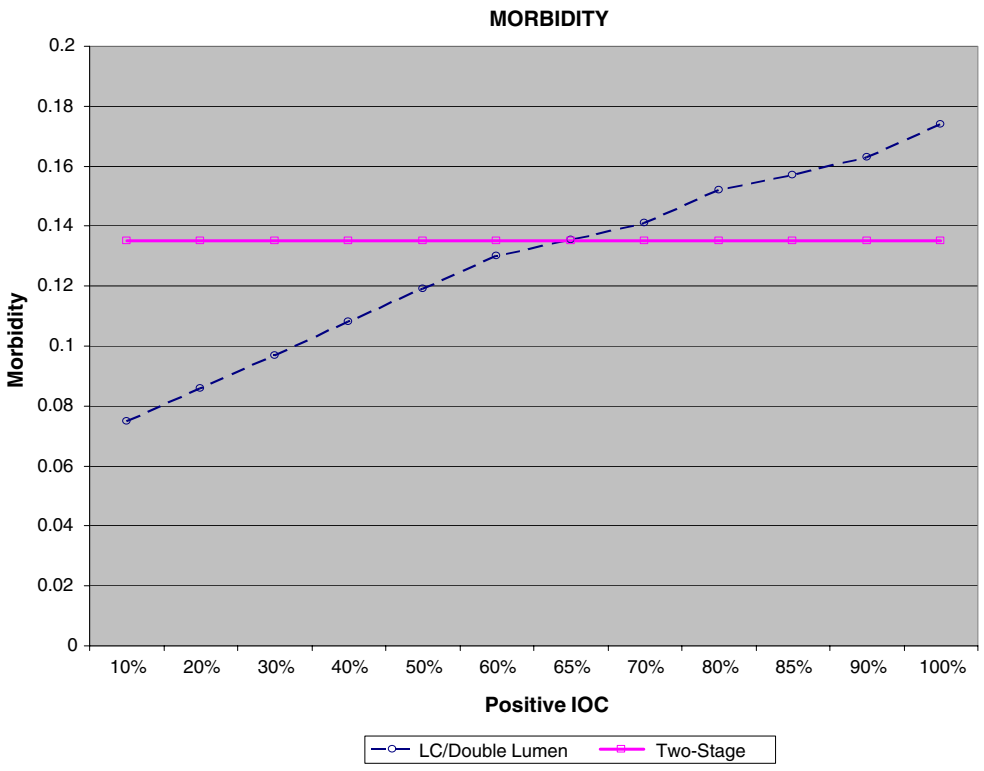

Figure 4 This Sensitivity Analysis for the Morbidity associated with the placement of the Transcystic Double Lumen Catheter after LC compared to Two-Stage Management with Variable incidence of positive IOC showing that the Morbidity of LC/Placement of the Catheter will be higher than the Two-Stage Management when the positive IOC incidence is more than 65%.

65%, preoperative ERCP followed by laparoscopic cholecystectomy leads to less morbidity.

Discussion

In this decision analysis, we show that, using the average rates of morbidity and mortality for LC, LCBDE, preoperative ERCP, and use of a transcystic double-lumen biliary stent, one-stage management of LC with IOC followed by LCBDE for positive choledocholithiasis has the lowest rate of morbidity and mortality. However, there are caveats to this conclusion. Firstly, the higher the incidence of choledocholithiasis found on IOC, the relatively higher the overall morbidity and mortality associated with LC/LCBDE and the placement of the Fitzgibbons catheter. Sensitivity analysis was performed varying the incidence of choledocholithiasis as found by IOC with the associated morbidity and mortality (Fig. 2). This showed that, even with a 100% positive IOC, the morbidity and mortality of the one-stage management with LC/LCBDE are 9.4% and 0.5%, respectively, which are less than that of the one-stage management (13.5% and 0.5%; Fig. 2). Performing LCBDE requires surgeon's certain skills and operative experience. This issue was addressed by performing sensitivity analysis varying the degree of LCBDE added morbidity and mortality in comparison to that of the two-stage management. Therefore, in skilled hands, the strategy of LC with IOC followed by LCBDE is always superior.

There are several reasons for this. The reported success rate for LCBDE was over 92% using a variety of techniques. These include: flushing of the CBD with the use of IV glucagon, which is especially useful when the common bile duct stones are smaller than 2 mm, when sludge is present, or sphincter spasm is the cause of the retained stones; balloon manipulation with biliary Fogarty catheters; use of Dormia baskets to capture the stone; choledochoscopy; and lithotripsy.[3,6,7,12,25,26] Transcystic approach is preferred over the transductal approach in cases with smaller stones <6 mm or smaller bile duct <6–10 mm because of the higher success rate and lower complication rate in these circumstances.[3,7,12]

However, LCBDE does require a surgeon comfortable and facile with this technique. Sensitivity analysis revealed that, when LCBDE-added morbidity and mortality is 32% and 1.8%, respectively, then the one-stage management option will have higher morbidity and mortality rates compared to the two-stage management (Fig. 3). Therefore, the surgeon must be able to assess that the risk of morbidity and mortality of LCBDE exploration in his or her hands and in the institution that he or she works in is less than these threshold values, either as a whole or for the particular patient he or she is operating upon.

The sensitivity analysis showed that, with a positive IOC incidence of <65%, the LC with the placement of the Fitzgibbons tube will have a lower complication rate than two-stage management with preoperative ERCP/ES followed by LC and with less mortality (Fig. 4). In fact, there are very few situations in which the expected incidence of choledocholithiasis is higher than 65%. In addition, when one compares the breath of complications and their incidence, it appears that preoperative ERCP has a higher rate of the more severe complications. Placement of a Fitzgibbons catheter will allow for expectant management with follow-up catheter cholangiography, which can reassess the status of the CBD. Reports have shown a spontaneous CBD stone clearance rate of more than 50%.[7,9,31] Negative follow-up cholangiogram may also be attributed to an initial false-positive cholangiogram with reported incidence of 16%.[7] And only those with persistent positive Fitzgibbons tube cholangiography will undergo an assisted ERCP/ES with a success rate reaching 100% using the Rendezvous approach.[7] If the assumed morbidity of the ERCP/ES performed for those patients was 7.6% and this was included in the overall morbidity of this approach (LC, catheter placement and ERCP/ES for persistent CBD stones), then only if the incidence of positive IOC is over 50% this approach will have a higher morbidity than the two stage management but still less mortality even with 100% positive IOC.

Laparoscopic cholecystectomy with postoperative ERCP/ES for patients with positive IOC is another option of management; however, it carries the combined morbidity and mortality of both procedures but is theoretically still less than preoperative ERCP/ES followed by LC because only those with positive IOC will have to undergo ERCP/ES.[32] This assessment is supported by the results of this decision analysis.

Studies have shown that ERCP/ES has less morbidity than surgery in patients with cirrhosis and acute suppurative cholangitis, biliary sepsis with CBD stones.[34] In fact, such recommendation is consistent with this decision analysis. We have shown in the sensitivity analysis that when the added morbidity and mortality rates of LCBDE exceed 32% and 1.8%, respectively, then preoperative ERCP becomes the favored approach (Fig. 3), which are rates that can be expected in these very high-risk patients. Therefore, patients with symptomatic CBD stones and who are high operative risk [American Society of Anesthesiologists (ASA) IV, V or elderly patient over 70] may be considered for ERCP/ES without cholecystectomy.[18]

Laparoscopic cholecystectomy and IOC with LCBDE, when choledocholithiasis is found without preoperative ERCP, is recommended for surgeons with the skill and facilities to do LCBDE. If surgeons are not skilled in LCBDE or practice in hospitals which cannot support LCBDE, then a Fitzgibbons tube is a good alternative.

Another advantage of a Fitzgibbons tube is that, for surgeons who do not have LCBDE nor ERCP/ES available (for example, in rural hospitals), a Fitzgibbons tube alleviates the obstruction and, therefore, turns a potentially urgent condition into a controlled, elective condition. ERCP/ES would only be recommended in patients with suppurative cholangitis or whose operative risk is so high that avoidance of an operation becomes a priority.

In addition to reduction in morbidity and mortality, other advantages to the one-stage management approach exist. Several studies have reported that single-stage management had significantly shorter hospital stay than two-stage management [7,10–12,25] with a randomized controlled multicenter study reporting length of stay of 3 vs. 6 days.[11] Other studies have shown that one-stage management is more cost effective compared to the two-stage management.[7,12,15]

In conclusion, one-stage management with LC/LCBDE for patients presenting with suspected or symptomatic common bile duct stones has less morbidity, mortality, and hospital length of stay than two-stage management with preoperative ERCP/ES followed by LC. The use of transcystic double-lumen catheter can be used with less morbidity and mortality in cases where LCBDE is not feasible for reasons of experience, resources, or patient's high surgical risk. ERCP/ES is preferred in patients with suppurative cholangitis or biliary sepsis and high-risk surgical patients.

References

1. Clayton ESJ, Connor S, Alexakis N, Leandros E. Meta-analysis of endoscopy and surgery versus surgery alone for common bile duct stones with the gallbladder in situ. Br J Surg 2006;93:1185–1191. doi:10.1002/bjs.5568.
2. Vezakis A, Davides D, Ammori BJ, Martin IG, Larvin M, McMahon MJ. Intraoperative cholangiography during laparoscopic cholecystectomy. Surg Endosc 2000;14:1118–1122. doi:10.1007/s004640000076.
3. Ebner S, Rechner J, Beller S, Erhart K, Riegler FM, Szinicz G. Laparoscopic management of common bile duct stones. Surg Endosc 2004;18:762–765. doi:10.1007/s00464-003-9029-5.
4. Petelin JB. Laparoscopic common bile duct exploration lessons learned from >12 years' experience. Surg Endosc 2003;17:1705–1715. doi:10.1007/s00464-002-8917-4.
5. Velanovich V, Morton JM, McDonald M, Orlando R III, Maupin G, Traverso LW. Analysis of the SAGES outcomes initiative registry. Surg Endosc 2006;20:43–50. doi:10.1007/s00464-005-0378-0.
6. Hamouda AH, Goh W, Mahmud S, Khan M, Nassar AHM. Intraoperative cholangiography facilitates simple transcystic clearance of ductal stones in units without expertise for laparoscopic bile duct surgery. Surg Endosc 2007;21:955–959. doi:10.1007/s00464-006-9127-2.
7. Fitzgibbons RJ Jr, Gardner GC. Laparoscopic surgery and the common bile duct. World J Surg 2001;25:1317–1324. doi:10.1007/s00268-001-0117-1.
8. Misra M, Schiff J, Rothschild J, Schwaitzberg S. Laparoscopic cholecystectomy after a learning curve. Surg Endosc 2005;19:1266–1271. doi:10.1007/s00464-004-8919-5.
9. Tranter S, Thompson M. Spontaneous passage of bile duct stones: frequency of occurrence and relation to clinical presentation. Ann R Coll Surg Engl 2003;85:174–177. doi:10.1308/003588403321661325.
10. Giger U, Michel JM, Vonlanthen R, Becker K, Kocher T, Krähenbühl L. Laparoscopic cholecystectomy in acute cholecystitis: indication, technique, risk and outcome. Arch Surg 2005;390:373–380.
11. Cuschieri A, Lezoche E, Morino M, Croce E, Lacy A, Toouli J et al. Hanna1 GB. E.A.E.S. multicenter prospective randomized trial comparing two-stage vs single-stage management of patients with gallstone disease and ductal calculi. Surg Endosc 1999;13:952–957. doi:10.1007/s004649901145.
12. Rosenthal RJ, Rossi RL, Martin RF. Options and strategies for the management of choledocholithiasis. World J Surg 1998;22:1125–1132. doi:10.1007/s002689900531.
13. Hong DF, Xin Y, Chen DW. Comparison of laparoscopic cholecystectomy combined with intraoperative endoscopic sphincterotomy and laparoscopic exploration of the common bile duct for cholecystocholedocholithiasis. Surg Endosc 2006;20:424–427. doi:10.1007/s00464-004-8248-8.
14. Tranter SE, Thompson MH. Comparison of endoscopic sphincterotomy and laparoscopic exploration of the common bile duct. Br J Surg 2002;89:1495–1504.
15. Schroeppel TJ, Lambert PJ, Mathiason MA, Kothari SN. An economic analysis of hospital charges for choledocholithiasis by different treatment strategies. Am Surg 2007;73:472–477.
16. Stefanidis G, Karamanolis G, Viazis N, Sgouros S, Papadopoulou E, Ntatsakis K et al. A comparative study of postendoscopic sphincterotomy complications with various types of electrosurgical current in patients with choledocholithiasis. Gastrointest Endosc 2003;57:192–197. doi:10.1067/mge.2003.61.
17. Schreurs WH, Juttmann JR, Stuifbergen WNHM, Oostvogel HJM, Van Vroonhoven TJMV. Management of common bile duct stones. Surg Endosc 2002;16:1068–1072. doi:10.1007/s00464-001-9104-8.
18. Siddiqui AA, Mitroo P, Kowalski T, Loren D. Endoscopic sphincterotomy with or without cholecystectomy for choledocholithiasis in high-risk surgical patients: a decision analysis. Aliment Pharmacol Ther 2006;24:1059–1066. doi:10.1111/j.1365-2036.2006.03103.x.
19. Enochsson L, Lindberg B, Swahn F, Arnelo U. Intraoperative endoscopic retrograde cholangiopancreatography (ERCP) to remove common bile duct stones during routine laparoscopic cholecystectomy does not prolong hospitalization. Surg Endosc 2004;18:367–371.
20. Sarli L, Pietra N, Franzé A, Colla G, Costi R, Gobbi S, Trivelli M. Routine intravenous cholangiography, selective ERCP, and endoscopic treatment of bile duct stones before laparoscopic cholecystectomy. Gastrointest Endosc 1999;50:200–208.
21. Hungness ES, Soper NJ. Management of common bile duct stones. J Gastrointest Surg 2006;10:612–618.
22. Fitzgibbons RJ, Ryberg AA, Ulualp KM, Nguyen NX, Litke BS, Camps J, McGinn TR, Jenkins JX, Filipi CJ. An alternative technique for treatment of choledocholithiasis found at laparoscopic cholecystectomy. Arch Surg 1995;130:638–642.
23. Shea JA, Healey MJ, Berlin JA, Clarke JR, Malet PF, Staroscik RN, Schwartz JS, Williams SV. Mortality and complications associated with laparoscopic cholecystectomy: a meta-analysis. Ann Surg 1996;224:609–620.
24. Griniatsos J, Karvounis E, Isla A. Early versus delayed single-stage laparoscopic eradication for both gallstones and common bile duct stones in mild acute biliary pancreatitis. Am Surg 2005;71:682–686.
25. Akopian G, Blitz J, Vander Laan T. Positive intraoperative cholangiography during laparoscopic cholecystectomy: is laparo-

scopic common bile duct exploration necessary? Am Surg 2005;71:750–753.
26. Thompson MH, Tranter SE. All-comers policy for laparoscopic exploration of the common bile duct. Br J Surg 2002;89:1608–1612.
27. Weinstein MC, Fineberg HV. Clinical Decision Analysis. Philadelphia: WB Saunders, 1980.
28. Sugiyama M, Izumisato Y, Hatano N, Mori T, Atomi Y. Management of unsuspected common bile duct stones found during laparoscopic cholecystectomy by means of transcystic catheter placement and papillary dilation. Gastrointest Endosc 1999;50:837–840.
29. Giger UF, Michel J-M, Opitz I, Inderbitzin DT, Kocher T, Krähenbühl L. Risk factors for perioperative complications in patients undergoing laparoscopic cholecystectomy: analysis of 22,953 consecutive cases from the Swiss Association of Laparoscopic and Thoracoscopic Surgery Database. J Am Coll Surg 2006;203:723–728.
30. Phillips EH, Liberman M, Carroll BJ, Fallas MJ, Rosenthal RJ, Hiatt JR. Bile duct stones in the laparoscopic era: is preoperative sphincterotomy necessary? Arch Surg 1995;130:880–886.
31. Fitzgibbons RJ Jr, Deeik RK, Martinez-Serna T. Eight years' experience with the use of a transcystic common bile duct duodenal double-lumen catheter for the treatment of choledocholithiasis. Surgery 1998;124:699–706.
32. Chang L, Lo S, Stabile BE, Lewis RJ, Toosie K, de Virgilio C. Preoperative versus postoperative endoscopic retrograde cholangiopancreatography in mild to moderate gallstone pancreatitis: a prospective randomized trial. Ann Surg 2000;231:82–87.
33. Acosta JM, Katkhouda N, Debian KA, Groshen SG, Tsao-Wei DD, Berne TV. Early ductal decompression versus conservative management for gallstone pancreatitis with ampullary obstruction: a prospective randomized clinical trial. Ann Surg 2006;243:33–40.
34. Chijiiwa K, Kozaki N, Naito T, Kameoka N, Tanaka M. Treatment of choice for choledocholithiasis in patients with acute obstructive suppurative cholangitis and liver cirrhosis. Am J Surg 1995;170:356–360.

J Gastrointest Surg (2008) 12:1981–1990
DOI 10.1007/s11605-008-0641-5

TGF-β1 and IGF-1 and Anastomotic Recurrence of Crohn's Disease After Ileo-Colonic Resection

Marco Scarpa · Marina Bortolami · Susan L. Morgan · Andromachi Kotsafti · Cesare Ruffolo · Renata D'Incà · Eugenia Bertin · Lino Polese · Davide F. D'Amico · Giacomo C. Sturniolo · Imerio Angriman

Received: 19 May 2008 / Accepted: 22 July 2008 / Published online: 13 August 2008

Abstract
Background After bowel resection, Crohn's disease (CD) recurs frequently in the site of the anastomosis. Alteration of normal healing processes may play a role in this phenomenon. Transforming growth factor beta (TGF-β) and insulin-like growth factor (IGF-1) are involved in wound healing mechanisms with pro-fibrogenic properties. The aim of this study was to assess the expression of TGF-β1 and insulin-like growth factor 1 (IGF-1) in the different zones of the bowel wall to understand why side-to-side anastomosis are associated to a lower recurrence rate compared to end-to-end ones.
Patients and Methods Seventeen patients affected by CD who underwent ileo-colonic resection from 2004 to 2005 were enrolled in this study. Full-thickness tissue samples were obtained from the mesenteric, the lateral, and the anti-mesenteric sides of the macroscopically diseased and healthy ileum for each patient. TGF-β1 and IGF-1 messenger RNAs (mRNAs) were quantified by real-time polymerase chain reaction. Myeloperoxidase activity and histological disease activity were assessed to quantify the ileal inflammation. Vimentin, desmin, and α-smooth muscle actin were stained with immunohistochemistry to assess the fibroblast, smooth muscle cell, and myofibroblasts populations. Comparisons and correlations were carried out with nonparametric tests.
Results In diseased ileum, TGF-β1 mRNA transcripts in the antimesenteric side were significantly lower than those of the mesenteric side ($p=0.05$), and a significant correlation between TGFβ-1 levels in diseased bowel and the sampling site was observed ($\tau=0.36$, $p=0.03$). On the contrary, neither the IGF-1 mRNA transcripts nor the distribution of fibroblast, smooth muscle cell, and myofibroblasts populations showed any relation with the sampling site.
Conclusion TGF-β1 mRNA expression was lower in the anti-mesenteric side of the diseased ileum, and this was consistent with the success of side-to-side anastomosis in preventing CD recurrence. Since high expression of TGF-β1 was associated to early recurrence, it seems rationale to construct the anastomosis on the anti-mesenteric side of the bowel.

Presented as a poster at the Digestive Disease Week, San Diego, CA, USA, May 19–24, 2008.

M. Scarpa (✉) · C. Ruffolo · E. Bertin · L. Polese · D. F. D'Amico · I. Angriman
Clinica Chirurgica I, Dipartimento di Scienze Chirurgiche e Gastroenterologiche,
Policlinico Universitario,
Università di Padova,
via Giustiniani 2,
35128 Padova, Italy
e-mail: marcoscarpa73@yahoo.it

M. Bortolami · A. Kotsafti · R. D'Incà · G. C. Sturniolo
Gastroenterologia, Dipartimento di Scienze Chirurgiche e Gastroenterologiche, University of Padova,
Padova, Italy

S. L. Morgan
Department of Pathology, Institute for Cancer Studies,
Birmingham Medical School, University of Birmingham,
Birmingham, UK

Keywords Crohn's disease · Recurrence · TGF-β1 · IGF-1 · Anastomosis

Introduction

One of the most common problems in the surgical treatment of Crohn's disease (CD) is the high frequency of recurrence in the site of the anastomosis after bowel resection.[1,2] Several factors have been investigated for their supposed influence in this phenomenon but only elimination of smoking and prophylactic treatment with full dose 5ASA after resection seem to reduce Crohn's recurrence rate after surgery.[3–5]

The role of the type of anastomosis appears to be still controversial. While some authors denied any influence of the type of the anastomosis,[4–7] some other evidenced that stapled side-to-side anastomosis after ileo-colonic resection obtained less anastomotic recurrence compared to hand-sewn end-to-end anastomosis.[8–11] Their hypothesis was that, even if the presence of the anastomosis on itself seems to predispose to recurrent CD, some local factors such as suture material, local ischemia, and sub-acute obstruction with subsequent fecal stasis might play a major role in the pathogenesis of anastomotic recurrence.[11–13] In our previous studies, the side-to-side configuration resulted to delay the anastomotic recurrence independently from the type of suture.[14,15] This conclusion was exclusively clinical since it was obtained from the analysis of the recurrence rate after the different type of anastomosis, and the physiopathology of this phenomenon remains still unknown. While end-to-end or end-to-side anastomoses involve all the ileal wall sides, the side-to-side anastomosis involves primarily the anti-mesenteric side of the gut wall. A fascinating hypothesis was that, beside the width of the anastomosis, the site of the anastomosis may play a crucial role in CD recurrence.

Transforming growth factor beta (TGF-β) belongs to a family of multi-functional 12-kDa polypeptide dimers produced by a wide variety of lymphoid and non-lymphoid cells appearing to be involved in the regulation of organ fibrosis.[16] TGF-β functions as a healing mediator as well as an inhibitor of T and B cell proliferation and cytokine production.[17,18] In an our previous study, the high levels of TGF-β1 in healthy ileum of patients who undergo ileo-colonic resection for CD were demonstrated to be associated with early clinical disease recurrence.[19]

Insulin-like growth factor 1 (IGF-1) is the main local effector of growth hormone stimulation on target cells in the liver and other target tissues including the intestine.[20] It is a potent enterotrophic factor in the healthy intestine playing a relevant role in chronic inflammation and wound healing process in CD because of its pro-fibrogenic actions.[20,21] In the intestinal tract, IGF-1 stimulates proliferation of fibroblasts, myofibroblasts, and smooth muscle cells, all implicated as cellular mediators of fibrosis in CD.[22]

The main aim of this study was to evaluate the expression of TGF-β1 and IGF-1 in the different (mesenteric, lateral, and anti-mesenteric) sides of the ileum wall that could be involved in the anastomosis in patients with CD. Secondary end-point was to analyze the in vivo interaction of these cytokines with mesenchymal cell populations (fibroblast, smooth muscle cell, and myofibroblast) in healthy and diseased bowel wall in CD.

Patients and Methods

Patients and Study Design

Seventeen patients affected by CD who underwent ileo-colonic resection from 2004 to 2005 in our department were enrolled in this study. The study was performed according to the Helsinki declaration principles, and adequate informed consent was obtained from all persons involved. Patients were enrolled consecutively provided that adequate intestinal samples were available. Patients who presented also other bowel diseases, such as cancer, or were submitted to procedures different from ileo-colonic resection and patients with an ileostomy were excluded. All the patients received oral mesalazine as prophylactic therapy at the dose of 2.4 g/die at their discharge and were strongly advised against smoking. Patient's characteristics are shown in Table 1.

Clinical disease activity was quantified with a modified version of the Harvey–Bradshaw Activity Index (HBAI)[23,24] that included a number of soft stools per day, abdominal pain, general well-being, extra-intestinal complications, and the presence of abdominal mass.

Tissue Sampling

Ileal wall samples from the operative specimens had been stored at −80°C immediately after the operation. Tissue samples were obtained from the surgical specimen of the terminal ileum at the ileo-colonic resection. Complete rings (1-cm thickness) of ileal wall from the diseased ileum and from the healthy ileum were obtained as shown in Fig. 1. After an accurate cleaning of mesenteric fat, the "rings" were divided in the four sectors (mesenteric, anti-mesenteric, and two lateral). A 3-mm full thickness intestinal wall sample was obtained from each sector of the macroscopically diseased and healthy ileum. Each sample was divided in two parts, and one was stored in liquid nitrogen (−80°C) for molecular analysis, and one was preserved in 10% formalin solution for histological analysis. In every side standard histology, myeloperoxidase (MPO) activity assay, vimentin,

Table 1 Patients Clinical Characteristics

Patients characteristics	Median	Range
Demography		
Gender	11 males	6 females
Age at ileocolonic resection (years)	37.5	19–73
Age at CD diagnosis (years)	21.5	14–43
CD duration (months)	90	8–276
Indication for operation		
Recurrent CD	3/17	
Fistulizing CD	2/17	
Stenosing CD	15/17	
Disease activity at operation		
Harvey–Bradshaw activity index	4	1–11
Number of daily stool	2	1–12
Abdominal mass	5/17	
Abdominal pain	15/17	
Weight (kg)	59	46–80
Hb g/l	14.1	10.5–16.3
Ht %	41.75	34.5–48
WBC×10.9/l	9.355	4.61–12.17
PMN×10.9/l	6.805	3.21–10.52
CRP mg/l	15	3.19–64.3
ESR mm/h	36	17–73
albumin g/l	34.16	20.76–45.5

No correlation between any of the serum markers of inflammation, ESR, or CRP and tissue inflammation or disease recurrence was observed.

desmin, and α-smooth muscle actin (α-SMA) immunohistochemical staining, and the determination of IGF-1 and TGF-β1 tissutal expression were performed. Each sample was then analyzed separately.

Tissutal Expression of TGF-β1 and IGF-1

RNA Isolation

Total RNA was extracted from frozen small bowel tissue by acid guanidium thiocyanate–phenol–chloroform according to the Chomczynski and Sacchi method.[25] RNA concentration was quantified spectrophotometrically. Integrity of the RNA sample was assessed by electrophoresis on a 2% agarose gel (FMC Bio Product, Rockland, ME, USA) containing ethidium bromide. Moreover, the quality of the isolated RNA was assessed using RNA 6000 Nano Assay and the Agilent 2100 bioanalyzer (Agilent technologies Palo Alto, CA, USA). Bioanalyzer uses gel electrophoresis in the confines of a micro-fabricated chip and highly sensitive laser induced fluorescence detection using an intercalating dye, which is added to the polymer.

Reverse Transcription

Complementary DNA (cDNA) was synthesized with 2 μg of RNA, which was reverse transcribed in a final volume of 40 μl in the presence of 1X polymerase chain reaction (PCR) buffer, 1 mM each of dNTPs (dATP, dTTP, dCTP, and dGTP), 1 U/μl RNase inhibitor, 2.5 μM random hexamers, 2.5 U/μl of murine leukemia virus (Perkin Elmer, Foster City, CA, USA). The reverse transcription reaction was performed at 25°C for 10 min, 42°C for 15 min, and 99°C for 5 min, and carried out in a Perkin Elmer GeneAmp PCR System 2400. The cDNA was stored at −20°C.

SYBR Green I Real Time PCR

The ABI 7900 Sequence Detection System (Applied Biosystems, Foster City, CA, USA) was used to develop a quantitative real time PCR with the fluorescent dye SYBR Green methodology. The reaction was performed in 96-well thin-wall optical plate. PCRs were carried out in a 25-μl final volume containing 1× SYBR Green Master Mix (Applied Biosystems), 300-nM primers (each), and 1-μl cDNA template. After one 2-min step at 50°C to allow uracil DNA glycosylase (UDG) to act and a second one at 95°C for 10 min to inactivate the UDG and activate Taq polymerase, samples were subjected to 45 cycles of 45 s at 94°C (denaturation) followed by 45 s at 62°C (annealing and extension) for TGF-β1, IGF-1, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH).

All the determinations were performed in triplicates in order to estimate the reproducibility. Samples in which the cDNA was omitted, as negative controls, were used. Each assay included "no template" controls and standard curve

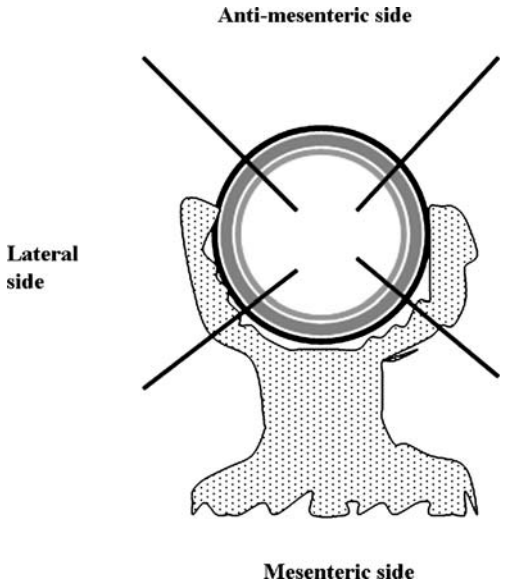

Figure 1 Complete rings (1-cm thickness) of ileal wall from the diseased ileum and from the healthy ileum were obtained, and after an accurate cleaning of mesenteric fat, the "rings" were divided in the four quadrants (mesenteric, anti-mesenteric, and two lateral).

for each gene of interest. Nucleotide sequences for sense and anti-sense primers were synthesized to generate the following oligonucleotides. The sequences for the primer of TGF-β1 were 5′ AACCCACAACGAAATCTATGACAAG 3′ (forward) and 5′ AGAGCAACACGGGTTCAGGTA 3′ (reverse), and the length of this amplicone was 78 bp; those for IGF-1 were 5′ GGCGCTTGAGTTGCTGAGA 3′ (forward) and 5′ ACTAGTTGGCCAGTTATTTGGATAGC 3′ (reverse), and the length of this amplicone was 133 bp; those of GAPDH were 5′ GACACCCACTCCTCCACC TTT 3′ (forward) and 5′ TTGCTGTAGCCAAATTCG TTGT 3′ (reverse), and the length of this amplicone was 101 bp.

Quantification of Gene Expression

The messenger RNA (mRNA) amounts of the unknown samples were determined from the standard curves containing 10^8, 10^7, 10^6, 10^5, 10^4, 10^3, 10^2, and ten copies/well for each primer pair considered. To obtain the normalized amount of transcripts, the TGF-β1, IGF-1 mRNA amounts were divided by the GAPDH mRNA amount for each sample.

Histological Assessment

Histology

After fixation in 10% neutral buffered formalin, the specimens were dehydrated and embedded in paraffin wax; sections of 3 μm were produced and then stained with hematoxylin–eosin. In 2006, a gastro-intestinal pathologist (S.M.), unaware of the MPO, TGF-β1, and IGF-1 expression results, reviewed the microscopic slides from surgical specimens. Since an established histological classification for disease activity was not evident in the literature, a ad hoc scoring system was devised to quantify the severity of inflammation as shown in Table 2.[19]

Histochemistry and Immunohistochemistry

Histochemical staining for assessment of collagen deposition was performed using a standard Masson's trichrome protocol. Immunohistochemical staining was performed using the Dako EnVision horse radish peroxidase system according to the manufacturer's instructions (Dako Corporation, Carpenteria, California, USA). Primary antibodies were used at a dilution of 1:100 (Vimentin and α-SMA, Dako Corporation) and visualized using 3′3′-diaminobenzidine (Sigma).

Sections were independently evaluated by a gastrointestinal histopathologist (S.M.) and graded for the presence and severity of: fibrosis, neural hyperplasia, submucosal muscularization, and myofibroblast proliferation. These features were chosen because they were prominent features in these specimens and been identified as important morphological parameters of disease by other investigators.[26] Fibrosis was assessed on the hemotoxylin and eosin, Masson's trichrome, and immunohistochemical (Vimentin+, α-SMA−) stains. Neural hyperplasia was assessed on the hemotoxylin and eosin stain. Submucosal muscularization (Vimentin−, α-SMA+) and myofibroblast proliferation (Vimentin+, α-SMA+) was assessed using the hemotoxylin and eosin in conjunction with the immunohistochemical stains. All these features were evaluated on a semi-quantitative scale of 0–3, where 0 = none present, 1 = focal and/or mild degree, 2 = moderate degree, and 3 = prominent/severe degree. An example of prominent fibrosis, submucosal muscularization and myofibroblast proliferation is shown in Fig. 2.

MPO Activity Assay

Myeloperoxidase (MPO) activity was evaluated as parameter of local inflammation.[24,25] MPO activity assay was performed to quantify ileal inflammation. Ileal samples were minced in 1 ml of 50 mM potassium phosphate buffer (pH 6.0) containing 14 mM hexadecyltrimethyl–ammonium

Table 2 Histological Ad Hoc Inflammation Score

Score	Description
Inflammation score	
0	No inflammation (excluding mild serosal inflammation intraoperative)
1	Mild, acute, or chronic inflammation limited to the mucosa, without crypt abscesses or ulceration
2	Moderate inflammation, as above but including crypt abscesses, small apthous ulcers, and transmural inflammation
3	Large areas of acute ulceration, superficial, or fissuring
Granuloma score	
0	None
1	Occasional multinucleated giant cells
2	Microgranulomas
3	Well-formed granulomas

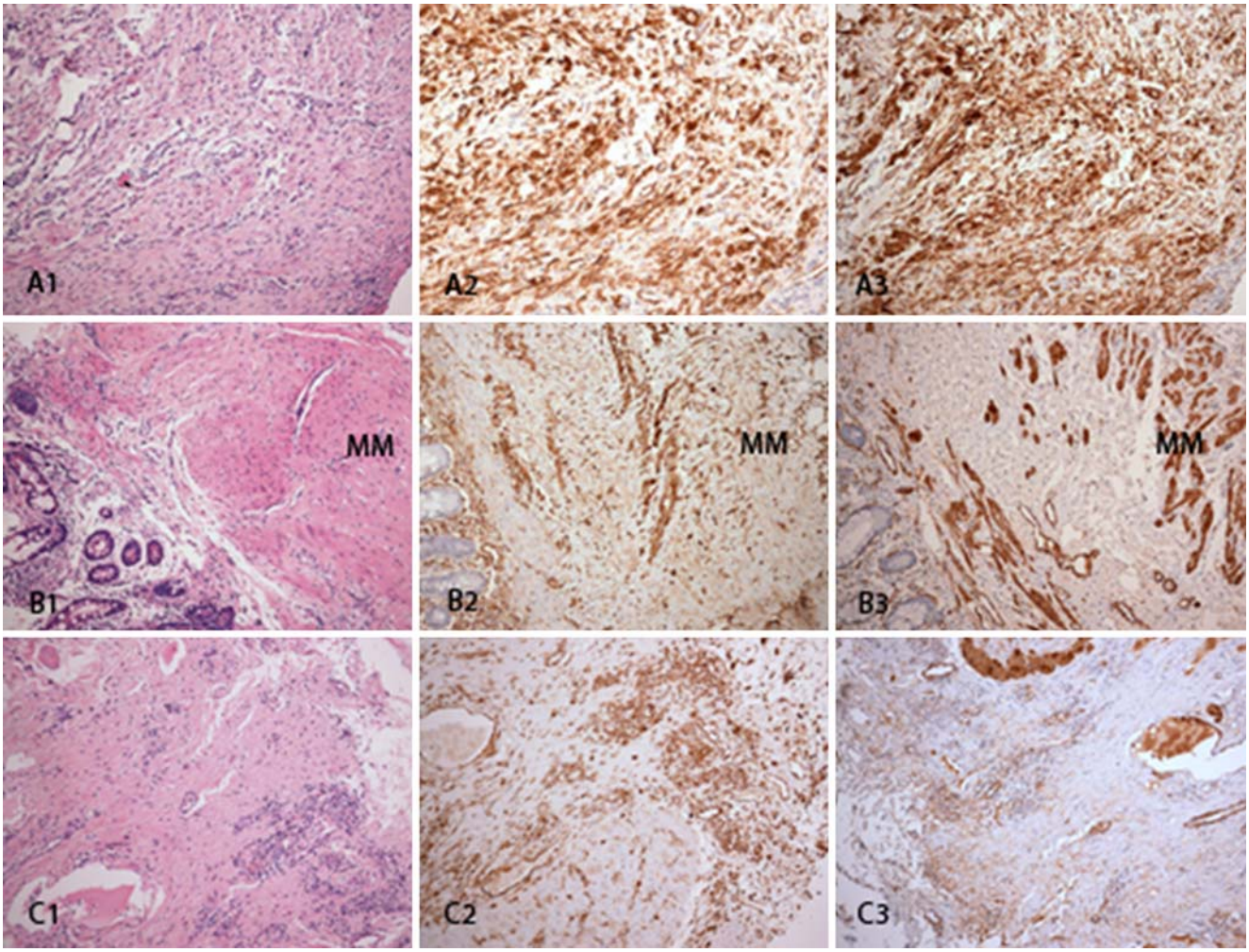

Figure 2 **a** (*1*) Hematoxylin- and eosin-stained section of affected bowel in Crohn's disease showing an area of myofibroblastic proliferation, (*2*) positive vimentin staining in the same area, and (*3*) positive α-smooth muscle actin in the same area. **b** (*1*) Hematoxylin- and eosin-stained section of affected bowel in Crohn's disease showing an area of submucosal muscularization, (*2*) negative vimentin staining in the same area, and (*3*) positive α-smooth muscle actin in the same area. *MM* muscularization. **c** (*1*) Hematoxylin- and eosin-stained section of affected bowel in Crohn's disease showing an area of fibrosis in the bowel wall, (*2*) positive vimentin staining in the same area, and (*3*) negative α-smooth muscle actin in the same area.

bromide (Fluka), homogenized, and sonicated. The lysates were frozen and thawed three times, then centrifuged for 2 min in cold at 15,000×*g*. Aliquots of the supernatants were mixed with potassium phosphate buffer containing *o*-dianisidine–HCl (Sigma-Aldrich, St. Louis, MO, USA) and 0.0005 % H_2O_2. MPO activity was expressed as units per gram of wet tissue. The change in absorbance at 460 nm was assessed with a spectrophotometer. The enzyme unit was defined as the conversion of 1 μmol of H_2O_2 per min at 25°C, and it was normalized as unit per gram tissue.[27,28]

Blood Tests

Blood samples were taken from fasting patients on the day before the operation. Systemic inflammatory activity was assessed by erythrocyte sedimentation rate (ESR), white blood cell count (WBC), polymorphonuclear cells count (PMN), and C-reactive protein (CRP). ESR was measured by the Westergren method. CRP was detected by immuno-nephelometry (normal, <6 mg/l; pathological, >6 mg/l). Total protein and albumin were assessed with the biurete method. WBC, PMN, and hemoglobinemia (Hb) were obtained with standard full blood cell count.

Statistical Analyses

Since no assumption on normality of the distribution of the data was possible, they were presented as median (range) unless otherwise specified and non-parametric statistics was used. Comparisons were performed with Wilcoxon

matched-pair test or with Kruskal–Wallis analysis of variance (ANOVA) where appropriated. Linear association between wound repair parameters was quantified using Kendall τ correlation test; only correlations with $\tau>0.30$ were considered relevant. Statistical significance was set at $p<0.05$ for all tests.

Results

In diseased ileum, TGF-β1 mRNA transcripts in the antimesenteric side were significantly lower than those of the mesenteric side [0 (0–0.118) versus 1.018 (0–11.497), $p=0.05$], and a significant correlation between TGFβ-1 mRNA transcripts and the sampling site was observed ($\tau=0.36$, $p=0.03$). As shown in Fig. 3, the closer the sampling site was to the mesenteric side, the higher were the TGFβ-1 mRNA transcripts. In comparison, neither IGF-1 mRNA transcripts nor MPO activity, inflammatory score, presence of granuloma, neural hyperplasia, submucosal muscularization, myofibroblast proliferation, and fibrosis showed any relation with the sampling site. Comparison of TGFβ-1, IGF-1 mRNA transcripts levels, MPO activity inflammatory score, presence of granuloma, neural hyperplasia, submucosal muscularization, myofibroblasts proliferation, and fibrosis in the different quadrants of the ileal wall are shown in Table 3.

As might be expected, histological scoring demonstrated a high median score for inflammatory parameters in macroscopically diseased bowel and a low median score in healthy bowel ($p<0.01$). Similarly, the prevalence of granuloma was higher in the diseased bowel compared to that in the healthy intestine (mean±standard deviation: 0.65±1.15 versus 0.26±0.77, $p=0.04$). No significant difference was observed in TGFβ-1 and IGF-1 mRNA transcripts levels in diseased ileum compared to the healthy one. Submucosal muscularization, fibrosis, and neural hyperplasia were significantly more evident in the diseased bowel compared to the healthy one ($p<0.01$, $p<0.01$, and $p=0.02$, respectively). In particular, active myofibroblasts were observed significantly more frequently in the diseased than in the healthy bowel (mean±standard deviation: 0.35±0.66 versus 0.02±0.15, $p=0.02$). A comparison of TGFβ-1, IGF-1 mRNA transcripts levels, MPO activity, inflammatory score, presence of granuloma, neural hyperplasia, submucosal muscularization, myofibroblast proliferation, and fibrosis in diseased versus healthy bowel is shown in Table 4.

In the diseased ileum and in the healthy ileum, TGFβ-1 mRNA transcripts levels correlated directly with the respective IGF-1 mRNA transcript levels. However, interestingly, TGFβ-1 expression in the diseased bowel correlated inversely with the IGF-1 expression and with the grade of submucosal muscularization in healthy bowel (even if this last correlation showed just a trend toward significance). In healthy ileum, TGFβ-1 mRNA transcript levels also correlated inversely with neural hyperplasia. In the diseased ileum, prevalence of myofibroblasts strongly correlated with IGF-1 mRNA transcript levels, while their correlation with TGFβ-1 mRNA levels showed just a trend toward significance. IGF-1 mRNA in the healthy bowel correlated directly with the MPO activity in the diseased bowel. Relevant correlation between TGFβ-1, IGF-1 mRNA transcripts levels in the ileum wall of patients with CD and local inflammation, and wound repair parameters were shown in Table 5.

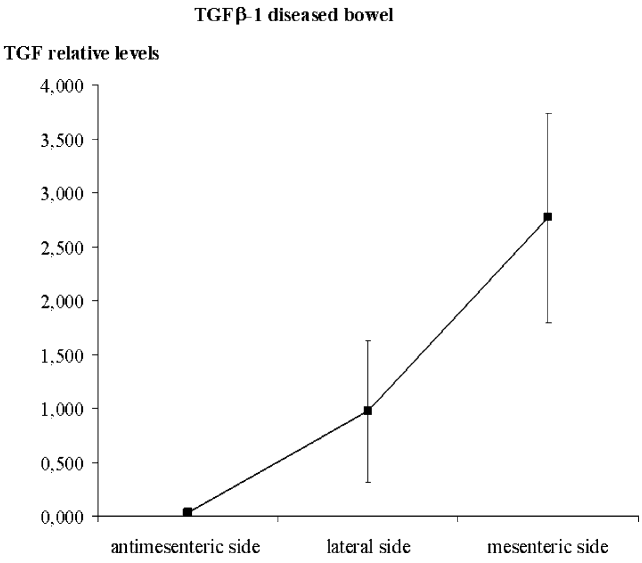

Figure 3 The closer the sampling site was to the mesenteric side, the higher were the TGFβ-1 mRNA transcripts levels.

Discussion

Our data showed that, in diseased ileum of CD patients, TGF-β1 mRNA expression was lower in the anti-mesenteric side, and a significant correlation between TGFβ-1 mRNA transcripts and the sampling site was observed. TGF-β1 mRNA expression in CD localized mostly to cells of the lamina propria with the highest concentration in inflammatory cells closest to the luminal surface.[29] The anti-mesenteric zone might have a relatively more peripheral vascular and lymphatic system compared to the mesenteric zone that could affect the number of lamina propria cells. The lack of activation of TGF-β-mediated pathways might decrease the extracellular matrix generation and, subsequently, the intramural fibrosis that leads to intestinal obstruction.[30] Since low expression of TGF-β1 in the ileum wall was associated to a lower rate of recur-

Table 3 Comparison of TGFβ-1, IGF-1 mRNA Levels, MPO Activity, Inflammatory Score, Granuloma Score, Neural Hyperplasia, Submucosal Muscularization, Myofibroblasts Proliferation, and Fibrosis (All These Features were Evaluated on a Semi-quantitative Scale of 0–3, Where 0 = None Present, 1 = Focal and/or Mild Degree, 2 = Moderate Degree, 3 = Prominent/Severe Degree) in the Different Sector of the Ileum Wall in Crohn's Disease with Kruskal–Wallis ANOVA

	Antimesenteric side Median (range)	Lateral side Median (range)	Mesenteric side Median (range)	Kruskal–Wallis's ANOVA *p* value
Diseased bowel				
Inflammatory score	2.5 (0–3)	3 (0–3)	3 (0–3)	0.871
Granuloma score	0 (0–3)	0 (0–3)	0 (0–3)	0.361
MPO activity (units per milligram tissue)	6.3 (1.64–20.10)	7.5 (0.67–20.78)	4.655 (0.08–21.83)	0.507
Neural hyperplasia scale	1 (0–3)	1 (0–2)	1 (0–3)	0.687
Submucosal muscularization scale	3 (0–3)	3 (0–3)	3 (0–3)	0.792
Myofibroblast proliferation scale	0 (0–2)	0 (0–2)	0 (0–1)	0.594
Fibrosis scale	2 (0–3)	2 (0–3)	1.5 (0–3)	0.443
TGFβ-1/GAPDH mRNA levels	0 (0–0.118)	0.334 (0–4.145)	1.018 (0–11.497)	0.198
IGF-1/GAPDH mRNA levels	0 (0–0.012)	0 (0–0.266)	0.003 (0–0.068)	0.488
Healthy bowel				
Inflammatory score	0 (0–2)	0 (0–3)	0 (0–3)	0.815
Granuloma score	0 (0–2)	0 (0–2)	0 (0–3)	0.782
MPO activity (units per milligram tissue)	5.585 (0.97–15.97)	6.66 (1.64–11.13)	5.18 (0.84–19.43)	0.923
Neural hyperplasia scale	1 (0–3)	0 (0–2)	1 (0–2)	0.182
Submucosal muscularization scale	0 (0–2)	0 (0–3)	0 (0–3)	0.934
Myofibroblast proliferation scale	0 (0–0)	0 (0–1)	0 (0–0)	0.331
Fibrosis scale	0 (0–3)	0 (0–2)	1 (0–1)	0.884
TGFβ-1/GAPDH mRNA levels	0.058 (0–3.784)	0.072 (0–0.51)	0.117 (0.84–19.43)	0.936
IGF-1 GAPDH mRNA levels	0 (0–0.415)	0.002 (0–3.547)	0.0005 (0–0.052)	0.832

rence,[19] this could explain, in part, why constructing the anastomosis on the anti-mesenteric side of the bowel in a side-to-side configuration could minimize the recurrence risk of CD. On the other hand, the fact that no other fibrogenic parameter showed any relation with the sampling site may suggest caution in taking this conclusion. From this point of view, the low mRNA levels of TGF-β1 in the antimesenteric side of the diseased ileum wall might be simply due to high frequency of ulceration in this peripheral zone that could have destroyed the lamina propria cells expressing TGF-β1.

Histological ad hoc score and the distribution of granuloma showed that there was a good correspondence between the macroscopical and the microscopical inflammation. Although some authors found that TGF-β1 mRNA levels were higher in active CD,[29] in our series, no significant difference in TGFβ-1 and IGF-1 mRNA levels were observed in diseased ileum compared to the healthy one. Similarly, Dal Zotto et al. observed that, TGF-β1 production in healthy and diseased bowel was comparable.[31] In patients with CD, the high expression of TGF-β1 was demonstrated to be associated to a failure of TGF-β1-mediated negative regulation of proinflammatory cytokine production because of increased intracellular expression of the endogenous inhibitor, Smad7.[32] Post-transcriptional

Table 4 Comparison of TGFβ-1, IGF-1 expression, MPO Activity Inflammatory Score, Presence of Granuloma, Neural Hyperplasia, Submucosal Muscularization, Myofibroblasts Proliferation, and Fibrosis in Diseased Versus Healthy Bowel with Wilcoxon Matched-Pair Test

	Diseased bowel Median (range)	Healthy bowel Median (range)	*Wilcoxon rank test* *p* value
Inflammatory score	3 (0–3)	0 (0–3)	0.000
Granuloma score	0 (0–3)	0 (0–3)	0.045
MPO activity (units per milligram tissue)	6.73 (0.08–21.83)	5.65 (0.84–19.43)	0.671
Neural hyperplasia scale	1 (0–3)	1 (0–3)	0.019
Submucosal muscularization scale	3 (0–3)	0 (0–3)	0.000
Myofibroblast proliferation scale	0 (0–2)	0 (0–1)	0.017
Fibrosis scale	2 (0–3)	0 (0–3)	0.000
TGFβ-1/GAPDH mRNA levels	0.034 (0–11.49)	0.074 (0–3.784)	0.826
IGF-1/ GAPDH mRNA levels	0 (0–0.266)	0.0002 (0–3.547)	0.182

Table 5 Relevant Correlation Between TGFβ-1, IGF-1 Expression in the Ileum Wall of Patients with CD, and Local Inflammation and Repair Parameter were Evaluated with Kendall's τ Correlation Test

Repairing mechanism	Bowel site	Correlation with	Kendall's τ	*p level*
TGFβ-1	Diseased	Sampling site in diseased ileum	−0.363	0.035
		IGF-1 in diseased bowel	0.361	0.036
		Myofibroblasts proliferation in diseased bowel	0.372	0.063
		IGF-1 in healthy bowel	−0.396	0.039
		Submucosal muscularization in healthy bowel	−0.349	0.069
	Healthy	IGF-1 in healthy bowel	0.495	0.000
		Neural hyperplasia in healthy bowel	−0.316	0.018
IGF-1	Diseased	TGFβ-1 in diseased bowel	0.361	0.036
		Myofibroblasts proliferation in diseased bowel	0.693	0.001
	Healthy	TGFβ-1 in healthy bowel	0.495	0.000
		TGFβ-1 in diseased bowel	−0.396	0.039
		MPO activity in diseased bowel	0.371	0.004

overexpression of Smad7 in the gut of patients with inflammatory bowel diseases blocks TGF-β1 signaling, and defective TGF-β1 signaling helps maintain high NF-κB activity, thereby expanding its local inflammatory response.[33] As suggested by TGF-β1's different effects on fibroblasts in strictures and in inflamed bowels, it is possible that its pro-fibrogenic activity remains and thus is enhanced.[34] In fact, according to our data, fibrosis, submucosal muscularization, myofibroblasts distribution, and neural hyperplasia were significantly more evident in the diseased bowel compared to the healthy one.

TGF-β seems to enhance the effects of IGF-I on cell proliferation and differentiation, and both IGF-1 and TGF-β seem to act synergistically to stimulate intestinal cells.[22,35] In fact, in our series, in the diseased and healthy ileum, TGFβ-1 mRNA transcripts levels correlated directly with the respective IGF-1 ones. Surprisingly, TGFβ-1 mRNA levels in the diseased bowel correlated inversely with the IGF-1 expression in healthy bowel, suggesting two different expression regulation in the two situations (healthy and diseased bowel) and a sort of negative feedback between the two growth factors. A similarly negative feedback might be hypothesized to explain the inverse correlation between TGFβ-1 mRNA levels in the diseased bowel and the grade of submucosal muscularization in surrounding healthy bowel. Curiously, in the healthy ileum, TGFβ-1 mRNA levels correlated inversely also with neural hyperplasia: Probably, where the disease is not active, TGFβ-1 has an inhibitory effect on the autonomic plexa. In the diseased ileum, the correlation between the distribution of myofibroblasts and IGF-1 mRNA was significantly stronger than that of TGFβ-1 mRNA, suggesting that IGF-1 could be the main in vivo growth factor for these mesenchymal cells. The low correlation between TGFβ-1 expression and myofibroblasts population might also be due to the production of TGFβ-1 by myofibroblasts on themselves.[36]

Surprisingly, no significant correlation between TGFβ-1 and IGF-1 mRNA expression and fibrosis was observed. In fact, the major drawback of the study was that TGF- β1 and IGF-1 mRNA levels may or may not correlate with fibrongenetic activity due to the complex regulation of these proteins both pre- and post-transcriptionally. Further studies focused on the examination of pre- and post-transcription signal of TGF-β1 and IGF-1, additional mediators of fibrosis, such as TGF-β2 and β3, and inflammatory mediators, such as TNFα and IL-6, will be essential to clarify the complex network that is at the basis of intestinal fibrosis in CD.

On the other hand, even the most comprehensive immunohistochemical or molecular analyses of resected bowel from patients with CD can provide only a snapshot at one particular point in time and cannot define the complex relation between growth factors and mesenchymal cells during initiation or progression of fibrosis.[37] Moreover, these studies are limited by patients' heterogeneity and disease presentation variability, in contrast to studies with cell lines; however, they are crucial if basic mechanisms elucidated in vitro are to be translated to humans.[32]

In conclusion, our study showed that TGF-β1 mRNA expression is lower in the anti-mesenteric side of the ileum affected by active CD, and this is consistent with the success of side-to-side anastomosis in preventing CD recurrence. However, no other relation with bowel sides were observed among the inflammation and repair parameters. Although no difference in the expression of TGFβ-1 and IGF-1 in healthy and diseased bowel was observed, the inverse correlation between TGFβ-1 expression in the diseased bowel and that of IGF-1 in healthy bowel suggested two different expression regulation in the two situations (healthy and diseased bowel) and a sort of negative feedback between the two growth factors. Finally, myofibroblasts proliferation in small bowel affected by active CD appeared to be strictly correlated with IGF-1 levels.

Acknowledgment We are very grateful to Mrs. C. Carlotto (Gastroenterology, University of Padova, Italy) for her technical help in the detection of MPO levels and mRNA extraction and isolation. We are also very grateful to Dr. Duilo Pagano (Clinica Chirurgica I, University of Padova, Italy) for retrieving part of the bowel samples. This paper was funded, in part, by the MIUR grant ex 60%.

References

1. Williams JG, Wong WD, Rothenberger DA, Goldberg SM. Recurrence of Crohn's disease after resection. Br J Surg 1991;78:10–19. doi:10.1002/bjs.1800780106.
2. Tytgat GNJ, Mulder GJI, Brummerlkamp WH. Endoscopic lesion in Crohn's disease early after ileocecal resection. Endoscopy 1988;20:260–262.
3. Wolff BG. Factors determining recurrence following surgery for Crohn's disease. World J Surg 1998;22:364–369. doi:10.1007/s002689900398.
4. Boreley NR, Mortensen NJ, Jewell DP. Preventing postoperative recurrence of Crohn's disease. Br J Surg 1997;84(11):1493–1502. doi:10.1002/bjs.1800841104.
5. Moskovitz D, McLeod RS, Greenberg GR, Cohen Z. Operative and environmental risk factors for recurrence of Crohn's disease. Int J Colorectal Dis 1999;14(4–5):224–226. doi:10.1007/s003840050215.
6. Scott NA, Sue-Ling HM, Hughes LE. Anastomotic configuration does not affect recurrence of Crohn's disease after ileo-colonic resection. Int J Colorectal Dis 1995;10:67–69. doi:10.1007/BF00341197.
7. Cameron JL, Hamilton SR, Coleman J, Sitzmann JV, Bayless TM. Patterns of ileal recurrence in Crohn's disease. A prospective randomized study. Ann Surg 1992;215(5):546–551. doi:10.1097/00000658-199205000-00018.
8. Hashemi M, Novell JR, Lewis AA. Side-to-side anastomosis may delay recurrence in Crohn's disease. Dis Colon Rectum 1998;41(10):1293–1296. doi:10.1007/BF02258231.
9. Yamamoto T, Bain IM, Mylonakis E, Allan RN, Keighley MRB. Stapled functional end-to-end anastomosis versus sutured end-to-end anastomosis after ileocolonic resection in Crohn's disease. Scand J Gastroenterol 1999;7:708–713. doi:10.1080/00365529975002592 1.
10. Ikeuchi H, Kusunoki M, Yamamura T. Long term results of stapled and hand sewn anastomosis in patients with Crohn's disease. Dig Surg 2000;17(5):493–496. doi:10.1159/000051946.
11. Munoz-Juarez M, Yamamoto T, Wolff BG, Keighley MRB. Wide-lumen stapled anastomosis versus conventional end-to-end anastomosis in the treatment of Crohn's disease. Dis Colon Rectum 2001;44(1):20–25. doi:10.1007/BF02234814.
12. Scott AD, Uff C, Phillips RK. Suppression of macrophage function by suture materials and anastomotic recurrence of Crohn's disease. Br J Surg 1993;80:387–391. doi:10.1002/bjs.1800800342.
13. Osborne MJ, Hudson M, Piasecki C, Dhillon AP, Lewis AAM, Pounder RE et al. Crohn's disease and anastomotic recurrence microvascular ischemia and anastomotic healing in an animal model. Br J Surg 1993;80:226–229. doi:10.1002/bjs.1800800236.
14. Scarpa M, Angriman I, Barollo M, Polese L, Ruffolo C, Bertin M et al. Role of stapled and hand-sewn anastomoses in recurrence of Crohn's disease. Hepatogastroenterology 2004;51(58):1053–1057.
15. Scarpa M, Ruffolo C, Bertin E, Polese L, Filosa T, Prando D et al. Surgical predictors of recurrences of Crohn's disease after ileocolonic resection. Int J Colorectal Dis 2007;22(9):1061–1069. doi:10.1007/s00384-007-0329-4.
16. Del Zotto B, Mumolo G, Pronio AM, Montesani C, Tersigni R, Boirivant M. TGF-b1 production in inflammatory bowel disease: differing production patterns in Crohn's disease and ulcerative colitis. Clin Exp Immunol 2003;134:120–126. doi:10.1046/j.1365-2249.2003.02250.x.
17. Massague J. Transforming growth factor beta. Annu Rev Cell Biol 1990;6:597–646. doi:10.1146/annurev.cb.06.110190.003121.
18. Walia B, Wang L, Merlin D. Sitaraman TGF-beta down-regulates IL-6 signalling in intestinal epithelial cells: critical role of SMAD-2. FASEB J 2003;17(14):2130–2132.
19. Scarpa M, Bortolami M, Morgan SL, Kotsafti A, Ferraro S, Ruffolo C et al. TGF-b1 and IGF-1 production and recurrence of Crohn's disease after ileo-colonic resection. J Surg Res 2008; in press. doi:10.1016/j.jss.2008.04.014.
20. Theiss AL, Fruchtman S, Lund PK. Growth factors in inflammatory bowel disease the actions and interactions of growth hormone and insulin-like growth factor-I. Inflamm Bowel Dis 2004;10:871–880. doi:10.1097/00054725-200411000-00021.
21. El Yafi F, Winkler R, Delvenne P, Boussif N, Belaiche J, Louis E. Altered expression of type I insulin-like growth factor receptor in Crohn's disease. Clin Exp Immunol 2005;139:526–533. doi:10.1111/j.1365-2249.2004.02724.x.
22. Simmons JG, Pucilowska JB, Keku TK, Lund PK. IGF-1 and TGF-b1 have distinct effects on phenotype and proliferation of intestinal fibroblasts. Am J Physiol Gastrointest Liver Physiol 2002;283:G809–G818.
23. Harvey RF, Bradshaw JM. A simple index of Crohn's disease activity. Lancet 1980;1:514. doi:10.1016/S0140-6736(80)92767-1.
24. Kane SV, Sandborn WJ, Rufo PA, Zholudev A, Boone J, Lyerly D et al. Fecal lactoferrin is a sensitive and specific marker in identifying intestinal inflammation. Am J Gastroenterol 2003;98(6):1309–1314. doi:10.1111/j.1572-0241.2003.07458.x.
25. Chomczynski P, Sacchi N. Single step method of RNA isolation by acid guanidinium thiocyanate-phenol-chloroform extraction. Anal Biochem 1987;162:156–159. doi:10.1016/0003-2697(87)90021-2.
26. Pucilowska JB, Williams KL, Lund PK. Fibrosis and inflammatory bowel disease: cellular mediators and animal models. Am J Physiol Gastrointest Liver Physiol 2000;279:G653–G659.
27. La JH, Kim TW, Sung TS, Kang JW, Kim HJ, Yang IS. Visceral hypersensitivity and altered colonic motility after subsidence of inflammation in a rat model of colitis. World J Gastroenterol 2003;9(12):2791–2795.
28. Krawisz JE, Sharon P, Stenson WF. Quantitative assay for acute intestinal inflammation based on myeloperoxidase activity. Assessment of inflammation in rat and hamster models. Gastroenterology 1984;87:1344–1350.
29. Babyatsky MW, Rossiter G, Podolsky DK. Expression of transforming growth factors alpha and beta in colonic mucosa in inflammatory bowel disease. Gastroenterology 1996;110(4):975–984. doi:10.1053/gast.1996.v110.pm8613031.
30. Di Mola FF, Friess H, Scheuren A, Di Sebastiano P, Graber H, Egger B et al. Transforming growth factor-bs and their signaling receptors are coexpressed in Crohn's disease. Ann Surg 1999;229(1):67–75. doi:10.1097/00000658-199901000-00009.
31. Del Zotto B, Mumolo G, Pronio AM, Montesani C, Tersigni R, Boirivant M. TGF-b1 production in inflammatory bowel disease: differing production patterns in Crohn's disease and ulcerative colitis. Clin Exp Immunol 2003;134:120–126. doi:10.1046/j.1365-2249.2003.02250.x.
32. Monteleone G, Del Vecchio Blanco G, Monteleone I, Fina D, Caruso R, Gioia V et al. Post-transcriptional regulation of Smad7 in the gut of patients with inflammatory bowel disease. Gastroenterology 2005;129(5):1420–1429. doi:10.1053/j.gastro.2005.09.005.

33. Monteleone G, Mann J, Monteleone I, Vavassori P, Bremner R, Fantini M et al. A failure of transforming growth factor-b1 negative regulation maintains sustained NF-kB activation in gut inflammation. J Biol Chem 2004;279(6):3925–3932. doi:10.1074/jbc.M303654200.
34. Stallmach A, Schuppan D, Riese HH, Matthes H, Riecken EO. Increased collagen type III synthesis by fibroblasts isolated from strictures of patients with Crohn's disease. Gastroenterology 1992;102(6):1920–1929.
35. Zimmermann EM, Li L, Hou YT, Mohapatra NK, Pucilowska JB. Insulin-like growth factor I and insulin-like growth factor binding protein 5 in Crohn's disease. Am J Physiol Gastrointest Liver Physiol 2001;280:G1022–G1029.
36. McKaig BC, Hughes K, Tighe PJ, Mahida YR. Differential expression of TGF-b isoforms by normal and inflammatory bowel disease intestinal myofibroblasts. Am J Physiol Cell Physiol 2002;282:C172–C182.
37. Pucilowska JB, McNaughton KK, Mohapatra NK, Hoyt EC, Zimmermann EM, Sartor RB et al. IGF-I and procollagen a1(I) are coexpressed in a subset of mesenchymal cells in active Crohn's disease. Am J Physiol Gastrointest Liver Physiol 2000;279:G1307–G1322.

J Gastrointest Surg (2008) 12:1991–1994
DOI 10.1007/s11605-008-0611-y

Clinical Features and Management of Postoperative Pouch Bleeding after Ileal Pouch–Anal Anastomosis (IPAA)

Lei Lian · Zuzana Serclova · Victor W. Fazio · Ravi P. Kiran · Feza Remzi · Bo Shen

Received: 17 June 2008 / Accepted: 8 July 2008 / Published online: 6 August 2008

Abstract
Aim The clinical features of postoperative bleeding from the ileal pouch–anal anastomosis(IPAA) vary and its management can be difficult. There is no published literature regarding pouch bleeding and its treatment.
Materials and Methods Pouch bleeding was defined as the passage of blood or clots transanally or into the ileostomy bag with or without hypotension or a drop in hemoglobin within 30 days after surgery. Patients were identified from a prospectively maintained pouch database.
Results Pouch bleeding developed in 47 (1.5%) patients out of 3,194 patients undergoing IPAA since 1983. Forty-two patients had inflammatory bowel disease, four had familial adenomatous polyposis, and one had colonic inertia. Sixty-six percent of bleeding occurred within 7 days postoperatively and 59.6% required transfusion; 72.3% patients developed transanal bleeding, nine from ileostomy and two from both. After initial fluid resuscitation, five patients were observed while 28 patients had pouch endoscopy and clot evacuation followed by cauterization or epinephrine(1:100,000) enemas, 27 of these had cessation within 24 h. Epinephrine enema was used as initial treatment in the remaining 12 patients. Overall success rate of epinephrine enema was 96%.
Conclusion Postoperative pouch bleeding after IPAA is uncommon, and it usually requires nonsurgical intervention. Epinephrine enema appears to be successful in managing this complication.

Keywords Restorative proctocolectomy · Ileal pouch–anal anastomosis · Pouch bleeding · Management

Introduction

Ileal pouch–anal anastomosis (IPAA) after proctocolectomy was first described by Parks et al.[1] in the 1970s and has become the surgical procedure of choice ever since for patients with ulcerative colitis and familial adenomatous polyposis. The terminal segment of the ileum is utilized to construct a pouch as a reservoir for stool storage. Pouch configuration includes two (J-shaped), three (S-shaped), or four (W-shaped) loops of the small intestine.[2] The J-pouch configuration has become the preferred pouch type for most colorectal surgeons.[3] Continuity is then restored with a hand-sewn or stapled anastomosis after pouch construction. Although modifications and improvements have been made to the technique for pouch configuration,[4] postoperative complications may occur even in experienced hands. Common complications include pouchitis, anastomotic leak, pelvic abscess, etc.[5]

Postoperative bleeding from the pouch is a less frequent complication after this procedure and is seldom described. A previous study from our institution reported 38 cases with post-IPAA bleeding from the pouch in a consecutive series of 1,005 patients undergoing pouch surgery.[6] The

This abstract was presented as a poster at the Digestive Disease Week 2008, San Diego.

L. Lian · Z. Serclova · V. W. Fazio · R. P. Kiran · F. Remzi · B. Shen
Digestive Disease Institute, Cleveland Clinic Foundation, Cleveland, OH 44195, USA

V. W. Fazio (✉)
Digestive Disease Center-A30, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA
e-mail: faziov@ccf.org

details of clinical features were, however, not provided. The clinical features of postoperative pouch bleeding vary depending on severity and the management can be difficult. Furthermore, it may result in longer length of stay and increased rate of readmission. The diagnostic and therapeutic methods include endoscopy, observation, fluid resuscitation, and interventional managements. The limited information on outcomes of this particular complication prompted us to take on the current study. The aim of the study was to review our experience in its management.

Materials and Methods

Patients

The study was approved by Institutional Review Board at the Cleveland Clinic Foundation. Data of 3,194 patients undergoing restorative proctocolectomy and IPAA were recorded in a prospectively maintained pouch database since 1983. As of October 2007, 47 patients who had post-IPAA bleeding were identified. Retrospective chart review was performed to confirm all the data in the database including demographics, clinical parameters, and surgical technique. Review of records for data related to bleeding such as initial manifestation, symptoms, severity, bleeding sites, and management was performed. There were incomplete data pertaining to medication for two patients due to unavailability of pertinent chart volumes. These patients were included for other analyses.

Inclusion and Exclusion Criteria

Pouch bleeding was considered as a short-term complication and defined as the occurrence of passage of blood or clots transanally or into an ileostomy bag with or without hypotension or a drop in hemoglobin within 30 days after surgery. Patients who developed pouch bleeding more than 30 days after surgery were excluded.

Outcome Measurement

Primary outcome was defined as cessation of visible bleeding. Secondary outcome was readmission and death.

Surgical Technique

The IPAA was performed as previously described.[7] After the left colon and right colon were mobilized and the splenic flexure and hepatic flexure were taken down, the terminal ileum was transected. The ileocolic vessels were then ligated, divided, and excised. A low ligation was carried out in the inferior mesenteric artery and vein, as well as the sigmoid branches. The rectum was mobilized down to the coccyx. When necessary, incisions were made in the anterior and posterior leaves of the mesentery overlying the superior mesenteric artery in order to get adequate reach. An approximately 20 cm J-pouch was then constructed with two firings of the ILA-100 stapler. The pouch was tested to ensure that it was airtight and watertight. The PI-30 was used to close off the tip of the "J" and this was reinforced with a running suture. Hemostasis inside the pouch was checked visually. A purse string suture was applied and the anvil inserted and deployed. The linear staple line was reinforced by some surgeons. A diverting ileostomy was made, usually 40–50 cm upstream of the pouch.

Statistical Analysis

Descriptive statistics were performed for all variables. These include the mean and standard deviation for continuous variables and frequencies for categorical factors. Statistical significance was tested using chi-squared or Fisher's exact probability tests. Student's t tests or Wilcoxon rank sum tests were used for continuous factors. Differences were statistically significant when the p value was less than 0.05 (two-sided). To further assess the risk factor of pouch bleeding, we compared the 47 patients to the rest of the patients in the pouch database for investigator selected variables.

Results

Pouch bleeding developed in 47 (1.5%) patients out of 3,194 patients undergoing IPAA since 1983. IPAA was performed in patients with inflammatory bowel disease, including ulcerative colitis (n=25), indeterminate colitis favoring UC (n=5), indeterminate colitis favoring CD (n=1), indeterminate colitis (n=9), Crohn's disease (n=2), familial adenomatous polyposis (n=4), and colonic inertia (n=1).

We compared the 47 patients to the rest of the patients in the pouch database for selected variables as shown in Table 1. There were no differences in gender distribution, pouch configuration, and anastomotic type between patients with and without pouch bleeding. The patients with pouch bleeding, however, were younger than the rest of the patients in the database.

Reinforcement of the linear staple line was performed after J-pouch formation in 17 (44.7%) patients with J-pouch. Sixty-six percent bleeding occurred within 7 days; 41.9% of these patients had postoperative anticoagulant use for thrombosis prophylaxis.

Thirty-four (72.3%) patients bled transanally, nine from ileostomy and two from both locations. Two patients had

Table 1 Comparison: Patients with or without Pouch Bleeding

	Pouch bleeding (n=47)	No pouch bleeding (n=3147)	p value
Age	33.3±10.5	38.1±13.3	0.01
Male gender	34 (72.3%)	1,752 (55.5%)	0.1
Diagnosis=ulcerative colitis	25 (53.2%)	2,472 (78.6%)	0.001
J-pouch	38 (80.9%)	2,764(87.8%)	0.15
Staple anastomosis	35 (74.5%)	2,618 (83.2%)	0.11

concurrent abdominal bleeding and two had anemic symptoms. The latter two were later found to be bleeding from the pouch at endoscopy.

Among the two patients who had concurrent abdominal bleeding, one patient was reoperated on and the other died after being transferred to the intensive care unit due to concurrent intraabdominal bleeding. The management of the remaining 45 patients is shown in Fig. 1. Twenty-eight patients had pouch endoscopy and clot evacuation, 12 patients underwent initial epinephrine enema, and five patients underwent observation only. Of the 28 who underwent endoscopy with clot evacuation, 15 (53.6%) patients had active bleeding from the linear staple line which was cauterized. Generalized oozing was found in the remaining 13 (46.4%) cases and these patients were treated by saline with epinephrine (1:100,000) enemas. Of these 28 patients, 27 had cessation of bleeding within 24 h. One patient required 3 days of enema treatment before complete cessation. Of the 12 patients treated with epinephrine enema as initial treatment, one patient failed to respond and had endoscopy with cauterization of bleeding point.

Overall, 28 (59.6%) patients underwent blood transfusion. Twenty patients bled within 7 days after surgery. None of the patients required surgery for postoperative bleeding from the pouch. Two patients treated with enema had rebleeding 3 and 5 days, respectively, after initial treatment and required readmission. They were treated successfully with epinephrine enema.

Discussion

Total proctocolectomy and IPAA was introduced as an alternative to end ileostomy and continent ileostomy. This procedure preserves the natural route of defecation by using the patient's own sphincters to maintain continence and has a relatively low reoperation rate for complications with a high patient satisfaction.[6,8] Pouch-related complications including surgical and mechanical complications, inflammatory disorders, functional disorder, and systemic complications have been demonstrated.[9] Perioperative pouch bleeding as a rare complication has not been specially addressed previously in the literature.

Because patients undergoing IPAA might have a diverting ileostomy, bleeding from the pouch could present as bleeding from the ileostomy bag. Therefore, the diagnosis of pouch bleeding is suspected when clinical signs of bright red blood per rectum or excessive bloody stoma output are noticed. The reasons for bleeding from the pouch are not clear. Technical failure in terms of inadequate hemostasis in the operative field or a misfired stapler could be causative, while patients' underlying hematological disorders and postoperative anticoagulant use could be predisposing. Due to the rarity of the condition with small numbers of patients, we were unable to analyze these potential risk factors. From a technical aspect, a J-shaped ileal pouch has approximately a single 20-cm staple line[10] and an S-shaped pouch has approximately three 15-cm hand-sewn suture lines.[11] In our study, the distribution of pouch configuration (J versus S) was not significantly different between patients with and without pouch bleeding. Hence, we did not find the association between pouch configuration and bleeding.

When bleeding from the pouch develops in the postoperative period, a standardized algorithm for its management

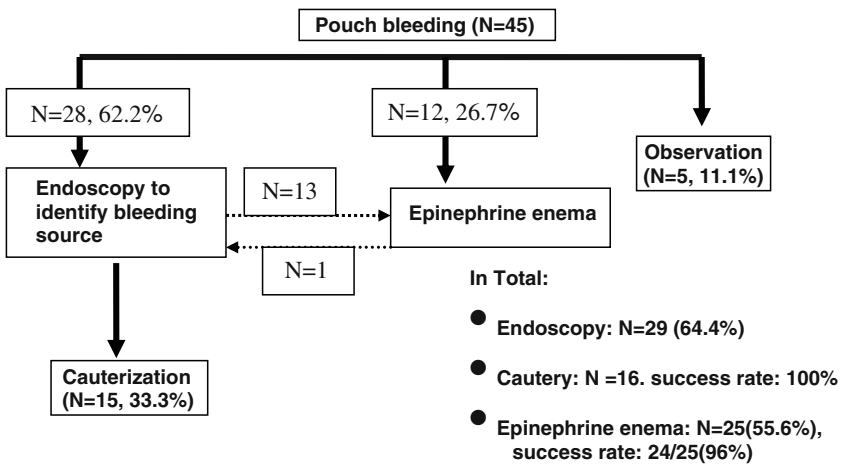

Figure 1 Management of pouch bleeding.

has not been previously defined. Based on the findings in our series of patients, pouch endoscopy can be used to diagnose as well as treat pouch bleeding. Endoscopy and clot evacuation followed by cauterization of a specific bleeding point might be the most effective way in managing this complication, which was associated with 100% success rate in our study. When presented with diffuse bleeding, treatment with epinephrine enema can instead be used. However, the use of endoscopy depends on the surgeon's preference and the severity of the bleeding.

Epinephrine, because of its pharmacological properties of vasoconstriction, has been widely used in the management of intraluminal bleeding, such as upper gastrointestinal (GI) bleeding,[12] nasal bleeding, and even lower GI bleeding when the bleeding site can be adequately reached.[13] It can be used by local irrigation or local injection of diluted epinephrine. Local injection of epinephrine is the most popular therapeutic method in treating bleeding peptic ulcers.[14] Of patients who were evaluated via endoscopy in this series, 46.4% could be successfully treated with an epinephrine enema. Twenty-five patients in total received local enema of 0.9% saline and epinephrine (1:200,000). The current study showed that it was associated with a high success rate of 96%. Hence, an epinephrine enema could be the initial treatment of choice considering the related cost, low risk of recurrent bleeding, and ease of instillation when compared with endoscopy and cauterization.

The limitation of this study is that the risk factors for the occurrence of pouch bleeding were not evaluated due to the sample size and the lack of availability of relevant data. Furthermore, the choice of initial treatment in this case series was mainly based on the surgeon's preference. Therefore, it is difficult to define the superiority of one treatment over the other.

Conclusion

Postoperative pouch bleeding after IPAA usually requires intervention but can be managed nonsurgically. Pouch endoscopy with clot evacuation and cauterization of visible bleeding point followed by iced saline and saline with epinephrine enema appears to be effective in managing this complication.

References

1. Parks AG, Nicholls RJ. Proctocolectomy without ileostomy for ulcerative colitis. BMJ 1978;2:85–8.
2. Nicholls RJ. Restorative proctocolectomy with various types of reservoir. World J Surg 1987;11:751–62. doi:10.1007/BF01656598.
3. McHugh SM, Diamant NE, McLeod R, et al. S-pouches vs. J-pouches. A comparison of functional outcomes. Dis Colon Rectum 1987;30:671–77. doi:10.1007/BF02561686.
4. Utsunomiya J, Iwama T, Imajo M, Matsuo S, Sawai S, Yaegashi K, et al. Total colectomy, mucosal proctectomy, and ileoanal anastomosis. Dis Colon Rectum 1980;23:459–66.
5. Shen B, Fazio VW, Remzi FH, Lashner BA. Clinical approach to diseases of ileal pouch–anal anastomosis. Am J Gastroenterol 2005;100:2796–807. doi:10.1111/j.1572-0241.2005.00278.x.
6. Fazio VW, Ziv Y, Church JM, Oakley JR, Lavery IC, Milsom JW, et al. Ileal pouch–anal anastomoses complications and function in 1005 patients. Ann Surg 1995;222:120–7. doi:10.1097/00000658-199508000-00003.
7. Ballantyne GH, Pemberton JH, Beart RW Jr, Wolff BG, Dozois RR. Ileal J pouch-anal anastomosis. Current technique. Dis Colon Rectum 1985;28:197–202. doi:10.1007/BF02554246.
8. Farouk R, Pemberton JH, Wolff BG, et al. Functional outcomes after ileal pouch–anal anastomosis for chronic ulcerative colitis. Ann Surg 2000;231:919–26. doi:10.1097/00000658-200006000-00017.
9. Shen B, Remzi FH, Lavery IC, Lashner BA, Fazio VW. A proposed classification of ileal pouch disorders and associated complications after restorative proctocolectomy. Clin Gastroenterol Hepatol 2008;6:145–58. doi:10.1016/j.cgh.2007.11.006.
10. Hughes JP, Bauer AR Jr, Bauer CM. Stapling techniques for easy construction of an ileal J-pouch. Am J Surg 1988;155:783–5. doi:10.1016/S0002-9610(88)80043-6.
11. Rothenberger DA, Vermeulen FD, Christenson CE, Balcos EG, Nemer FD, Goldberg SM, et al. Restorative proctocolectomy with ileal reservoir and ileoanal anastomosis. Am J Surg 1983;145:82–8. doi:10.1016/0002-9610(83)90171-X.
12. Lau JY, Chung S. Management of upper gastrointestinal haemorrhage. J Gastroenterol Hepatol 2000;15(Suppl):G8–12. doi:10.1046/j.1440-1746.2000.02258.x.
13. Kim YI, Marcon NE. Injection therapy for colonic diverticular bleeding. A case study. J Clin Gastroenterol 1993;17:46–8. doi:10.1097/00004836-199307000-00013.
14. Vergara M, Calvet X, Gisbert JP. Epinephrine injection versus epinephrine injection and a second endoscopic method in high risk bleeding ulcers. Cochrane Database Syst Rev 2007;18:CD005584.

J Gastrointest Surg (2008) 12:1995–2000
DOI 10.1007/s11605-008-0582-z

How Can We Control Intraoperative Bacterial Contamination and Surgical-Site Infection During an Anterior Resection or Hartmann's/Miles' Operation?

Katsunori Nishikawa · Nobuyoshi Hanyuu · Masami Yuda · Yuujiro Tanaka · Akira Matsumoto · Hideharu Yasue · Takenori Hayashi · Susumu Kawano · Teruyuki Usuba · Toshio Iino · Ryouji Mizuno · Shuuichi Iwabuchi

Received: 17 May 2008 / Accepted: 16 June 2008 / Published online: 18 July 2008

Abstract
Purpose Intraoperative bacterial contamination (IBC) is a major cause of surgical-site infection (SSI). Therefore, we investigated whether the ingenuity of surgical procedures could reduce the incidence of IBC/SSI.
Methods Sixty patients who were surgically treated for recto-sigmoid cancer were investigated. Among these patients, the colon was transected during the early perioperative period (ET) in 29 patients and during the late period (LT) in 31 patients. Three samples for IBC were obtained from the irrigation fluid before abdominal closure (LAVAGE), the remaining cut sutures after peritoneal closure (SUTURE), and a subcutaneous swab of the wound (SUBCUT).
Results The overall SSI and IBC rates were 25% and 55.2%, respectively. Patients who developed SSI had an extremely high IBC rate (85%), and IBC patients also had a high SSI rate (68%). IBC was highest in the LAVAGE (26%) followed by the SUBCUT (26%), and the SUTURE (12%). The incidence of IBC in the LT was significantly lower than that in the ET (19% vs. 55%, $p < 0.01$), although the incidence of SSI was similar in both IBC groups.
Conclusion Shortening the exposure of the colonic mucosa decreased the incidence of IBC/SSI; thus, careful operations to minimize IBC are recommended.

Keywords Surgical site infection · Bacterial contamination · Anterior resection · Hartmann's/Miles' operation

Introduction

Surgical stresses can weaken the immune systems of patients during the perioperative period, resulting in immuno-compromise and a susceptibility to pathogens. Under these circumstances, surgical-site infections (SSIs) are well known as a major complication of gastrointestinal surgery. Presence of SSIs does not only make the patients lose their satisfaction with their treatment as a result of prolonged hospitalization, but also substantially increase morbidity, mortality, and the cost of care.[1,2] Several surveillance reports regarding SSI have been carried out and have played important roles in SSI prevention.[3–5] Patient factors (i.e., diabetes, smoking, obesity, steroid use, blood transfusion, etc.), environmental factors (i.e., ventilation in operating room, sterilization of surgical instruments, etc.), and bacterial factors are thought to be the main causes of SSIs.[6–12] Based on these investigations and other reports, various strategies for reducing the incidence of SSI have been recommended, including the administration of prophylactic antibiotics, bowel preparation, and appropriate surgical technique. Most studies have examined post-contaminated bacterial control; however, a few reports have shown a relation between the incidence of SSI and bacterial contamination during surgery.[8,13–15] We recently confirmed that intraoperative bacterial contamination (IBC) is strongly related to subsequent surgical wound infections.[14]

K. Nishikawa (✉) · N. Hanyuu · M. Yuda · Y. Tanaka · A. Matsumoto · H. Yasue · T. Hayashi · S. Kawano · T. Usuba · T. Iino · R. Mizuno · S. Iwabuchi
Division of Surgery, Machida Municipal Hospital,
2-15-41 Asahimachi,
Machida-shi, Tokyo 194-0023, Japan
e-mail: ka2nissy@aol.com

The aim of this study was to determine whether different surgical procedures may contribute to IBC control, thereby reducing the incidence of SSI.

Patients and Methods

The study population consisted of patients who had undergone either an anterior resection or a Hartmann's/Miles' operation for recto-sigmoid cancer and in whom intraoperative bacterial culture specimens had been collected at Machida Municipal Hospital between November 2004 and March 2008. In this study, SSI was restricted to superficial wound infections and was defined as the presence of pus or discharge confirmed by third-person identification within 30days after surgery. SSI was defined as a wound infection because a primary infection originating from the abdominal cavity may have caused a secondary infection on the abdominal wall. Therefore, patients who developed deep incisional and organ/space SSI, including postoperative anastomotic leakage, were excluded from this study.

The study population was divided into two groups. Patients who underwent colon or rectum transection early during intestinal mobilization (the protocol that was utilized between April 2004 and February 2006) were classified as belonging to the "early transection" (ET) group. On the other hand, patients who did not undergo colon or rectum transection until just before anastomosis or stoma-construction (the protocol that was utilized between November 2006 and March 2008) were classified as belonging to the "late transection" (LT) group. All surgeries were performed during open abdominal surgery using standard procedures by a well-trained specialist or a junior surgeon assisted by a specialist. To standardize the operative procedure, all anastomoses after anterior resections were performed using the double stapling technique. In all the patients, 2l of either polyethylene glycol lavage or sodium phosphate were used for preoperative mechanical bowel preparation. The use of preoperative oral antibiotics (LVFX, 300mg × 1day) and a wound retractor (Applied Medical, CA, USA) were decided by each surgeon. All the patients received 1g of cefmetazole intravenously at the time of anesthesia induction and 2g/day for three consecutive days after surgery. The abdominal cavity was washed out with copious amounts (2–6l) of warmed saline solution before wound closure. Abdominal suction drains were used 3 to 5days after surgery, if necessary. The abdominal wall was closed using absorbable coated braid or monofilament surgical suture, and the skin was closed using a skin stapler without subcutaneous suturing.

Three specimens were collected intraoperatively from the surgical field for bacteria cultures: the remaining fluid after peritoneal lavage (LAVAGE), post-knotted cut abdominal sutures (SUTURE), and subcutaneous swabs after abdominal closure (SUBCUT). Statistical analyses were performed using a chi-squared test, and $P < 0.05$ was considered significant.

Result

A total of 68 patients were entered into the study during the 40-month period. Patients who met the perioperative exclusion criteria (perioperative specimens for bacteria culture were not collected in six patients, and two patients developed anastomotic leakage) were excluded from the study. Finally, 60 patients were enrolled in the study; 29 patients were classified as ET, and 31 patients were classified as LT. A comparison of the demographic characteristics, type of surgery, and other variables associated with SSI is shown in Table 1. No significant

Table 1 Patient characteristics

Characteristics	Early transaction $n = 29$	Late transaction $n = 31$	P-value
Age (mean)	69.9 (52–83)	69.3 (52–83)	0.86
Gender			
Male	19	14	0.11
Female	10	17	
Operation performed			
Anterior resection	20	21	0.92
Hartmann's operation	2	2	0.95
Miles' operation	7	8	0.88
Diverting stoma	1	2	0.59
Mechanical Bowel preparation	29	31	1.00
Oral antibiotic administration (LVFX 300mg)	8	0	0.002
Blood transfusion	8	14	0.16
Use of wound retractor	3	3	0.93

differences were observed between the two groups except with regard to the preoperative administration of oral antibiotics.

SSI occurred more frequently among patients undergoing a Harmann's/Miles' operation (H–M) than among those undergoing an anterior resection (AR), regardless of the timing of colon transection (AR vs. H-M: ET, $P = 0.003$; LT, $P = 0.005$; ET + LT, $P = 0.0008$). When all the patients of ET and LT were compared, the incidence of SSI was statistically lower in the LT ($P = 0.03$; Fig. 1).

Bacteria were isolated from more than 50% of the ET among patients undergoing either AR or H–M, while the bacteria isolation rates among the LT were 9.5% and 40%, respectively (Fig. 2). IBC was found in 36.7% of the overall study population, with SSI occurring in 68% of the cases. The IBC rates of the ET (55.2%) and LT (19.4%) were significantly different ($P = 0.004$). The incidences of SSI in the ET and LT patients with IBC were similar, at 69% and 67%, respectively (Fig. 3).

The positive bacterial culture rate in the intraoperative specimens was lower for the SUTURE specimens than for the SUBCUT and LAVAGE specimens, although the rate of SSI was similar in all three groups (SSI rate: 50%, 64%, and 65%, respectively) (Fig. 4).

The isolated organisms from samples collected from the surgical field were compared with those collected from SSI wounds. Gram-positive anaerobic bacillus was isolated significantly more frequently from the surgical fields than from SSI wounds ($P = 0.006$). In contrast, enterococcus species were isolated significantly more frequently from SSI wounds than from the surgical fields ($P = 0.01$; Table 2).

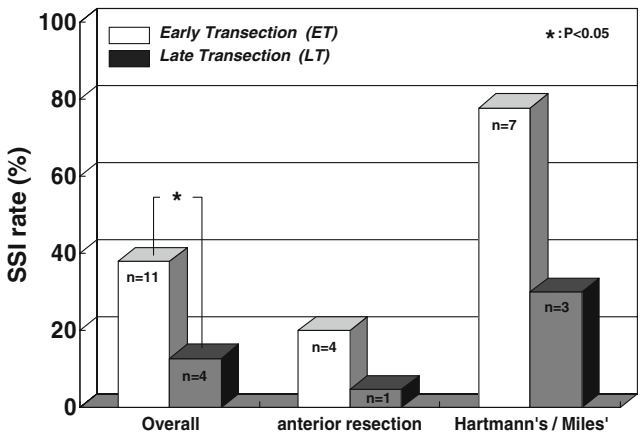

Figure 1 SSI occurred more frequently in H–M procedures than in anterior resection procedures regardless of either early or late colon transection. The LT had a lower incidence of SSI than the ET when compared with in total ($P<0.05$).

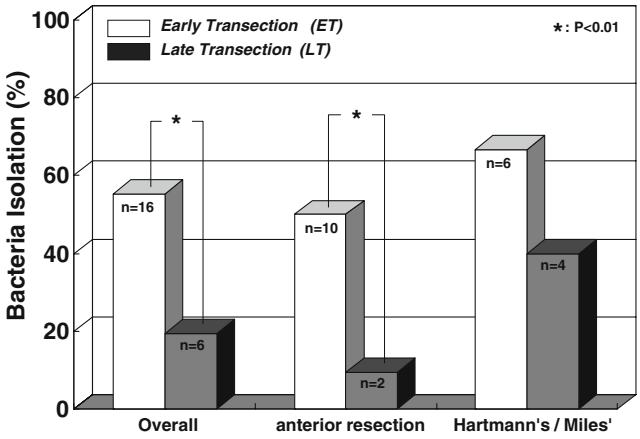

Figure 2 Bacteria were isolated in more than 50% of the cases undergoing an ET procedure in both the AR and H–M, while the rates of isolation were 9.5% and 40% in the LT, respectively.

Discussion

Several factors that affect the incidence of SSI, including patient and environmental factors, have been considered and reported previously.[3–5] As long as SSI cannot occur without existence of pathogens, however, minimizing bacterial contamination in the surgical field remains the best way to reduce the occurrence of SSI. In fact, Claesson et al. and Nishikawa et al. have reported that bacterial contamination of the surgical field is a strong predictor of postoperative wound infection.[14,15]

The presence of bacteria can lead to its proliferation and growth in healing tissue, affecting all processes of healing and promoting the impairment of collagen synthesis and the release of proteolytic enzymes.[16] These conditions may consequently lead to wound infection, delayed healing, and wound dehiscence.[17]

The spillage of bowel contents when the bowel is opened can easily contaminate both the abdominal cavity and the extraperitoneal area. Thus, the higher incidence of SSI in patients undergoing H–M, rather than AR, can be explained by contamination from the stoma. Once the surgical field has been contaminated, it is almost impossible to eliminate the spilled bacteria entirely, regardless of the amount of lavage fluid that is used. In this study, interestingly, the incidence of contamination in the LT was significantly less than half the incidence in the ET; however, the incidence of SSI was similar in the two groups (67% and 69%, respectively). Although the difference in the bacterial isolation rates between the ET and LT groups can be explained somewhat by possible differences in attempts to perform SSI surveillance, the difference in the surgical procedures may be the main reason for the large difference.

Controlling contamination of the surgical field is indeed essential; however, as long as bacteria exists in the stump of the transected bowel, it may be impossible to control

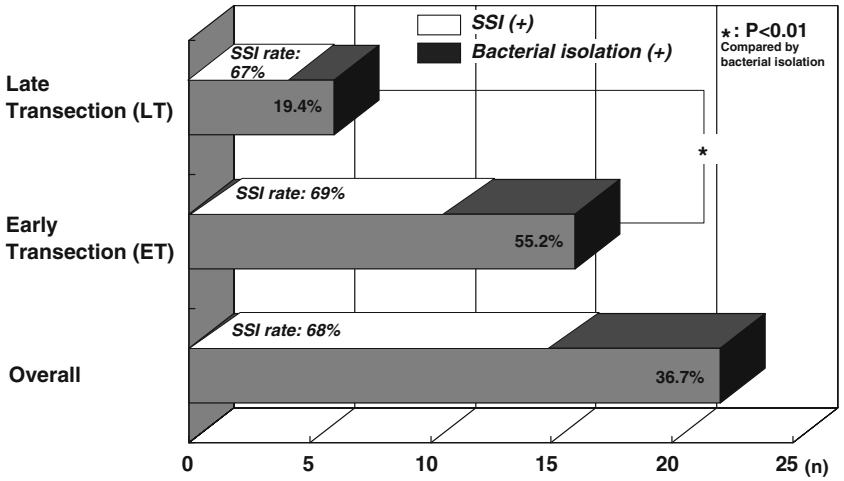

Figure 3 The IBC rates of the ET and LT were significantly different (P=0.004). However, the incidences of SSI in the ET and LT with IBC were similar at 69% and 67%, respectively.

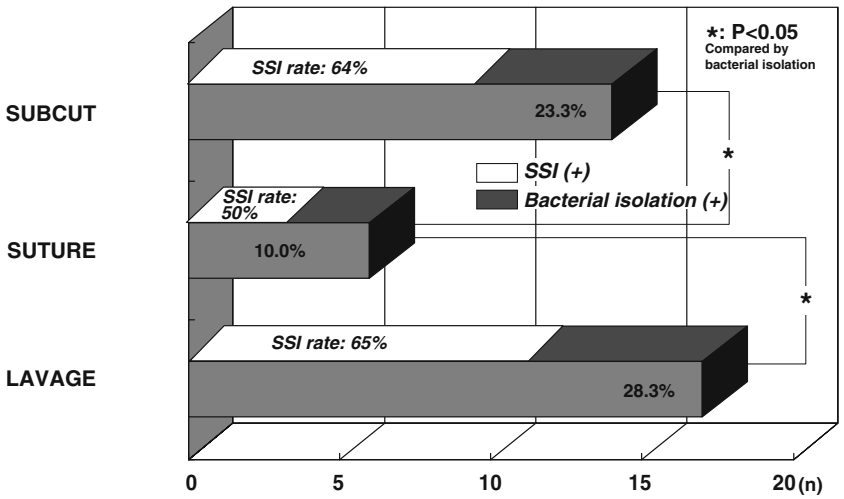

Figure 4 The SUTURE samples had a significant lower rate of bacterial isolation, compared with the SUBCUT and LAVAGE samples. The incidence of SSI was similar in all three groups: 50%, 64%, and 65%, respectively.

Table 2 Organisms isolated intraoperatively and those from SSI Wound

Intraoperative isolated pathogens		Isolated organisms		Significance
		SSI wound (26*)	Surgical field (38*)	
Gram-positive coccus				
Aerobes	Streptococcus sp.	0 (0%)	1 (2.6%)	NS
	Staphylococcus sp.	5 (19.2%)	9 (23.7%)	NS
	Enterococcus sp.	6 (23.1%)	1 (2.6%)	P<0.05
Gram-positive bacillus				
Aerobes				
	Corynebacterium sp.	2 (7.7%)	1 (2.6%)	NS
Anaerobes		1 (3.8%)	12 (31.6%)	P<0.01
Gram-negative bacillus				
Aerobes	*Escherichia coli*	0 (0%)	2 (5.3%)	NS
	Enterobacter sp.	2 (7.7%)	1 (2.6%)	NS
	Krebsiella pneumoninae	0 (0%)	1 (2.6%)	NS
	Pseudomonas aeruginosa	2 (7.7%)	0 (0%)	NS
Anaerobes		8 (30.7%)	9 (23.7%)	NS
Candida albicans		0 (0%)	1 (2.6%)	NS

bacterial contamination entirely, despite the use of mechanical stapling devices. Therefore, the chance of contamination presumably increases with the length of time that the bowel is being disconnected such as ET. Even in LT, postoperative abdominal contamination because of bacteria spillage from the bowel stump can occur. However, because the immune system recovers from its compromised status after surgery, such small contamination might not affect the SSI incidence, compared with the patients who are already bacterially contaminated intraoperatively. Other advantages of transecting the bowel during the late operative period include demarcation assurance in bowel viability. Additional bowel resection is sometimes needed for anastomosis or stoma construction when the bowel is transected with the mesentery during the early operative period. Conversely, the transection line can be determined easily in LT procedures because bowel viability is clearly demarcated during recto-sigmoid mobilization.

The isolation of bacteria from the SUTURE samples was lower than that from the LAVAGE or SUBCUT samples, presumably because the sutures that we used were absorbable coated braid sutures or monofilament sutures, which are less susceptible to contamination.[18] The similarity of the contamination rates in the LAVAGE and SUBCUT samples can be explained by the exposure of the subcutaneous tissue to the irrigation fluid during abdominal lavage. In contrast, the organisms isolated from SSI wounds and surgical fields were different, presumably because of the use of antibiotics. Cefmetazole is preferred for use in colorectal surgery because of its high sensitivity against *Escherichia coli*, *Bacteroides* sp., *Staphylococcus* sp., etc.; however, it has a low antibacterial activity against *Enterococcus* sp.. Thus, bacteria in the healing tissue that were not eliminated by the antibiotic during the perioperative period may proliferate and overgrow.

In this study, we found that minimizing bacterial contamination originating from the gut lumen reduced the incidence of SSI. For this reason, the bowel should not be transected until the surgeon is ready to perform the bowel anastomosis or abdominal wall closure. However, if it is unavoidable to open the bowel during the early operative period, the transected bowel stump should be sealed closed. Performing a recto-sigmoid operation with retained bowel continuity can be somewhat awkward for surgeons. Nevertheless, patients who undergo LT benefit from several advantages, including a reduced chance of SSI and assured bowel transection.

Conclusion

The results of the present study build upon those of previous reports in which bacterial contamination was found to be a predictor of SSI and LT were found to have more benefits than ET. To reduce SSI using a multi-faceted approach, minimizing the patient's immuno-compromised status and thoroughly controlling bacterial contamination are recommended.

Reference

1. Collins TC, Daley J, Henderson WH, Khuri SF. Risk factors for prolonged length of stay after major elective surgery. Ann Surg 1999;230:251–259. doi:10.1097/00000658-199908000-00016.
2. Taylor GD, Kirkland TA, McKenzie MM, Sutherland B, Wiens RM. The effect of surgical wound infection on postoperative hospital stay. Can J Surg 1995;38:149–153.
3. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Hospital infection control practices advisory committee. Infect Control Hosp Epidemiol 1999;20:250–278. doi:10.1086/501620.
4. Sørensen LT, Hemmingsen U, Kallehave F, Wille-JØrgensen P, Kjaerqaard J, MØller LN, JØrgensen T. Risk factors for tissue wound complications in gastrointestinal surgery. Ann Surg 2005;241:654–8. doi:10.1097/01.sla.0000157131.84130.12.
5. Saito T, Aoki K, Ebara K, Hirai S, Kitamura Y, Kasaoka Y et al. Surgical-site infection surveillance at a small-scale community hospital. J Infect Chemother 2005;11:204–206. doi:10.1007/s10156-005-0393-z.
6. Classen DC, Evans RS, Pestotnik SL, Horn SD, Menlove RL, Burke JP. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. N Engl J Med 1992;326:281–286.
7. Ishida H, Yokoyama M, Nakada H, Inokuma S, Hashimoto D. Impact of oral antimicrobial prophylaxis on surgical site infection and methicillin-resistant *Staphylococcus aureus* infection after elective colorectal surgery. Results of a prospective randomized trial. Surg Today 2001;31:979–983. doi:10.1007/s005950170006.
8. Takesue Y, Yokoyama T, Akagi S, Ohge H, Murakami Y, Sakashita Y et al. A brief course of colon preparation with oral antibiotics. Surg Today 2000;30:112–116. doi:10.1007/PL00010059.
9. Morita S, Nishisho I, Nomura T, Fukushima Y, Morimoto T, Hiraoka N et al. The significance of the intraoperative repeated dosing of antimicrobials for preventing surgical wound infection in colorectal surgery. Surg Today 2005;35:732–738. doi:10.1007/s00595-005-3026-3.
10. Miettinen RP, Laitinen ST, Mäkelä JT, Pääkkönen ME. Bowel preparation with oral polyethylene glycol electrolyte solution vs. no preparation in elective open colorectal surgery: prospective, randomized study. Dis Colon Rectum 2000;43:669–675. doi:10.1007/BF02235585.
11. Zmora O, Pikarsky AJ, Wexner SD. Bowel preparation for colorectal surgery. Dis Colon Rectum 2001;44:1310–1314. doi:10.1007/BF02234789.
12. Zmora O, Mahajna A, Bar-Zakai B, Rosin D, Hershko D, Shabtai M et al. Colon and rectal surgery without mechanical bowel preparation: a randomized prospective trial. Ann Surg. 2003;237:363–7. doi:10.1097/00000658-200303000-00010.
13. Furukawa K, Onda M, Suzuki H, Maruyama H, Akiya Y, Ashikari M et al. The usefulness of conducting investigations on intra-abdominal bacterial contamination in digestive tract operations. Surg Today. 1999;29:701–706. doi:10.1007/BF02482312.

14. Nishikawa K, Tanaka Y, Matsumoto A, Hayashi T, Kawano S, Suzuki H et al. Where does the surgical infection (SSI) originate from?—influence of surgical field contamination to the SSI (wound)—(in Japanese with English abstract). Nippon Shokaki Geka Gakkai Zasshi 2008;41:12–21. Jpn J Gastroenterol Surg.
15. Claesson BE, Holmlund DE. Predictors of intraoperative bacterial contamination and postoperative infection in elective colorectal surgery. J Hosp Infect 1988;11:127–135. doi:10.1016/0195-6701(88)90054-0.
16. Ahrendt GM, Tantry US, Barbul A. Intra-abdominal sepsis impairs colonic reparative collagen synthesis. Am J Surg 1996;171:102–107. doi:10.1016/S0002-9610(99)80082-8.
17. De Haan BB, Ellis H, Wilks M. The role of infection on wound healing. Surg Gynecol Obstet 1974;138:693–700.
18. Togo S, Kubota T, Takahashi T, Yoshida K, Matsuo K, Morioka D et al. Usefulness of absorbable sutures in preventing surgical site infection in hepatectomy. J Gastrointest Surg 2008;12:1041–1046. doi:10.1007/s11605-007-0297-6.

J Gastrointest Surg (2008) 12:2001–2009
DOI 10.1007/s11605-008-0568-x

Laparoscopic-assisted vs. Open Colectomy for Cancer: Comparison of Short-term Outcomes from 121 Hospitals

Karl Y. Bilimoria · David J. Bentrem · Ryan P. Merkow · Heidi Nelson · Edward Wang · Clifford Y. Ko · Nathaniel J. Soper

Received: 21 April 2008 / Accepted: 4 June 2008 / Published online: 24 June 2008

Abstract
Background Overall postoperative morbidity and mortality after laparoscopic-assisted colectomy (LAC) and open colectomy (OC) have been shown to be generally comparable; however, differences in the occurrence of specific complications are unknown. The objective of this study was to determine whether certain complications occurred more frequently after LAC vs. OC for colon cancer.
Methods Using the American College of Surgeons-National Surgical Quality Improvement Project's (ACS-NSQIP) participant-use file, patients were identified who underwent colectomy for cancer at 121 participating hospitals in 2005–2006. Multiple logistic regression models including propensity scores were developed to assess the risk-adjusted association between surgical approach (LAC *vs*. OC) and 30-day outcomes. Patients were excluded if they underwent emergent procedures, were ASA class 5, or had metastatic disease.
Results Of the 3,059 patients who underwent elective colectomy for cancer, 837 (27.4%) underwent LAC and 2,222 (72.6%) underwent OC. There were no significant differences in age, comorbidities, ASA class, or body mass index (BMI) between patients undergoing LAC vs. OC. Patients undergoing LAC had a lower likelihood of developing any adverse event compared to OC (14.6% *vs.* 21.7%; OR 0.64, 95% CI 0.51–0.81, *P<0.0001*), specifically surgical site infections, urinary tract infections, and pneumonias. Mean length of stay was significantly shorter after LAC vs. OC (6.2 vs. 8.7 days, *P*<0.0001). There were no differences between LAC and OC in the reoperation rate (5.5% vs. 5.8%, *P*=0.79) or 30-day mortality (1.4% vs. 1.8%, *P*=0.53).
Conclusions Laparoscopic-assisted colectomy was associated with lower morbidity compared to OC in select patients, specifically for infectious complications.

Keywords Colon cancer · Colectomy · Laparoscopy · Cancer · Surgery · National Surgical Quality Improvement Program

This study was presented in part at the 2008 Annual Meeting of the Society for Surgery of the Alimentary Tract in San Diego, CA on May 21, 2008.

K. Y. Bilimoria (✉) · D. J. Bentrem · E. Wang · N. J. Soper
Department of Surgery, Feinberg School of Medicine,
Northwestern University,
251 E. Huron Street, Galter 3-150,
Chicago, IL 60611, USA
e-mail: k-bilimoria@northwestern.edu

R. P. Merkow
Department of Surgery,
University of Colorado School of Medicine,
Denver, CO, USA

H. Nelson
Department of Surgery, Mayo Clinic,
Rochester, MN, USA

C. Y. Ko
Department of Surgery, University of California, Los Angeles (UCLA) and VA Greater Los Angeles Healthcare System,
Los Angeles, CA, USA

Introduction

Colon cancer continues to be a major healthcare concern in the United States. Malignancies of the colon account for the fourth highest cancer incidence and the second leading cause of cancer death in the United States.[1] Surgery remains the primary treatment modality; however, colectomy is associated with appreciable perioperative morbidity

and mortality rates.[2,3] Laparoscopic-assisted colectomy (LAC) for cancer was first reported in the early 1990s[4,5], and with the success of laparoscopic cholecystectomy, it was suggested that a minimally invasive approach for colectomy could lead to improved short-term outcomes after colectomy.[6]

Numerous studies have examined short-term outcomes and have established that LAC can be performed with overall morbidity and mortality rates, which are comparable to OC.[7–13] Most of these studies have been from single institutions or multi-institutional groups, which are high-volume and have an expertise in laparoscopic colon surgery. Although these reports have provided important information regarding the overall safety of LAC, they have been underpowered to examine specific complications and short-term outcomes at a broad range of hospitals. Moreover, the classification of complications varies widely between these studies and hinders comparisons.

Thus, specific differences in postoperative complications between LAC and OC have not been well described, particularly outside of specialized centers. The objectives of this study were to compare prospectively collected, risk-adjusted short-term outcomes after LAC and OC for cancer using the American College of Surgeons National Surgical Quality Improvement Project (ACS-NSQIP) database, which provides a large sample of patients from 121 hospitals in the United States. Specifically, we sought to determine whether certain complications occurred more frequently based on the surgical approach, laparoscopic vs. open, for colon cancer.

Methods

Data Acquisition and Patient Selection

Originally developed as a quality improvement initiative by the Veteran's Health Administration in 1991, NSQIP was adopted by the ACS in 2001. ACS-NSQIP (http://www.acsnsqip.org/) is a prospective, multi-institutional, risk-adjusted outcomes program, which provides participating hospitals with comparative data for the purposes of quality improvement.[14] In July 2007, a participant-use file (PUF) was made available to hospitals enrolled in the ACS-NSQIP program.[15] The ACS-NSQIP 2007 dataset contains information on 152,490 patients who underwent surgery in 2005 and 2006 at 121 hospitals (59% academic and 41% community).[14]

The details of the ACS-NSQIP sampling strategy, data abstraction, variables collected, and outcomes monitored have been previously described.[14,16–19] Briefly, the program collects detailed data regarding patient demographics, preoperative risk factors, and laboratory values prior to the index surgical procedure. Operative variables are also collected. Perioperative outcomes including surgical site infections (SSI), respiratory events, renal complications, central nervous system events, cardiac complications, other events, reoperation, length of stay, and mortality are evaluated at 30 days after surgery irrespective of whether the event occurs as an inpatient or outpatient. The sampling strategy currently requires reporting of the first 40 consecutive eligible cases on an 8-day cycle such that the subsequent cycle starts on a different day of the week in order to capture a different variety of cases. Major cases are eligible for inclusion and certain cases with low morbidity and mortality are limited to less than three cases per cycle (e.g., lumpectomy and inguinal herniorraphy). Data abstraction is overseen at each site by surgical certified nurse reviewers who go through an initial intensive training process and continuing education courses to standardize data abstraction.[20] Data consistency and reliability are assessed annually at each hospital through an on-site audit during which an inter-rater reliability analysis is performed.[17,18]

Using the ACS-NSQIP PUF, all patients who underwent a colon resection were identified using Current Procedural Terminology (CPT) codes.[21] To identify only those patients with malignancy, patients were limited by International Classification of Disease, 9th Edition (ICD-9) postoperative diagnosis codes for malignant neoplasms of the colon.[10] All patients with appendiceal and rectal cancers were excluded. High-risk patients were excluded including those with emergent operations, disseminated cancer, preoperative ventilator dependence, American Society of Anesthesiologists (ASA) class 5, preoperative sepsis or Systemic Inflammatory Response Syndrome (SIRS), or preoperative renal failure (acute or requiring dialysis).

Preoperative Variables

Potential independent variables included patient demographics, comorbidities, preoperative laboratory values, and intraoperative variables (Table 1). Standard definitions for these variables have been described previously.[16] The surgical approach was dichotomized based on CPT coding into laparoscopic-assisted colectomy (LAC) or open colectomy (OC). Patient demographic variables included age (<60, 60–75 years, >75 years), gender, and race/ethnicity (white, black, other) (Table 1). The location of the tumor was also included (cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid, other). Lifestyle factors consisted of smoking status (within year prior to surgery) and alcohol intake (more than two drinks per day). The patient's preoperative risk was evaluated according to ASA class (1/2 vs. 3/4) and functional status (independent vs. partially/totally depen-

Table 1 Characteristics of 3,059 Patients Undergoing Laparoscopic-Assisted *vs.* Open Colectomy for Cancer in 2005–2006

	Laparoscopic-assisted Colectomy (n=837)	Open Colectomy (n=2,222)	P value
Gender (%female)	51.7%	49.4%	P=0.25
Median age (interquartile range) in years	70 (59–78)	68 (57–78)	P=0.094
Race/Ethnicity			P=0.006
White	74.1%	70.6%	
Black	8.6%	9.2%	
Other	17.3%	20.2%	
Smoking Status (within past year)	10.5%	13.3%	P=0.040
Alcohol Intake (>2 drinks/day)	3.8%	4.0%	P=0.86
Tumor Location			P<0.0001
Cecum	20.1%	13.5%	
Ascending Colon	27.0%	17.0%	
Hepatic Flexure	4.1%	3.0%	
Transverse Colon	5.1%	6.8%	
Splenic Flexure	1.9%	2.4%	
Descending Colon	3.9%	4.2%	
Sigmoid Colon	18.1%	33.7%	
Other/Not Otherwise Specified	19.8%	19.4%	
American Society of Anesthesiologists (ASA) Class			P=0.12
1	3.7%	3.5%	
2	50.7%	46.0%	
3	41.9%	46.4%	
4	3.7%	4.1%	
Body Mass Index (mean in kg/m^2)	27.7	28.1	*P=0.078*
Dyspnea (At Rest or Moderate Exertion)	15.9%	15.6%	P=0.59
Past Medical History			
Diabetes	15.3%	16.4%	P=0.51
Chronic Obstructive Pulmonary Disease	5.1%	6.1%	P=0.34
Congestive Heart Failure (within 30 days of surgery)	1.0%	1.5%	P=0.30
Coronary Artery Disease[a]	12.2%	13.6%	P=0.34
Peripheral Vascular Disease[b]	12.3%	14.5%	P=0.12
Neurologic Event/Disease[c]	7.9%	8.7%	P=0.46
Bleeding Disorders	3.3%	4.1%	P=0.31
Ascites	0.5%	1.5%	P=0.17
Steroid Use for Chronic Condition	2.5%	2.9%	P=0.62
Weight Loss (>10% of Body Weight in last 6 months)	2.4%	6.1%	P<0.0001
Transfusion			
Preoperative (>4 units)	0.1%	0.5%	P=0.31
Wound Classification			
Clean-Contaminated	97.3%	94.0%	P=0.001
Contaminated/Dirty/Infected	2.7%	6.0%	
Operative Time (mean ± SD)	155.4±62.7	152.1±83.0	P=0.23

[a] Includes a history of angina, myocardial infarction (within 6 months of surgery), percutaneous cardiac intervention, or cardiac surgery

[b] Includes a history of revascularization for peripheral vascular disease, claudication, rest pain, amputation, or gangrene

[c] Includes a history of stroke (with or without residual deficit), TIAs, hemiplegia, paraplegia, quadriplegia, or impaired sensorium

dent). Comorbidity variables evaluated include the presence or absence of ascites, diabetes (requiring oral medication or insulin vs. none), chronic obstructive pulmonary disease, congestive heart failure (within 30 days prior to surgery), coronary artery disease (includes angina, myocardial infarction within 6 months of surgery, percutaneous cardiac intervention, or cardiac surgery), peripheral vascular disease (includes revascularization for peripheral vascular disease, claudication, rest pain, amputation, or gangrene), neurologic event/disease (includes stroke with or without residual deficit, transient ischemic attacks, hemiplegia, paraplegia, quadraplegia, or impaired sensorium), renal failure (includes acute or chronic disease), or bleeding disorders. Other variables assessed were steroid use for

chronic condition, weight loss >10% of body weight in 6 months prior to surgery, and transfusion requirements (intraoperative/postoperative vs. none). Laboratory values were dichotomized using NSQIP definitions of abnormal values (Table 2).

Outcomes

Standard definitions for NSQIP outcomes have been described previously.[16] Patients were followed for 30 days in-hospital and as outpatients. Thirty-day outcomes examined include surgical site infection, pneumonia, pulmonary embolism, unplanned intubation, renal failure, urinary tract infection, ventilator dependence for >48 hours, stroke, coma >24 hours, cardiac arrest, myocardial infarction, bleeding, deep venous thrombosis, or sepsis. The occurrence of any postoperative complications was also assessed. In addition, return to the OR within 30 days was assessed. Thirty-day mortality was evaluated irrespective of whether the death was in-hospital, after the patient was discharged, or readmitted to another hospital. Length of stay (LOS) after the index surgery was dichotomized based on the median LOS.

Statistical Analysis

Continuous variables were compared using *t* tests. Categorical variables were compared using χ^2 tests. Medians were compared with the Mann–Whitney *U* test. For each dichotomous variable, differences between LAC and OC were compared using χ^2 tests. Variables that had a *P* value <0.20 were potential candidates for inclusion in multiple logistic regression models. If on univariate analysis, the outcome by surgical approach had a *P* value <0.10, multivariable models were developed to assess the association between surgical approach (laparoscopic-assisted vs. open colectomy) and specific postoperative outcomes. Variables were added to the model in a forward stepwise fashion. The surgical approach variable was forced into the regression model.

To reduce bias related to nonrandom assignment of treatment, propensity score methods were employed.[22] Using a multiple logistic regression model, which included all preoperative patient characteristics, comorbidities, and laboratory values, propensity scores were computed as the predicted probability that the patient underwent LAC as opposed to OC. Propensity scores were categorized into quintiles. To decrease selection issues when examining the association between surgical approach and outcome, the categorized propensity score was included in the logistic regression model.

Odds ratios (OR) with 95% confidence intervals (CI) were generated. The Hosmer–Lemeshow goodness-of-fit test and the c-index of the receiver-operator characteristic (ROC) curves were used to assess the models.[23] All analyses were performed using SPSS, version 15 (Chicago, IL). All *P* values reported are two-sided.

Results

Of the 152,490 patients in the ACS-NSQIP PUF, 3,059 patients were identified who underwent colectomy for cancer at 121 hospitals and met the inclusion criteria. Of

Table 2 Comparison of Preoperative Laboratory Values for Patients Undergoing Laparoscopic-Assisted *vs.* Open Colectomy for Cancer

	Laparoscopic-assisted Colectomy (*n*=837)	Open Colectomy (*n*=2,222)	*P* value
Sodium <135 mmol/L	3.6%	5.2%	*P*=0.062
Sodium >145 mmol/L	0.9%	1.7%	
Blood Urea Nitrogen (BUN) > 40 mg/dL	0.7%	1.3%	*P*=0.20
Creatinine > 1.2 mg/dL	14.6%	14.3%	*P*=0.83
Albumin (mean±SD) g/dL	3.9±0.5	3.8±0.6	*P*<0.0001
Total Bilirubin >1.0 mg/dL	8.5%	7.9%	*P*=0.66
Aspartate transaminase (SGOT) >40 U/L	3.4%	6.9%	*P*=0.003
Alkaline Phosphatase >125 IU/L	4.3%	8.2%	*P*=0.003
White Blood Cell (WBC) count ≤4,500/cumm	7.1%	8.4%	*P*=0.15
White Blood Cell (WBC) count >11,000/cumm	5.0%	6.5%	
Hematocrit <38%	43.8%	53.3%	*P*<0.0001
Hematocrit >45%	8.8%	2.2%	
Platelet Count <150,000/cumm	4.8%	5.0%	*P*=0.16
Platelet Count >400,000/cumm	9.3%	11.8%	
Partial Thromboplastin Time (PTT) >35 sec	5.3%	9.2%	*P*=0.014

Missing values for sodium (*n*=325), BUN (*n*=360), creatinine (*n*=283), total bilirubin (*n*= 1,084), alkaline phosphatase (*n*=1,066), SGOT (*n*= 1,060), WBC count (*n*=205), hematocrit (*n*=328), platelet count (*n*=198), PTT (*n*=1,480). Thresholds for abnormal laboratory values based on standard NSQIP definitions.

those patients, 837 (27.4%) underwent LAC, and 2,222 (72.6%) underwent OC. The LAC and OC groups were similar with regard to gender, age, alcohol intake, ASA class, BMI, preexisting comorbidities, chronic steroid use, and preoperative transfusion requirements (Table 1). However, compared to those undergoing OC, patients undergoing LAC were more frequently white (74.1% vs. 70.6%, P=0.006), non-smokers (89.5% vs. 86.7%, P=0.04), had proximal colon tumors (51.2% vs. 33.5%, P<0.0001), did not have a >10% weight loss in the last 6 months (97.6% vs. 93.9%, P<0.0001), or had a wound classified as clean-contaminated (97.3% vs. 94.0%, P<0.0001). Preoperaative laboratory values were also similar between the two groups except for the OC group having a lower mean albumin level (statistically different but clinically comparable; 3.8 vs. 3.9 mg/dL) and a higher proportion of patients with abnormal aspartate transaminase levels (6.9% vs. 3.4%, P=0.003), alkaline phosphatase levels (8.2% vs. 4.3%, P=0.003), and partial thromboplastin times (9.2% vs. 5.3%, P=0.014) (Table 2).

Univariate Analysis

There was not a significant difference in operative time between the LAC and OC groups (155.4 min vs. 152.1 min, P=0.23). Patients undergoing OC experienced a postoperative complication more frequently than patients undergoing LAC (21.7% vs. 14.6%, P<0.0001). Specifically, patients undergoing OC had a significantly higher frequency of SSI (11.8% vs. 9.1%, P=0.03) and pneumonia (3.4% vs. 1.8%, P=0.022) than patients undergoing LAC. There was also a trend toward higher rates of urinary tract

Table 3 Thirty-Day Postoperative Outcomes for Laparoscopic-Assisted Compared to Open Colectomy for Cancer

Outcomes	Laparoscopic-assisted Colectomy (%) (n=837)	Open Colectomy (%) (n=2,222)	P value[a]	Multivariable Odds Ratio (95% Confidence Interval) *without* Propensity Score Adjustment[b]	Multivariable Odds Ratio (95% Confidence Interval) *with* Propensity Score Adjustment[b]
Any Adverse Event	14.6	21.7	P<0.0001	1.56 (1.25–1.95)	1.52 (1.22–1.91)
Surgical Site Infection (SSI)[c]	9.1	11.8	P=0.033	1.29 (1.02–1.62)	1.27 (0.97–1.67)
Superficial	6.0	8.1	P=0.54	~	~
Deep	0.8	1.3	P=0.45	~	~
Organ Space	2.9	2.1	P=0.22	~	~
Wound Disruption/ Dehiscence	0.5	1.5	P=0.025	2.99 (1.05–8.50)	2.70 (0.95–7.72)
Pneumonia	1.8	3.4	P=0.022	1.83 (1.04–3.22)	1.57 (0.99–2.80)
Pulmonary Embolism	0.5	0.8	P=0.47	~	~
Unplanned Intubation	1.6	2.5	P=0.13	~	~
Renal Failure (Acute and/or Progressive)	1.3	2.0	P=0.23	~	~
Urinary Tract Infection	1.9	3.2	P=0.066	1.79 (1.02–3.15)	1.78 (1.01–3.13)
On ventilator > 48 hours (failure to wean)	1.8	2.1	P=0.67	~	~
Stroke	0.2	0.4	P=0.74	~	~
Coma >24 hours	0.4	0.1	P=0.13	~	~
Cardiac Arrest	0.5	0.5	P=1.00	~	~
Myocardial Infarction	0.2	0.5	P=0.38	~	~
Bleeding Requiring Transfusion	0.7	0.5	P=0.60	~	~
Deep Venous Thrombosis	0.6	1.3	P=0.12	~	~
Sepsis	4.7	6.5	P=0.060	1.35 (0.94–1.95)	1.34 (0.98–1.82)
Return to Operating Room	5.5	5.8	P=0.79	~	~
Postoperative Length of Stay >6 days	26.3	49.7	P<0.0001	1.73 (1.26–2.39)	1.71 (1.17–2.51)
Mortality	1.4	1.8	P=0.53	~	~

[a] Univariate P value, χ^2 tests

[b] Odds ratio of experiencing the complication after OC (compared to LAC). Multivariate models adjusting for propensity scores were developed if P<0.10 on univariate analysis.

~Indicates that the univariate P value was ≥0.10, thus this outcome was not assessed in a multivariate model.

[c] Patients can be classified as having more than one type of SSI, so the subgroup percentages are larger than the overall SSI percentage.

Odds ratios >1.0 indicate a higher likelihood of the adverse event occurring.

All outcomes assessed at 30 days after the index operation.

infection (UTI) (3.2% vs. 1.9%, *P=0.*066) and sepsis (6.5% vs. 4.5%, *P*=0.060) for patients undergoing OC compared to LAC. On average, patients undergoing OC had significantly longer length of stay compared to LAC patients (6.2 days vs. 8.7 days, *P*<0.0001).

There was not a significant difference in postoperative complication rates between LAC and OC for PE, renal failure, stroke, coma, cardiac arrest, myocardial infarction, or bleeding requiring transfusion (Table 3). Patients undergoing OC had a statistically insignificant higher risk of unplanned intubation (1.6% vs. 2.5%, *P*=0.13) and DVT (0.6% vs. 1.3%, *P*=0.12). There was also not a significant difference in the proportion of patients who required a reoperation within 30 days. Moreover, 30-day mortality rates between LAC and OC did not differ significantly (1.4% vs. 1.8%, *P*=0.53). There were no complications evaluated which were significantly more likely after LAC compared to OC.

Multivariable Analysis

Multivariable models were created to assess the impact of surgical approach on specific complications and events while adjusting for potential confounders. On multivariable analysis, patients undergoing OC had a higher likelihood of developing a SSI (OR 1.29, 95% CI 1.02–1.62), wound disruption/dehiscence (OR 2.99, 95% CI 1.05–8.50), pneumonia (OR 1.83, 95% CI 1.04–3.22), and UTI (OR 1.79, 95% CI 1.02–3.15) compared to patients undergoing LAC (Table 3). Patients undergoing OC were also significantly more likely to have a longer length of stay (OR 1.73, 95% 1.26–2.39). When propensity scores were included in the model, the effect of surgical approach on outcomes diminished marginally, but the change was enough to make the differences for SSI, wound disruption/dehiscence, and pneumonia statistically insignificant, though likely still clinically meaningful. After adjusting for propensity scores, there was still a significantly lower risk of any adverse event (OR 1.52, 95% C 1.22–1.91), UTI (OR 1.78, 95% CI 1.01–3.13), and a longer length of stay (OR 1.71, 95% CI 1.17–2.51).

The predictors of overall morbidity adjusting for propensity scores are shown in Table 4. The risk of experiencing any complication (i.e., overall morbidity) was significantly higher for patients undergoing OC compared to LAC. Other factors associated with an increased risk of overall morbidity in patients undergoing colectomy for cancer included higher ASA class, preoperative dyspnea, greater BMI, history of COPD, a low WBC count, older age (>60 years), preoperative weight loss >10% in the last 6 months, a history of alcohol intake more than two drinks per day, and a contaminated/dirty/infected wound class.

Table 4 Factors Associated with the Occurrence of Any Adverse Event after Colectomy for Cancer

	Odds Ratio (95% Confidence Interval)	*P* value
Surgical Approach[a]		
Laparoscopic-Assisted Colectomy	1.0 (Referent)	
Open Colectomy	1.52 (1.22–1.91)	*P*<0.0001
ASA Class		
1/2	1.0 (Referent)	
3/4	1.53 (1.25–1.87)	*P*<0.0001
Dyspnea		
None	1.0 (Referent)	
At Rest or On Exertion	1.45 (1.14–1.86)	*P*=0.003
BMI (continuous)	1.03 (1.02–1.05)	*P<0.0001*
COPD		
None	1.0 (Referent)	
Present	1.58 (1.10–2.25)	*P*=0.012
WBC		
White Blood Cell (WBC) count 4,500 to 11,000/mm^3	1.0 (Referent)	
White Blood Cell (WBC) count ≤4,500/mm^3	1.68 (1.22–2.31)	*P*=0.001
Age		
<60 years	1.0 (Referent)	
60–75 years	1.27 (1.00–1.62)	*P*=0.053
>75 years	1.47 (1.14–1.89)	*P*=0.003
Weight Loss		
None	1.0 (Referent)	
>10% of Total Body Weight	1.54 (1.05–2.25)	*P*=0.027
Alcohol Intake		
Minimal	1.0 (Referent)	
>2 drinks/day	1.56 (1.01–2.41)	*P*=0.046
Wound Class		
Clean–Contaminated	1.0 (Referent)	
Contaminated/Dirty/Infected	1.46 (1.00–2.14)	*P*=0.048

Odds ratios >1.0 indicate a higher risk of any adverse event occurring. Propensity scores predicting likelihood of undergoing a LAC vs. OC were included in the model to adjust for nonrandom treatment assignment.

Variables dropped from the model include history of vascular disease, history of neurologic disease, history of coronary artery disease, CPT code, and creatinine.

[a] Forced into the logistic regression model.

Discussion

Although multiple studies have demonstrated comparable short-term outcomes for LAC and OC, there is little evidence to suggest whether specific types of complications occur more frequently after OC or LAC.[7–13] Most studies are underpowered to examine the frequency of specific complications after LAC and are typically based on single-institution experiences. Thus, the objective of this study was to compare differences in short-term outcomes for

elective LAC and OC using a large group of patients from more than 120 hospitals.

Overall morbidity rates vary widely in prospective randomized clinical trials from 4% to 33%, likely as a result of the different complication definitions employed.[12] Tjandra et al. examined the results from 17 prospective randomized controlled trials and found that LAC was associated with a significantly lower risk of postoperative complications compared to OC (20.7% vs. 22.6%, $P=0.05$).[12] In a population-based analysis using administrative data, Steele et al. found that the overall complication rate based on ICD-9 codes was lower for LAC compared to OC (18% vs. 22%), and there were no differences in specific complications between the two groups.[24,25] In our study, the LAC and OC groups were similarly matched on baseline characteristics. In addition, all 121 hospitals use standardized, validated ACS-NSQIP definitions with annual inter-rater reliability evaluations for each participating hospital.[18] Based on this standardized, clinically collected data, we found that the overall complication rate was considerably lower after LAC compared to OC (14.6% vs. 21.7%, $P<0.0001$), even after adjusting for patient demographics and comorbidities. Other than surgical approach, multiple additional factors were associated with a higher risk of postoperative complications after colectomy including ASA class, dyspnea, BMI, COPD, neutropenia, age >60 years, preoperative weight loss, alcohol intake, and wound class. The impact of surgical approach on the risk of experiencing a complication was comparable to other important factors such as age, ASA class, and BMI.

Although studies have examined the frequency of postoperative adverse events, few have identified specific complications that differ in frequency between LAC and OC. In an attempt to address this issue, a recent metaanalysis of clinical trials found that wound complications were the only individual postoperative adverse event that differed between LAC and OC.[12] In comparison to patients undergoing LAC, we found that patients undergoing OC had a higher risk of having a SSI, wound disruption, pneumonia, and UTI, even after adjusting for preoperative risk factors. Studies have investigated the impact of laparoscopy on the immune system and concluded that the immune response is better preserved after minimally invasive surgery compared to open surgery, and this may result in lower infection rates after LAC compared to OC.[26,27] Thus, LAC may offer an opportunity to reduce the frequency of infectious complications in select patients. The results of large, multicenter trials should be pooled to further compare the risk of specific complications in well-matched cohorts as was done recently for long-term outcomes.[28]

The efficiency of laparoscopic colon surgery, particularly a decrease in length of stay has been extensively studied.[12] In the prospective trials reported to date, the mean operative time was 28% longer for LAC (range 142 to 222 min) compared to OC (range 101 to 177 min), and all studies reported that LAC took more time than OC,[12] except one which found there was no difference in operative time between the two approaches.[29] We found no difference in operative time by surgical approach when colectomy is performed at these 121 hospitals. We found no difference in reoperation rates between LAC and OC, and these rates were comparable to those reported in clinical trials.[7,30] Conversely, length of stay was significantly shorter for LAC compared to OC. Thus, as has been postulated based on data from 14 randomized trials[12], LAC may offer an opportunity to reduce the length of stay, even in a large, multi-institutional setting.

Prospective randomized trials have reported mortality rates ranging from 0 to 1.1%.[12] In a recent population-based study using the National Inpatient Sample (NIS), Steele et al. demonstrated a perioperative mortality rate of 0.6%.[25] However, the NIS does not include deaths that occur in the outpatient setting or upon readmission. In examining the postoperative mortality rate at 30 days after LAC irrespective of where the death occurred, we found a mortality rate of 1.4%. Although this is higher than that reported in some multi-institutional clinical trials, the rate is comparable to many studies and is considerably lower than the 2.4% mortality rate observed in a study of more than 11,000 laparoscopic colectomies from 1,200 hospitals from the National Cancer Data Base.[31]

The results of this study should be interpreted in consideration of certain limitations. Importantly, retrospective comparisons of treatment may suffer from confounding by indication if patients are selected to undergo a specific treatment based on the clinical scenario. However, multiple steps were taken to minimize selection issues in this study. First, the preoperative clinically collected data in the ACS-NSQIP dataset allows detailed assessment of how well the LAC and OC groups are matched and facilitates adjustment for differences between the two groups in the analysis. Second, the patients included in the study were restricted by specifically excluding emergent and high-risk cases to minimize differences between the two groups. Third, propensity scores were used in the multivariable analysis to further account for differences in the likelihood of undergoing LAC or OC. Propensity scores did not qualitatively affect the results, but did somewhat blunt the differences in outcomes between LAC and OC. Nonetheless, some selection bias may still exist, and evidence from prospective randomized clinical trials should be considered the gold standard; however, in the case of specific postoperative complications, information from trials is not available.

A second limitation concerns the coding of the primary procedure. It is unknown how much of the procedure was

performed laparoscopically, how the anastomosis and vascular pedicle were addressed, or whether the patients underwent conversion from LAC to OC. The surgical approach was dichotomized into LAC and OC based on the CPT codes selected by the surgeon, likely representing how the bulk of the procedure was performed. Finally, the analyses were limited to those variables included in the ACS-NSQIP dataset, thus a missing variable bias may be present. For example, no information was available regarding the Stage of the disease, except for the presence of distant metastases, and those Stage IV patients were excluded from our analysis. However, distinctions of localized disease should not appreciably impact perioperative outcomes. In addition, the ACS-NSQIP dataset does not have information on hospital characteristics.

Conclusion

The results of this study demonstrate that LAC is safe in select patients from a large sample of hospitals. No complications occurred at a higher frequency after LAC, while a number of complications occurred more frequently after OC. In particular, patients undergoing OC had a higher risk of infectious complications including SSI, pneumonia, and UTI compared to the LAC group. Operative time and reoperation rates were comparable with reported rates from clinical trials. Although observational studies cannot completely adjust for potential selection bias and confounding, expanding the use of laparoscopic surgery for colon cancer is reasonable based on the short-term results demonstrated in this study, particularly as patients may be spared certain infectious complications.

Acknowledgments ACS NSQIP Disclaimer: The ACS NSQIP and the hospitals participating in the ACS NSQIP are the source of the data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

References

1. Jemal A, Siegel R, Ward E et al. Cancer statistics. CA Cancer J Clin 2007;57(1):43–66.
2. Prystowsky JB, Bordage G, Feinglass JM. Patient outcomes for segmental colon resection according to surgeon's training, certification, and experience. Surgery. 2002;132(4):663–670. Discussion 670–672. doi:10.1067/msy.2002.127550.
3. Schrag D, Cramer LD, Bach PB et al. Influence of hospital procedure volume on outcomes following surgery for colon cancer. JAMA. 2000;284(23):3028–3035. doi:10.1001/jama.284.23.3028.
4. Cooperman AM, Katz V, Zimmon D, Botero G. Laparoscopic colon resection: a case report. J Laparoendosc Surg. 1991;1(4):221–224.
5. Jacobs M, Verdeja JC, Goldstein HS. Minimally invasive colon resection (laparoscopic colectomy). Surg Laparosc Endosc. 1991;1(3):144–150.
6. Phillips EH, Franklin M, Carroll BJ et al. Laparoscopic colectomy. Ann Surg. 1992;216(6):703–707. doi:10.1097/00000658-199212000-00015.
7. Veldkamp R, Kuhry E, Hop WC et al. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol 2005;6(7):477–484. doi:10.1016/S1470-2045(05)70221–7.
8. Guillou PJ, Quirke P, Thorpe H et al. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. Lancet. 2005;365(9472):1718–1726. doi:10.1016/S0140-6736(05)66545-2.
9. Lacy AM, Garcia-Valdecasas JC, Delgado S et al. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. Lancet. 2002;359(9325):2224–2229. doi:10.1016/S0140-6736(02)09290-5.
10. Milsom JW, Bohm B, Hammerhofer KA et al. A prospective, randomized trial comparing laparoscopic versus conventional techniques in colorectal cancer surgery: a preliminary report. J Am Coll Surg. 1998;187(1):46–54. Discussion 54–55. doi:10.1016/S1072-7515(98)00132-X.
11. Hasegawa H, Kabeshima Y, Watanabe M et al. Randomized controlled trial of laparoscopic versus open colectomy for advanced colorectal cancer. Surg Endosc. 2003;17(4):636–640. doi:10.1007/s00464-002-8516-4.
12. Tjandra JJ, Chan MK. Systematic review on the short-term outcome of laparoscopic resection for colon and rectosigmoid cancer. Colorectal Dis. 2006;8(5):375–388. doi:10.1111/j.1463-1318.2006.00974.x.
13. Abraham NS, Byrne CM, Young JM, Solomon MJ. Meta-analysis of non-randomized comparative studies of the short-term outcomes of laparoscopic resection for colorectal cancer. ANZ J Surg. 2007;77(7):508–516. doi:10.1111/j.1445-2197.2007.04141.x.
14. Curet MJ, Putrakul K, Pitcher DE et al. Laparoscopically assisted colon resection for colon carcinoma: perioperative results and long-term outcome. Surg Endosc. 2000;14(11):1062–1066. doi:10.1007/s004640000092.
15. ACS-NSQIP Program Specfics. ACS NSQIP Data; Participant Use Data File. Available at http://acsnsqip.org/puf/PufRequestHomepage.aspx. Last accessed January 7, 2008.
16. ACS-NSQIP Participant Use File User's Guide. Available at https://acsnsqip.org/puf/docs/ACS_NSQIP_Participant_User_Data_File_User_Guide.pdf. Last accessed January 7, 2008.
17. Khuri SF. The NSQIP: a new frontier in surgery. Surgery. 2005;138(5):837–843. doi:10.1016/j.surg.2005.08.016.
18. Khuri SF, Henderson WG, Daley J et al. The patient safety in surgery study: background, study design, and patient populations. J Am Coll Surg. 2007;204(6):1089–1102. doi:10.1016/j.jamcollsurg.2007.03.028.
19. ACS-NSQIP Program Specfics. Surgical Case Inclusion/Exclusion Overview. Available at http://acsnsqip.org/main/program_case_inclusion_exclusion.asp. Last accessed January 7, 2008.
20. ACS-NSQIP Program Specfics. Surgical Clinical Nurse Reviewer Training. Available at http://acsnsqip.org/main/program_nurse_training.asp. Last accessed January 7, 2008.
21. CPT 2006. Current Procedural Terminology. Chicago: American Medical Association, 2005.
22. Luellen JK, Shadish WR, Clark MH. Propensity scores: an introduction and experimental test. Eval Rev. 2005;29(6):530–558. doi:10.1177/0193841X05275596.
23. Hosmer J, Lemeshow S. Applied Logistic Regression. New York: Wiley, 1999.

24. Department of Health and Human Services. The International Classification of Diseases. 9th revised. clinical modification: ICD-9-CM. Washington, DC: Government Printing Office, 1998.
25. Steele SR, Brown TA, Rush RM, Martin MJ. Laparoscopic vs open colectomy for colon cancer: results from a large nationwide population-based analysis. J Gastrointest Surg 2007;12:583–591.
26. Vittimberga FJ Jr, Foley DP, Meyers WC, Callery MP. Laparoscopic surgery and the systemic immune response. Ann Surg. 1998;227(3):326–334. doi:10.1097/00000658-199803000-00003.
27. Targarona EM, Balague C, Knook MM, Trias M. Laparoscopic surgery and surgical infection. Br J Surg. 2000;87(5):536–544. doi:10.1046/j.1365-2168.2000.01429.x.
28. Bonjer HJ, Hop WC, Nelson H et al. Laparoscopically assisted vs open colectomy for colon cancer: a meta-analysis. Arch Surg. 2007;142(3):298–303. doi:10.1001/archsurg.142.3.298.
29. Kang JC, Chung MH, Chao PC et al. Hand-assisted laparoscopic colectomy vs open colectomy: a prospective randomized study. Surg Endosc. 2004;18(4):577–581. doi:10.1007/s00464-003-8148-3.
30. Leung KL, Kwok SP, Lam SC et al. Laparoscopic resection of rectosigmoid carcinoma: prospective randomised trial. Lancet. 2004;363(9416):1187–1192. doi:10.1016/S0140-6736(04)15947-3.
31. Bilimoria K, Bentrem D, Nelson H, et al. Laparoscopic-Assisted Colectomy for Cancer: Utilization and Outcomes in the United States. Arch Surg. 2008; In press.

J Gastrointest Surg (2008) 12:2010–2014
DOI 10.1007/s11605-008-0638-0

Can Gastric Irrigation Prevent Infection During NOTES Mesh Placement?

Lauren Buck · Joel Michalek · Kent Van Sickle · Wayne Schwesinger · Juliane Bingener

Received: 4 June 2008 / Accepted: 22 July 2008 / Published online: 13 August 2008

Abstract
Background Natural orifice transluminal endoscopic surgery (NOTES) ventral hernia repair could avoid abdominal wall incisions. The infectious risk for mesh placement is of concern. We compared NOTES with laparoscopic mesh placement.
Methods Thirty-seven swine were randomized to abdominal wall polypropylene mesh placement via NOTES or laparoscopy or NOTES control. All animals received antibiotics and gastric irrigation; the laparoscopy group also received preoperative acid suppression. In the NOTES mesh group, the 2-cm^2 polypropylene mesh was placed using a transgastric transportation device and clipped to the anterior abdominal wall. The control animals underwent endoscopy (no gastrotomy) followed by laparoscopic mesh placement or NOTES only without mesh placement. Necropsy was performed at 14 days.
Results One NOTES mesh placement was incomplete (endoscope failure). All mesh animals survived to 14 days. At necropsy, significantly more mesh infections were noted in the NOTES mesh versus laparoscopy group (4:11 vs 0:14; $p=0.03$). Gastric irrigation reduced the bacterial load significantly in all groups ($p<0.001$). Infection was independent of gastric bacterial load. No difference between acid suppressed and non-suppressed animals was seen.
Conclusion The mesh placement via NOTES is technically feasible but has a high infection rate despite irrigation. Sterile conduits are needed to enable NOTES-type hernia repair with mesh.

Keywords NOTES · Mesh · Infection · Translumenal · Natural orifice surgery

Presented at the 49th annual meeting of the Society for Surgery of the Alimentary Tract, May 21, 2008, San Diego, CA.

L. Buck · J. Michalek · K. Van Sickle · W. Schwesinger
Department of Surgery,
University of Texas Health Science Center,
San Antonio, TX, USA

J. Michalek
Department of Biostatistics and Epidemiology,
University of Texas Health Science Center,
San Antonio, TX, USA

J. Bingener (✉)
Department of Surgery, Mayo Clinic,
200 First Street SW,
Rochester, MN 55902, USA
e-mail: bingenercasey.juliane@mayo.edu

Introduction

Natural orifice transluminal endoscopic surgery (NOTES) avoids incisions on the abdominal wall.[1] This may be of benefit for patients prone to abdominal wall hernias. Feasibility studies investigating technical aspects of herniorrhaphy and mesh placement in the porcine model have been published.[2,3]

The infectious implications of NOTES mesh placement have not been thoroughly evaluated. While contamination with antibiotic-resistant *S. aureus* may be avoided by circumventing the abdominal wall, the transport of a foreign body through a body cavity (colon, stomach, vagina) may not be compatible with the long-held surgical principle of avoiding intestinal contamination of the peritoneal cavity and especially of any nonabsorbable prosthetic material. However, recent human studies investigating NOTES reported that peritoneal exposure to low levels of bacteria appears to be well tolerated and clinically insignificant, especially if prophylactic antibiotics were given.[4]

Our prior study[5] revealed that, after stepwise 500-cc saline irrigation, the bacterial gastric content decreased significantly, and no infections in NOTES animals were noted. This study investigated whether gastric irrigation and the use of a transport balloon would permit safe transgastric NOTES mesh placement in comparison with laparoscopic mesh placement. In addition, we wanted to know whether gastric irrigation could lead to the same reduction in bacterial content for animals pretreated with proton pump inhibitors as in nonacid suppressed animals.

Materials and Methods

Thirty-seven (37) female 50-kg domestic swine were quarantined 2 weeks before the planned procedure. The swine were randomly assigned to three groups using a permuted block randomization table with blocks size 2. Group 1 (NOTES control group) underwent gastric irrigation and 90 min NOTES peritoneoscopy, group 2 (laparoscopic mesh and proton pump inhibitor [PPI] group) underwent PPI treatment, upper endoscopy with gastric irrigation followed by laparoscopic mesh placement, and group 3 (NOTES mesh group) underwent gastric irrigation and NOTES mesh placement (see Fig. 1).

The swine were fed with six cans of Ensure 2 days before the procedures and then fasted overnight. All swine were given oral antibiotics (enrofloxacin) before the procedure and intramuscular (i.m.) injection of 600,000 Units of a penicillin G benzathine+penicillin G procaine-based antibiotic at the start of the procedure. Swine in the acid suppression group received oral PPIs (omeprazole 20 mg po qd) for 2 weeks before and after the procedure. Swine were premedicated with i.m. pig cocktail: 83.3 mg/ml ketamine and 16.7 mg/ml xylazine at a dose of 1 cc/8 kg or telazol 3–5 mg/kg followed by oral intubation and maintenance anesthesia with isoflurane.

All swine underwent upper endoscopy using a Cidex OSA-treated endoscope through a sterile overtube placed into the oropharynx. This overtube permitted the endoscope to enter the esophagus without contact to the oropharyngeal mucosa to minimize contamination. Gastric succus was aspirated at baseline and after incremental irrigation with sterile saline injected through the endoscope for a total of 500 cc normal saline. The bacterial content of the gastric aspirate was evaluated by plating on a blood agar and observation for 48 h.

For animals undergoing NOTES, a gastrotomy was created using a needle knife (Boston Scientific) followed by a 15-mm dilating balloon over a guidewire. The endoscope was then advanced into the peritoneal cavity, pneumoperitoneum established and maintained for 90 min, visualizing liver, spleen, and colon. The pneumoperitoneum was aspirated, the endoscope withdrawn, and the gastrotomy closed with jumbo clips (Resolution, Boston Scientific). After closure, the stomach was insufflated with air to test for adequate approximation of the wound edges. For the laparoscopy, three trocars were placed and a 2×1-cm polypropylene mesh brought in through the umbilical trocar and fixed to the anterior abdominal wall using laparoscopic clips. For the NOTES mesh placement, the same size mesh was placed into a modified sterile dilation balloon for transport and advanced through the stomach into the peritoneal cavity over a wire alongside the endoscope (Fig. 2). The mesh was then retrieved using a biopsy forceps and affixed to the anterior abdominal wall using 2–3 jumbo clips (Fig. 3). Procedure time was preset at 90 min for all animals. All groups of swine had an identical pattern of wound dressing. Animals resumed pig chow on the first postoperative day (POD 1). They were monitored daily for feeding, well-being, weight gain, and signs of infection by veterinary technicians blinded to the procedure type. Survival was assessed to POD 14, at which point the swine were euthanized and necropsy was performed. Data analysis was performed using the chi^2-test, *t*-test, or a repeated measures linear model as appropriate using a SAS statistical software (SAS Institute, Cary, SC, USA; version 9.1.3 for Windows) all throughout. Power was calculated using PASS software (Hintz J. NCSS and PASS Number Cruncher Systems, Kaysville, UT, USA, 2004). Assuming the infection rate for ventral hernia repairs with mesh to be 8%, the power of a study with 13 subjects per group to detect a

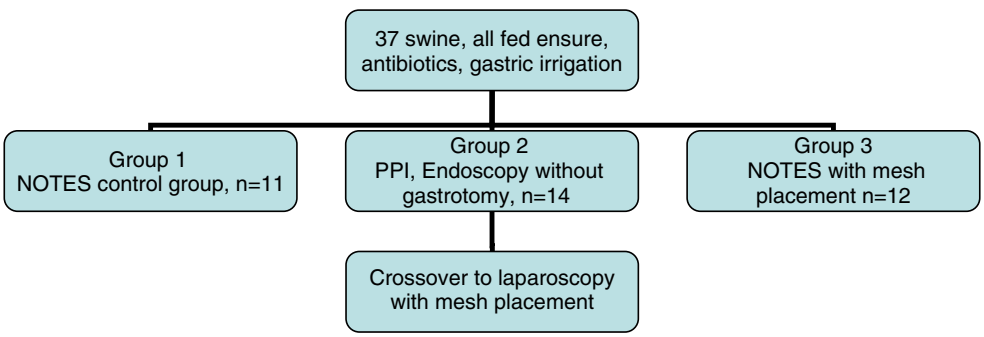

Figure 1 Schematic of study design.

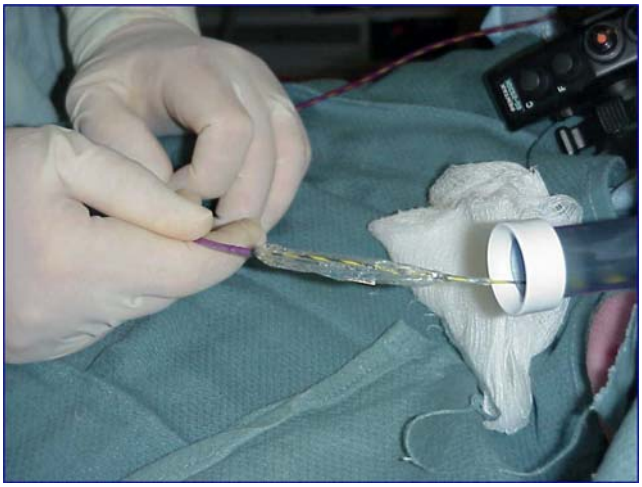

Figure 2 Mesh inside transport balloon.

fivefold increase in this rate (to 40%) is 83%. Power was computed for a one-sample test for the equality of binomial proportions and two-sided testing with a 5% level of significance.

The protocol was approved by the Institutional Animal Care and Use Committee.

Results

In 11 of 13 planned animals, NOTES mesh placement with commercially available instrumentation was successful. The use of a guidewire-related system next to the endoscope facilitated triangulation inside the peritoneal cavity, both for manipulation and stabilization. The wire was placed and utilized under direct visualization. No mesh was lost in the abdominal cavity. In one animal, transgastric (NOTES) mesh could not be placed because of endoscope failure (biopsy channel) after gastrotomy and pneumoperitoneum were established. The animal was included for the analysis of gastric irrigation but excluded for the analysis of mesh infections. After an apparently large number of infections seen in the NOTES mesh group, data analysis was performed by an investigator blinded to the groups, and the NOTES mesh arm was closed from an ethical perspective. Thus, in 12 animals, NOTES mesh placement had been attempted and completed in 11.

All endoscopy plus laparoscopy (n=14) and NOTES control experiments (n=11) were completed as described without difficulty. One animal in the NOTES control group died in the recovery period because of loss of airway. Immediate necropsy was performed, and no abdominal cause for the death was identified. Gastric irrigation data were included in the analysis (n=11) but no postoperative data (n=10). All other animals survived up to 14 days.

Gastric irrigation with sterile saline reduced bacterial content in the gastric aspirate significantly in all groups ($p<0.001$). There was no significant statistical difference in the mean bacterial count at any time before or after irrigation between the group that had undergone PPI treatment and the untreated groups (p=0.17). Specifically, no statistically significant difference in bacterial load was encountered between the group that received PPI and laparoscopic mesh placement and the group with NOTES mesh placement (Fig. 4, p=0.18). At necropsy, no peritoneal infection was seen in the NOTES control group (group 1) or the PPI-treated endoscopy plus laparoscopic mesh placement group (group 2; Fig. 5). All gastrotomy sites were well healed, and no signs of leak were encountered in the NOTES control or NOTES mesh group. Four of 11 animals in the

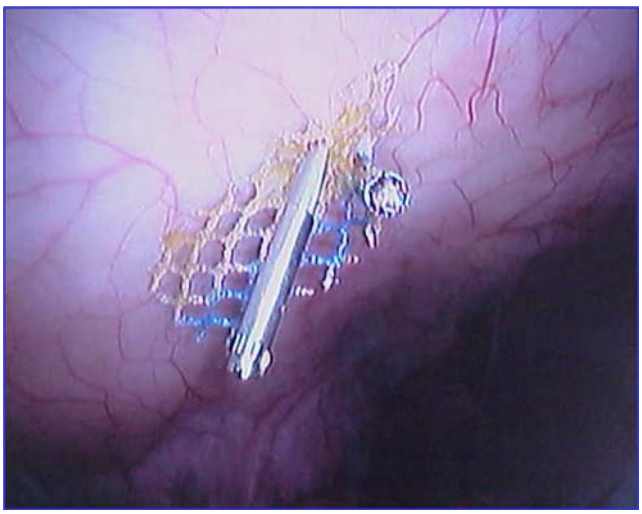

Figure 3 Tacking mesh to periumbilical peritoneum.

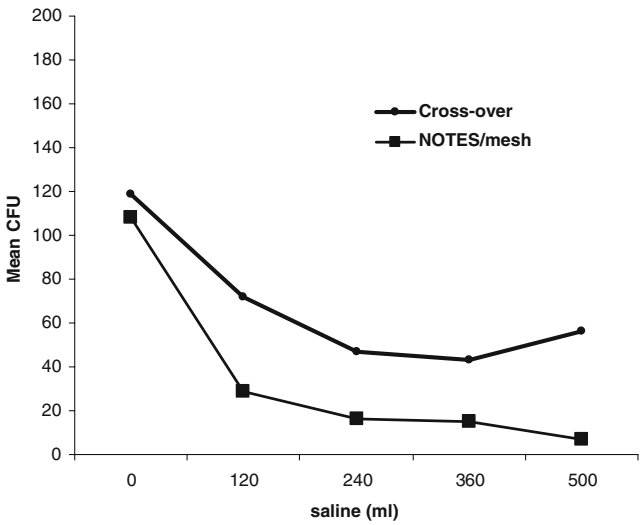

Figure 4 Bacterial growth after saline irrigation.

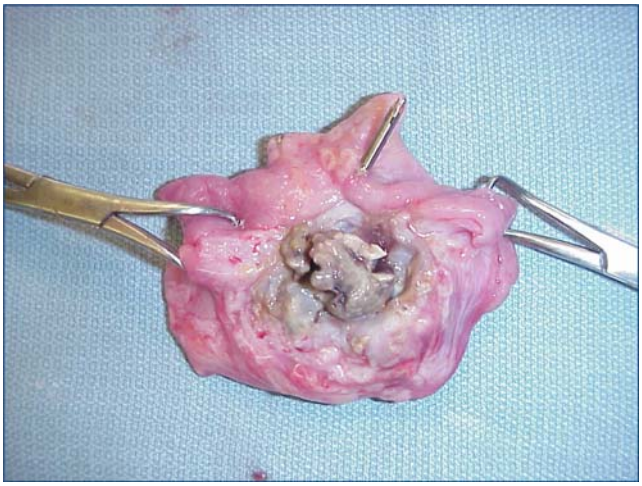

Figure 5 Infected NOTES mesh at 14 days.

NOTES mesh placement group (group 3) exhibited a grossly apparent mesh infection (p=0.03; Fig. 5); no infection was found in the NOTES control group (without mesh). The animals in the NOTES mesh group that revealed an infection did not differ in the mean number of colony forming units at 24 h from the NOTES mesh animals without mesh infection (6.3±7.2 versus 6.9±9.1; p=0.81).

Discussion

Although positive peritoneal cultures have been reported in up to 47% of patients with penetrating trauma of the stomach,[6–9] so far few abdominal infections have been reported in the porcine NOTES model.[10–13] Recent studies investigating NOTES in humans have shown that peritoneal exposure to low levels of bacteria appears to be well tolerated, especially if prophylactic antibiotics were given.[4] Other data revealed that bacterial contamination from a gastric source is not of concern because those bacteria are clinically insignificant.[14] Methods to avoid intestinal contamination have included saline lavage, antibiotic lavage, the use of sterile overtubes, and administration of prophylactic antibiotics.

The concept of introducing a prosthetic mesh into the peritoneal cavity via a translumenal approach is a potentially useful NOTES procedure. While skin contamination from antibiotic-resistant *S. aureus* species and abdominal incisions could be avoided, exposing the prosthetic mesh to the bacterial contents of the stomach could lead to significant infection-related complications. Two prior studies have investigated the concept of hernia repair utilizing the NOTES approach, one performing a primary repair with a prototype suturing device in the acute setting[3] and one with a prototype magnetic retraction device in a transcolonic route.[2] The second study did not detect any infection in three of three animals after 14 days survival. We focused on factors influencing or preventing infectious complications using mesh in the transgastric route. The infection rate is reported to be up to 8% for a transabdominal ventral hernia repair with mesh.[15] Our study was powered to detect a fivefold difference in infection rate. We used this large difference because it would reveal a "catastrophic" outcome that would be clinically not acceptable and would require either the NOTES approach to mesh implantation to be significantly altered or to be aborted altogether. Given the nascent technology, a small (although clinically relevant in the human environment) increase in infection may not lead to such considerations.

Some may question if this needed to be investigated in a randomized fashion. In the rodent experimental model, it can be assumed that the genetic makeup of experimental animals is reasonably similar if not identical to make randomization not necessary. In the porcine model used here (domestic swine), a substantial mix of races is usually provided by the suppliers, and recent methodologic papers suggest that randomization is of value.

In addition, we wanted to evaluate whether PPIs, on which many patients rely on for reflux symptoms and which alter bacterial loads,[16] can be cleared by antibiotics and saline irrigation.

PPI treatment did not make a difference in the mechanical clearance of gastric bacteria with saline irrigation. However, the irrigation and the protective (but not sealed) transport balloon did not prevent significant mesh infections. In addition, the impact of the mucosal not full-thickness closure utilized here has the potential of subclinical leaks influencing the mesh infection. We utilized a polypropylene mesh that is reported to be less prone to infection than polytetrafluoroethylene-based materials and was easier to handle with the currently available endoscopic instrumentation. Despite all of these precautions, an unacceptable 36% infection rate resulted. Further testing in this area needs to address methods for placing mesh into the peritoneal cavity in a sterile fashion, preferably through a sterile conduit from the natural orifice into the peritoneum and a sealed mesh transportation device.

Conclusion

While the current study supports previous findings that translumenal mesh placement is technically feasible, currently, the risk of infection appears much higher than in open or laparoscopic transabdominal ventral hernia repair. Saline irrigation decreased the gastric bacterial count significantly and independent of pretreatment with PPIs. However, gastric irrigation and a protective delivery device did not prevent an unacceptable infection rate. Development of a sterile translumenal conduit is necessary to allow further investigation in this area.

Acknowledgments We would like to acknowledge Mrs. Candace Baird, RVT, for her valuable contributions to the scientific development of the study.

Grant Support The work was supported by a grant from NOSCAR and material support grant from Boston Scientific.

References

1. Rattner D, Kalloo A, SAGES/ASGE Working Group on Natural Orifice Translumenal Endoscopic Surgery. White paper. Surg Endosc 2006; 20:329–333 and Gastrointest Endosc 2006; 63:199–203.
2. Fong DG, Ryou M, Pai RD, Tavakkolizadeh A, Rattner DW, Thompson CC. Transcolonic ventral wall hernia mesh fixation in a porcine model. Endoscopy. 2007;39:865–869. doi:10.1055/s-2007-966916.
3. Hu B, Kalloo AN, Chung SS, Cotton PB, Gostout CJ, Hawes RH, et al. Peroral transgastric endoscopic primary repair of a ventral hernia in a porcine model. Endoscopy. 2007;39:390–393. doi:10.1055/s-2007-966426.
4. Narula VK, Hazey JW, Renton DB, Reavis KM, Paul CM, Hinshaw KE, et al. Transgastric instrumentation and bacterial contamination of the peritoneal cavity. Surg Endosc. 2008;22:605–611. doi:10.1007/s00464-007-9661-6.
5. Bingener J, Michalek J, Van Sickle K, Winston J, Haines V, Schwesinger W, et al. Randomized blinded trial comparing the cardiopulmonary effects of NOTES with standard laparoscopy in a porcine survival model. Surg Endosc. 2008;22(6):1430–1434. doi:10.1007/s00464-008-9898-8.
6. Croce MA, Fabian TC, Patton JH Jr, Lyden SP, Melton SM, Minard G, et al. Impact of stomach and colon injuries on intra-abdominal abscess and the synergistic effect of hemorrhage and associated injury. J Trauma. 1998;45:649–655. doi:10.1097/00005373-199810000-00001.
7. Durham RM, Olson S, Weigelt JA. Penetrating injuries to the stomach. Surg Gynecol Obstet. 1991;172:298–302.
8. O'Neill PA, Kirton OC, Dresner LS, Tortella B, Kestner MM. Analysis of 162 colon injuries in patients with penetrating abdominal trauma: concomitant stomach injury results in a higher rate of infection. J Trauma. 2004;56:304–312. discussion 312–313. doi:10.1097/01.TA.0000109856.25273.07.
9. Stone HH, Kolb LD, Geheber CE. Incidence and significance of intraperitoneal anaerobic bacteria. Ann Surg. 1975;181:705–715. doi:10.1097/00000658-197505000-00027.
10. Jagannath SB, Kantsevoy SV, Vaughn CA, Chung SS, Cotton PB, Gostout CJ, et al. Peroral transgastric endoscopic ligation of fallopian tubes with long-term survival in a porcine model. Gastrointest Endosc. 2005;61:449–453. doi:10.1016/S0016-5107(04)02828-7.
11. Kalloo AN, Singh VK, Jagannath SB, Niiyama H, Hill SL, Vaughn CA, et al. Flexible transgastric peritoneoscopy: a novel approach to diagnostic and therapeutic interventions in the peritoneal cavity. Gastrointest Endosc. 2004;60:114–117. doi:10.1016/S0016-5107(04)01309-4.
12. Pai RD, Fong DG, Bundga ME, Odze RD, Rattner DW, Thompson CC. Transcolonic endoscopic cholecystectomy: a NOTES survival study in a porcine model (with video). Gastrointest Endosc. 2006;64:428–434. doi:10.1016/j.gie.2006.06.079.
13. Wagh MS, Merrifield BF, Thompson CC. Survival studies after endoscopic transgastric oophorectomy and tubectomy in a porcine model. Gastrointest Endosc. 2006;63:473–478. doi:10.1016/j.gie.2005.06.045.
14. Flora ED, Wilson TG, Martin IJ, O'Rourke NA, Maddern GJ. Review of natural orifice translumenal endoscopic surgery (NOTES) for intra-abdominal surgery: experimental models, techniques, and applicability to the clinical setting. Ann Surg. 2008;247:583–602.
15. Petersen S, Henke G, Freitag M, Faulhaber A, Ludwig K. Deep prosthesis infection in incisional hernia repair: predictive factors and clinical outcome. Eur J Surg. 2001;167:453–457. doi:10.1080/110241501750243815.
16. Sanduleanu S, Jonkers D, De Bruine A, Hameeteman W, Stockbrugger RW. Non-*Helicobacter pylori* bacterial flora during acid-suppressive therapy: differential findings in gastric juice and gastric mucosa. Aliment Pharmacol Ther. 2001;15:379–388. doi:10.1046/j.1365-2036.2001.00888.x.

J Gastrointest Surg (2008) 12:2015–2022
DOI 10.1007/s11605-008-0600-1

Postoperative Venous Thromboembolism Rates Vary Significantly After Different Types of Major Abdominal Operations

Debraj Mukherjee · Anne O. Lidor · Kathryn M. Chu · Susan L. Gearhart · Elliott R. Haut · David C. Chang

Received: 28 May 2008 / Accepted: 25 June 2008 / Published online: 31 July 2008

Abstract
Background Venous thrombolism (VTE) is a significant cause of morbidity for surgical patients. Comparative risk across major procedures is unknown.
Methods Retrospective analysis of the Nationwide Inpatient Sample (2001–2005) was conducted. Eight surgeries were identified: bariatric surgery, colorectal surgery, esophagectomy, gastrectomy, hepatectomy, nephrectomy, pancreatectomy, splenectomy. Age < 18, patients with multiple major surgeries, and those admitted for treatment of VTE were excluded. Primary outcome was occurrence of VTE. Independent variables included age, gender, race, Charlson score, hospital teaching status, elective procedures, cancer/metastasis, trauma, and year.
Results Patients, 375,748, were identified, 5,773 (1.54%) with VTE. Overall death rate was 3.97%, but 13.34% after VTE. Unadjusted rate (0.35%) and adjusted risk for VTE were lowest among bariatric patients. On multivariate analysis, highest risk for VTE was splenectomy (odds ratio 2.69, 95% CI 2.03–3.56). Odds ratio of in-hospital mortality following VTE was 1.84 (1.65–2.05), associated with excess stay of 10.88days and $9,612 excess charges, translating into $55 million/year nationwide.
Conclusion Highest risk for VTE was associated with splenectomy, lowest risk with bariatric surgery. Since bariatric patients are known to have greater risk for this complication, these findings may reflect better awareness/prophylaxis. Further studies are necessary to quantify effect of best-practice guidelines on prevention of this costly complication.

Keywords Deep vein thrombosis · Pulmonary embolism · Bariatic surgery · Major abdominal surgery

Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication in general surgery, representing a primary cause of preventable death.[1,2] The annual incidence of DVT in the United States may be as high as 122 per 100,000 in the population, and there are an estimated 200,000 deaths per year due to PE.[3–7] Among general surgery patients not receiving prophylaxis, previous studies have reported rates of observed DVT ranging from 15% to 30%, and a meta-analysis by Colditz et al. estimated an incidence of fatal PE ranging from 0.1% to 0.8%.[8–11]

Although there is a large body of research describing the incidence of VTE following orthopedic and neurological surgery, there has been minimal research describing the incidence and risks associated with developing VTE following major abdominal surgery.[12–22] Traditional risk factors for VTE have included immobility, trauma, age (>40years of age), malignancy, obesity, and surgery.[23–28] Within the field of surgery itself, common risk factors have included longer surgical procedures and the use of general versus regional anesthesia.[28–34] Given that patients under-

This paper was presented as a poster at the Digestive Disease Week conference in San Diego, California on Monday, May 19, 2008.

D. Mukherjee · A. O. Lidor · K. M. Chu · S. L. Gearhart · E. R. Haut · D. C. Chang (✉)
Department of Surgery, Johns Hopkins School of Medicine, 600 North Wolfe Street, Blalock 610, Baltimore, MD 21287, USA
e-mail: dchang1@jhmi.edu

going bariatric surgery have several risk factors for VTE, this type of surgery has traditionally been viewed as placing patients at relatively high risk for developing VTE.[35, 36] As a result, more than 90% of American Society of Bariatric Surgery members report regular use of thromboprophylaxis in patients undergoing bariatric surgery.[37]

Although there have been some limited reports characterizing VTE among specific general surgical procedures, there has yet to be a published report highlighting variation in the odds of developing VTE following major general surgery procedures.[28,38,39] This analysis is the first to compare the odds of developing DVT/PE following splenectomy, nephrectomy, gastrectomy, pancreatectomy, hepatectomy, esophagectomy, bariatric surgery, and colorectal resection. This study also provides relevant outcomes data regarding mortality, length of stay, and total hospital charges associated with postsurgical DVT/PE.

Methods

A retrospective analysis of the Nationwide Inpatient Sample (NIS) from 2001–2005 was performed. The NIS is an inpatient database compiling discharge information from 20% of all hospitals in 37 participating states. The Johns Hopkins Institutional Review Board deemed this publically available dataset exempt from review.

Patients who underwent isolated splenectomy, nephrectomy, gastrectomy, pancreatectomy, hepatectomy, esophagectomy, bariatric surgery, or colorectal resection were included (See Table 1 for relevant ICD-9 procedure codes). Individuals under 18 years of age were excluded.

DVT was defined by the following ICD-9 diagnosis codes: phlebitis and thrombophlebitis of deep vessels of the lower extremity (451.11 and 451.19), phlebitis and thrombophlebitis of the lower extremity, unspecified (451.2), phlebitis and thrombophlebitis of the iliac vein (451.81), phlebitis and thrombophlebitis of an unspecified site (451.9), venous embolism or thrombosis of deep vessels of the lower extremity (453.40, 453.41, 453.42), and venous embolism or thrombosis (453.8, 453.9). Pulmonary embolism was defined by the ICD-9 diagnosis codes 415.1, 415.11, and 415.19. In an effort to select only those patients who developed postoperative VTE, we excluded patients who were admitted with a primary diagnosis of either preexisting DVT or PE.

The primary outcomes were diagnosis of either DVT or PE. Secondary outcomes were in-hospital mortality, LOS, and total hospital charges. Independent variables included age, gender, race, Charlson Comorbidity Index, hospital teaching status, elective procedure status, diagnosis of cancer or metastasis, trauma, and calendar year. Elective procedure status was identified by using a data element specific for elective procedures and inherent to the NIS. Patients with a diagnosis of cancer or metastasis were identified through the Charlson index. Trauma patients were identified by ICD-9 diagnosis codes ranging from 800 to 959 in the primary position, excluding 905 to 909 (late

Table 1 Surgical Codes

Type of surgery	Surgical procedure	ICD-9 code
Nephrectomy	Partial nephrectomy	55.4
	Complete nephrectomy	55.5
	Nephroureterectomy	55.51
	Solitary kidney nephrectomy	55.52
	Bilateral nephrectomy	55.54
Colorectal Surgery	Cecectomy	45.72
	Right hemicolectomy	45.73
	Transverse colon resection	45.74
	Left hemicolectomy	45.75
	Sigmoidectomy	45.76
	Total intra-abdominal colectomy	45.8
	Abdominoperineal resection of rectum	48.5
	Anterior resection of rectum with synchronous colostomy	48.62
	Other anterior resection of rectum	48.63
Bariatric Surgery	Gastroenterostomy without gastrectomy	44.3
	High gastric bypass	44.31
	Laparoscopic gastroenterostomy	44.38
	Other gastroenterostomy	44.39
	Laparoscopic gastroplasty	44.68
	Laparoscopic gastric restrictive procedure	44.95
	Operating room procedures for obesity	DRG 288[a]
Splenectomy	Partial splenectomy	41.43
	Total splenectomy	41.5
Gastrectomy	Proximal gastrectomy	43.5
	Distal gastrectomy	43.6
	Other partial gastrectomy	43.8
	Partial gastrectomy NOS	43.89
	Total gastrectomy	43.9
	Other total gastrectomy	43.99
Pancreatectomy	Partial pancreatectomy	52.5
	Proximal pancreatectomy	52.51
	Distal pancreatectomy	52.52
	Radical subtotal pancreatectomy	52.53
	Partial pancreatectomy NOS	52.59
	Total pancreatectomy	52.6
	Radical pancreaticoduodenectomy	52.7
Hepatectomy	Partial hepatectomy	50.22
	Hepatic lobectomy	50.3
Esophagectomy	Esophagectomy NOS	40.40
	Partial Esophagectomy	42.41
	Total Esophagectomy	42.42

NOS = Not Otherwise Specified
[a] DRG = Diagnosis-related group

effects of injury), 930 to 939 (foreign body), 940 to 949 (burn), and 958 (early complications of trauma).

Statistical analysis was performed using the software package STATA/MP 10 (College Station, TX, USA). Bivariate analysis of categorical data was performed using the Pearson's Chi-Squared test. Analysis of continuous data was performed using the Student's *t*-test. Multivariate analysis was performed using multiple logistic regression models, adjusting for age, gender, race, Charlson score, hospital teaching status, elective status, cancer/metastasis status, trauma, LOS, and year of procedure. A p value of <0.05 was considered to be statistically significant.

Results

A total of 375,748 patients were identified using ICD-9 procedural codes in this 20% sample of inpatients over a 4-year period (2001–2005; Table 1). Patients had a mean (median) age of 59.0 (60) years and a majority were female (58.20%). Most patients (81.11%) were white. Patients had a mean (median) Charlson index score of 2.43 (1) and a majority (51.62%) were treated at nonteaching hospitals. Colorectal (66.76%) and bariatric procedures(20.39%) were the most common. Most cases were performed electively (65.04%). The overall rate of VTE was 1.54%, with 1.12% of patients developing DVT, 0.56% of patients developing PE, and 0.14% developing both DVT and PE. Overall mortality was 3.97%, overall mean (median) LOS was 9.17 (7) days, and patients had mean (median) total hospital charges of $49,996.59 ($31,217.44; Table 2).

On bivariate analysis, the incidence of VTE was lowest among patients undergoing bariatric surgery (0.35%), while VTE rates were higher in patients undergoing nephrectomy (0.85%), hepatectomy (1.76%), colorectal resection (1.77%), splenectomy (2.36%), gastrectomy (2.58%), pancreactectomy (2.91%), and esophagectomy (3.66%). On bivariate analysis, mortality was higher in those who developed VTE (13.37%) than in those without VTE (3.82%; $p < 0.001$). The development of DVT/PE was more common following nonelective procedures (2.65%) than elective procedures (0.94%; $p < 0.001$).

On stratified analysis, mean (median) LOS was 22.42 (17) days in those who developed VTE, compared to 8.96 (6) days in those without VTE. Mean (median) total hospital charges were $129,178.50 ($84,197.08) in those with VTE and $48,762.97 ($30,903.97) in those without VTE.

On multivariate analysis, a comparison of the likelihood of developing DVT/PE following several major abdominal surgeries demonstrated the odds of developing DVT/PE following nephrectomy (OR: 1.19; 95% CI: 0.81–1.76; $p = 0.374$) were not significantly different from the baseline of bariatric surgery (Fig. 1). However, odds were notably higher in patients undergoing colorectal surgery (1.87; 1.47–2.39; $p < 0.001$), pancreatectomy (2.07; 1.47–2.93; $p < 0.001$), gastrectomy (2.44; 1.80–3.30; $p < 0.001$), esophagectomy (2.47; 1.66–3.65; $p < 0.001$), hepatectomy (2.55; 1.87–3.48; $p < 0.001$), and splenectomy (2.69; 2.03–3.56; $p < 0.001$; Fig. 1).

In a stratified analysis including only elective procedures, which constitute a majority (65.04%) of the procedures performed in this study, the magnitude and distribution of adjusted odds ratios across all procedures was similar to this study's overall results (Fig. 2).

Other notable findings on multivariate analysis included the observation that the likelihood of VTE increased starting within the 45–49 age range (OR: 1.50; CI: 1.07–2.10), with patients aged 90 years or older having 2.54 (1.74–3.70) times the odds of developing VTE, compared to patients aged 18–24years old, across all procedures (Fig. 3). Additionally, African-Americans were 1.27 (1.13–1.42) times as likely to develop VTE, and Asians were 0.35 (0.21–0.57) times less likely to develop VTE, compared with whites across all procedures. Hispanics (1.00, 0.85–1.19), Native Americans (0.76, 0.37–1.58), and other non-categorized racial groups (1.12, 0.92–1.37) had odds of developing VTE that were not significantly different than comparative odds among whites.

Multivariate analysis also confirmed the association of VTE with worse patient outcomes. Hospital mortality was 1.84 (1.65–2.05) times more likely in those with VTE than in those without VTE, with LOS that was 10.88 (10.18–11.58) days longer and with excess total hospital charges of $9,612.96 ($6,005.19–$13,220.72; Table 2).

Discussion

In this study, we demonstrated through multivariate analysis that the odds of developing VTE vary by type of major abdominal surgical procedure. We found bariatric surgery to be the operation least likely to be associated with postoperative VTE. Nephrectomy had no increased likelihood of developing VTE compared to bariatric surgery. All other operations were associated with significantly higher odds of developing VTE, ranging from 1.87 times the odds for colorectal surgery to 2.69 times the odds for splenectomy (Fig. 1). This variation in the likelihood of developing perioperative DVT/PE remained even after adjusting for elective procedure status, cancer/metastasis, and trauma.

Among specific abdominal procedures, more than a decade ago, Huber et al. reported a fourfold higher incidence of symptomatic PE following colorectal surgery compared to other general surgical procedures.[31] Furthermore, Tongren et al. reported a threefold higher incidence

Table 2 Demographics, Procedures, and Outcomes

Characteristics	Value	
Age, in years		
Mean (median)	59.0	(60)
Female gender		
n (%)	218,681	(58.20%)
Race[a]		
White, *n* (%)	217,119	(81.11%)
Black, *n* (%)	26,788	(10.01%)
Hispanic, *n* (%)	14,637	(5.47%)
Asian, *n* (%)	2,229	(0.83%)
Charlson index score		
Mean (median)	2.43	(1)
Type of hospital		
Nonteaching, *n* (%)	193,949	(51.62%)
Procedures, overall		
Teaching, *n* (%)	181,777	(43.38%)
Colorectal surgery	250,847	66.76%
Bariatric surgery	76,630	20.39%
Gastrectomy	9,938	2.64%
Nephrectomy	7,191	1.91%
Splenectomy	16,032	4.27%
Hepatectomy	6,346	1.69%
Pancreatectomy	6,553	1.74%
Esophagectomy	2,211	0.59%
Total	375,748	100.00%
Procedures, elective		
Colorectal surgery	142,100	58.15%
Bariatric surgery	71,334	29.19%
Gastrectomy	6,482	2.65%
Nephrectomy	6,390	2.61%
Splenectomy	6,209	2.54%
Hepatectomy	5,249	2.15%
Pancreatectomy	4,774	1.95%
Esophagectomy	1,849	0.76%
Total	244,387	100.00%
DVT/PE		
Both DVT and PE	522	(0.14%)
Either DVT or PE, n (%)	5,773	(1.54%)
DVT, n (%)	4,208	(1.12%)
PE, n (%)	2,087	(0.56%)
In-hospital mortality		
All patients, *n* (%)	14,883	(3.97%)
Patients with both DVT and PE, *n* (%)	67	(12.84%)
Patients with either DVT or PE, *n* (%)	770	(13.34%)
Patients with DVT, *n* (%)	469	(11.15%)
Patients with PE, n (%)	368	(17.67%)
OR (DVT on mortality) in multivariate analysis	1.84	(1.65–2.05)
LOS (in days)		
All patients, mean (median)	9.17	(7)
Patients with DVT/PE, mean (median)	22.42	(17)
Excess LOS on multivariate analysis (in days)	10.88	(10.18–11.58)
Total hospital charges (in dollars, $)[b]		
All patients, mean (median)	$49,996.59 ($31,217.44)	
Patients with DVT/PE, mean (median)	$129,178.50 ($84,197.08)	
Excess total hospital charges on multivariate analysis (in dollars, $)	$9,612.96 ($6,005.19–$13,220.72)	

LOS=Length of stay

[a] Not all states collected information on race. 31% of data on race is was missing.

[b] Adjusted to 2006 medical inflation

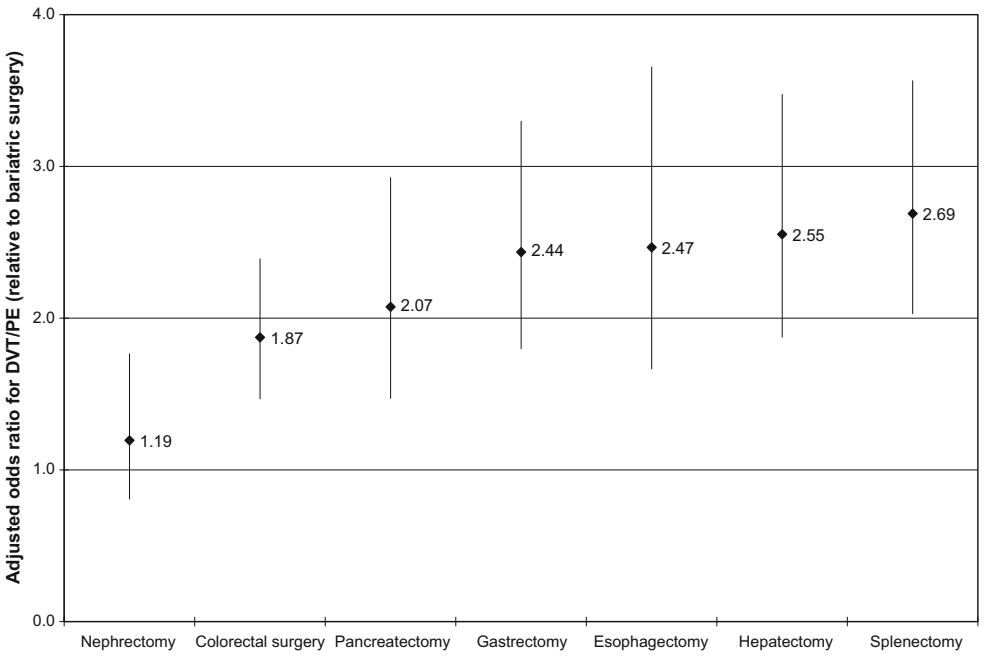

Figure 1 Odds of developing DVT/PE by surgical procedure relative to bariatric surgery, adjusted for age, gender, year, Charlson score, length of stay, hospital teaching status, elective procedure status, trauma, and malignancy.

of fatal PE following colorectal surgery relative to other general surgery operations.[40] The current study continues to show that colorectal surgery places patients at increased odds of developing VTE compared to baseline. The study further reports, though, that other major abdominal procedures have even higher odds of developing VTE than colorectal surgery.

The finding that bariatric surgery patients had the lowest risk for VTE is somewhat surprising given the prevalence of risk factors among these patients. This lower rate of VTE may reflect greater use of thromboprophylaxis among bariatric surgeons relative to other surgical specialties. Several studies of bariatric surgeons have demonstrated that strict adherence to VTE prophylaxis guidelines, including the use of pneumatic compression devices and low-dose unfractionated heparin or low-molecular weight heparin, is associated with lower rates of patient VTE.[36,41,42] While the ENDORSE trial recently found that only 58.5% of all surgical patients at risk for VTE received American College of Chest Physicians (ACCP)-recommen-

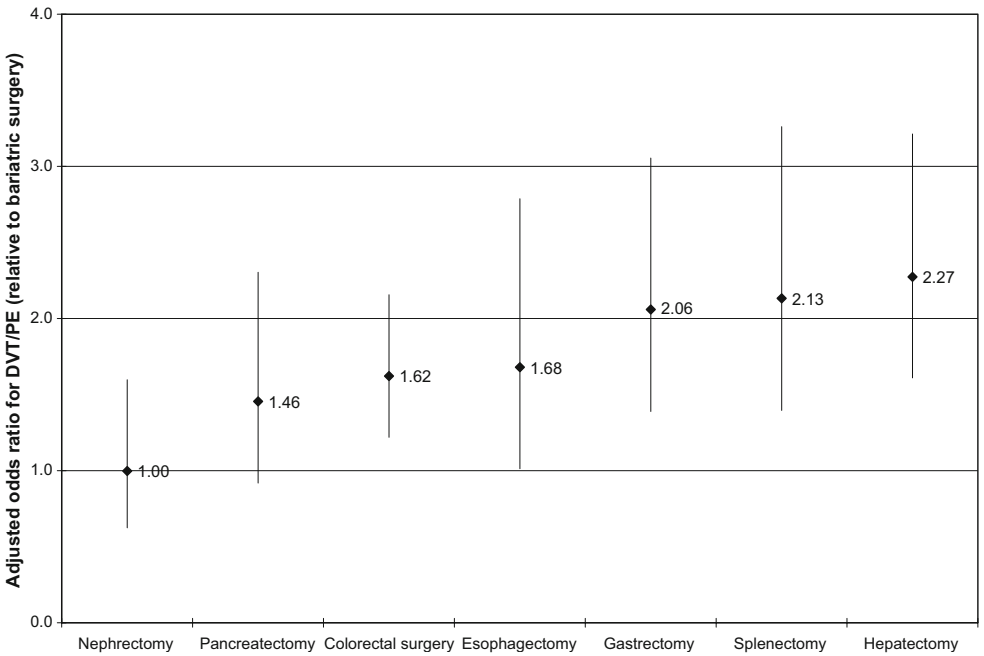

Figure 2 Odds of developing DVT/PE by surgical procedure relative to bariatric surgery among elective procedures only, adjusted for age, gender, year, Charlson score, length of stay, hospital teaching status, elective procedure status, trauma, and malignancy.

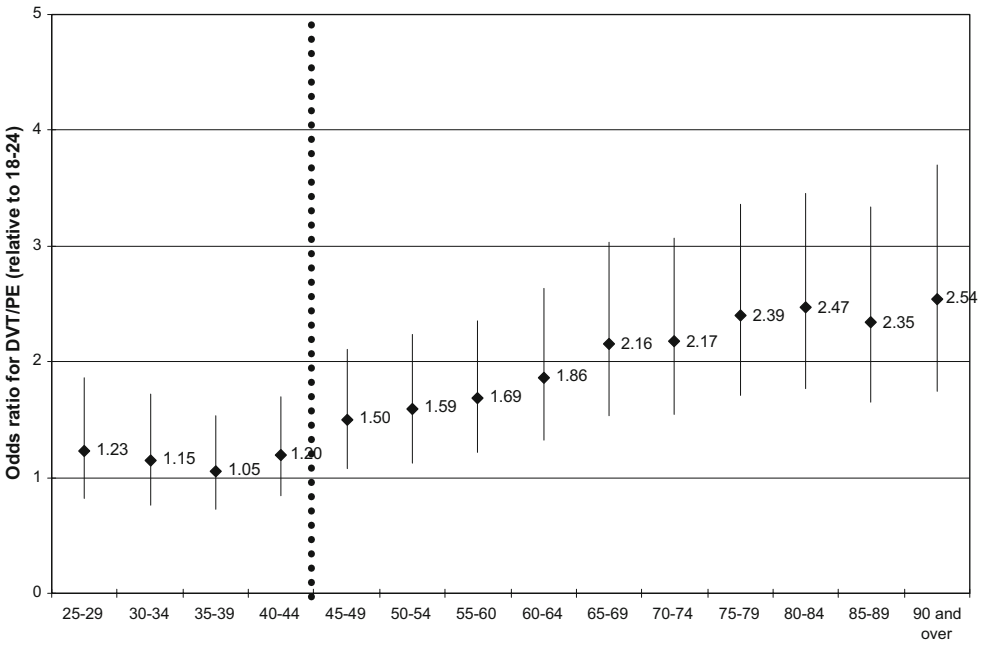

Figure 3 Odds of developing DVT/PE by age range (relative to the 18- to 24-year-old age range), adjusted for gender, year, Charlson score, length of stay, hospital teaching status, elective procedure status, trauma, and malignancy. Odds begin to significantly increase during the 45–49 age range (indicated by the *vertical dashed line*).

ded VTE prophylaxis, Wu and Barba showed that more than 95% of bariatric surgeons regularly adhere to thromboprophylaxis guidelines.[28,37,43] In contrast, Alizadeh et al. reported that only 30% of patients undergoing colorectal surgery received proper thromboembolic prophylaxis.[44] Similarly, a study by Beekman et al. reported a large proportion (13.6%) of surgeons performing splenectomies without proper VTE prophylaxis.[45] Lack of adherence to prophylaxis guidelines was more than twice as likely in surgeons performing splenectomies compared to those performing colorectal resections.[45] Such variability to practice patterns, if nationally prevalent, may explain the relatively high rates of VTE seen in patients undergoing splenectomy, or other operations, relative to bariatric patients.

Variations in health care delivery have been less well described in surgical fields than in general medicine.[46–48] A study by Caprini et al. showed wide variation in rates of regular thromboprophylaxis among surgeons.[49] Mommertz et al. further showed significant variation in thromboprophylaxis care between vascular surgeons and general surgeons.[50] Attempts have been made to reduce this variation via the implementation of practice guidelines. For example, guidelines identifying patients at high-risk for developing postsurgical VTE have identified abdominal surgery, thoracic surgery, and trauma as major risk factors (OR > 10), malignancy, congestive heart failure, and previous VTE as moderate risk factors (OR = 2–9), and increasing age, obesity, and immobility as minor risk factors (OR < 2).

Our study also found the risk for VTE to significantly, steadily increase starting at age 45 across all major abdominal operations. This steady increase continued until approximately age 75, after which the risk plateaued. This finding extends results from previous studies which reported increasing rates of VTE in patients more than 40 years old.[3,51–53] This study also demonstrated that African-Americans were more likely, and Asians were less likely, to develop VTE across all procedures, compared to whites. The observation that Asians were relatively protected from postsurgical DVT/PE is similar to results from a retrospective study of 68,142 colorectal cancer patients conducted by Alcalay et al.[54] Furthermore, we found that the development of VTE was associated with higher mortality, longer LOS, and higher total hospital charges. By using our estimate of $9,612.96 in excess total hospital charges per surgical patient developing VTE, we may extrapolate that approximately $55,495,618 in excess total hospital charges nationwide go toward the treatment of surgical patients who develop VTE.

This study is subject to the weaknesses inherent to all retrospective studies utilizing national administrative databases. Our results may underrepresent the true incidence of VTE among surgical patients for several reasons. Given that the dataset did not capture repeat hospital visits or patient outcomes after discharge, VTE may be under-coded. Also, clinical criteria to verify DVT or PE diagnosis were not available. However, rates of VTE are higher in the current study than in select previous studies.[55,56] Furthermore, such limitations, inherent to all administrative databases, are likely to be distributed evenly among the various operations examined. We believe the large group of patients analyzed in this study provides a valid characterization of VTE rates in postsurgical patients. Confounding factors,

such as the observation that bariatric surgery patients often remain hospitalized for fewer days and that trauma or cancer increase risk of VTE, have been addressed by adjusting for LOS, trauma, and cancer in our multivariate analyses. Given our relatively precise outcome measures of VTE, death, LOS, and total hospital charges, we believe our findings offer useful insight into the relationship between various major abdominal operations and the subsequent development of DVT/PE.

While we believe the variation in VTE outcomes across different abdominal surgical procedures is a reflection of variation in practice patterns between different types of surgeons, this cannot be confirmed with a retrospective database analysis alone. Furthermore, recent work has alluded to the fact that outcomes such as the ratio of PE to DVT may be a better indicator of quality than rates of VTE observed in isolation. Future prospective studies would be helpful to more fully elucidate the etiology of this national variation in surgical care, to define which specific prophylaxis algorithms may be best for different patient populations, and to more fully appreciate how the degree of adherence to prophylaxis guidelines impacts patient outcomes. This study reports the first nationwide assessment of variation in VTE rates following various major abdominal operations. Given the significant economic and clinical burden of VTE, increased awareness and implementation of policies and guidelines to decrease potentially preventable VTE are vital to help decrease unnecessary death, to increase patient safety, and to contain rising costs in health care.

References

1. Bulger CM, Jacobs C, Patel NH. Epidemiology of acute deep vein thrombosis. Tech Vasc Interv Radiol 2004;7:50–54. doi:10.1053/j.tvir.2004.02.001.
2. Michota F. Venous thromboembolism: epidemiology, characteristics, and consequences. Clin Cornerstone 2005;7:8–15. doi:10.1016/S1098-3597(05)80098-5.
3. Anderson FA Jr, Wheeler HB, Goldberg RJ et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. Arch Intern Med 1991;151:933–938. doi:10.1001/archinte.151.5.933.
4. Cushman M. Epidemiology and risk factors for venous thrombosis. Semin Hematol 2007;44:62–69. doi:10.1053/j.seminhematol.2007.02.004.
5. Silverstein MD, Heit JA, Mohr DN et al.Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med. 1998;158:585–593. doi:10.1001/archinte.158.6.585.
6. Huisman MV, Buller HR, ten Cate JW et al. Unexpected high prevalence of silent pulmonary embolism in patients with deep venous thrombosis. Chest 1989;95:498–502. doi:10.1378/chest.95.3.498.
7. Fowkes FJ, Price JF, Fowkes FG. Incidence of diagnosed deep vein thrombosis in the general population: systematic review. Eur J Vasc Endovasc Surg 2003;25:1–5. doi:10.1053/ejvs.2002.1778.
8. Clagett GP, Reisch JS. Prevention of venous thromboembolism in general surgical patients. Results of meta-analysis. Ann Surg 1988;208:227–240. doi:10.1097/00000658-198808000-00016.
9. Pezzuoli G, Neri Serneri GG, Settembrini P et al. Prophylaxis of fatal pulmonary embolism in general surgery using low-molecular weight heparin Cy 216: a multicentre, double-blind, randomized, controlled, clinical trial versus placebo (STEP). STEP-Study Group. Int Surg 1989;74:205–210.
10. Mismetti P, Laporte S, Darmon JY et al. Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. Br J Surg 2001;88:913–930. doi:10.1046/j.0007-1323.2001.01800.x.
11. Colditz GA, Tuden RL, Oster G. Rates of venous thrombosis after general surgery: combined results of randomised clinical trials. Lancet 1986;2:143–146. doi:10.1016/S0140-6736(86)91955-0.
12. Turpie AG, Levine MN, Hirsh J et al. A randomized controlled trial of a low-molecular-weight heparin (enoxaparin) to prevent deep-vein thrombosis in patients undergoing elective hip surgery. N Engl J Med 1986;315:925–929.
13. Hull RD, Raskob GE, Gent M et al. Effectiveness of intermittent pneumatic leg compression for preventing deep vein thrombosis after total hip replacement. JAMA 1990;263:2313–2317. doi:10.1001/jama.263.17.2313.
14. Semrad TJ, O'Donnell R, Wun T et al. Epidemiology of venous thromboembolism in 9489 patients with malignant glioma. J Neurosurg 2007;106:601–608. doi:10.3171/jns.2007.106.4.601.
15. Ghanim AJ, Daskalakis C, Eschelman DJ et al. A five-year, retrospective, comparison review of survival in neurosurgical patients diagnosed with venous thromboembolism and treated with either inferior vena cava filters or anticoagulants. J Thromb Thrombolysis 2007;24:247–254. doi:10.1007/s11239-007-0025-9.
16. Tabori U, Beni-Adani L, Dvir R et al. Risk of venous thromboembolism in pediatric patients with brain tumors. Pediatr Blood Cancer 2004;43:633–636. doi:10.1002/pbc.20149.
17. Auguste KI, Quinones-Hinojosa A, Gadkary C et al. Incidence of venous thromboembolism in patients undergoing craniotomy and motor mapping for glioma without intraoperative mechanical prophylaxis to the contralateral leg. J Neurosurg 2003;99:680–684.
18. Nurmohamed MT, van Riel AM, Henkens CM et al. Low molecular weight heparin and compression stockings in the prevention of venous thromboembolism in neurosurgery. Thromb Haemost. 1996;75:233–238.
19. Enyart JJ, Jones RJ. Low-dose warfarin for prevention of symptomatic thromboembolism after orthopedic surgery. Ann Pharmacother 2005;39:1002–1007. doi:10.1345/aph.1E536.
20. Leizorovicz A, Turpie AG, Cohen AT et al. Epidemiology of venous thromboembolism in Asian patients undergoing major orthopedic surgery without thromboprophylaxis. The SMART study. J Thromb Haemost 2005;3:28–34. doi:10.1111/j.1538-7836.2004.01094.x.
21. Gordois A, Posnett J, Borris L et al. The cost-effectiveness of fondaparinux compared with enoxaparin as prophylaxis against thromboembolism following major orthopedic surgery. J Thromb Haemost 2003;1:2167–2174. doi:10.1046/j.1538-7836.2003.00396.x.
22. Reis SE, Hirsch DR, Wilson MG et al. Program for the prevention of venous thromboembolism in high-risk orthopaedic patients. J Arthroplasty 1991;6(Suppl):S11–S16.
23. Thromboembolic Risk Factors (THRIFT) Consensus Group. Risk of and prophylaxis for venous thromboembolism in hospital patients. BMJ 1992;305:567–574.

24. Geerts WH, Heit JA, Clagett GP et al. Prevention of venous thromboembolism. Chest 2001;119:132S–175S. doi:10.1378/chest.119.1_suppl.132S.
25. Seligsohn U, Lubetsky A. Genetic susceptibility to venous thrombosis. N Engl J Med 2001;344:1222–1231. doi:10.1056/NEJM200104193441607.
26. Federman DG, Kirsner RS. An update on hypercoagulable disorders. Arch Intern Med 2001;161:1051–1056. doi:10.1001/archinte.161.8.1051.
27. Heit JA. Venous thromboembolism epidemiology: implications for prevention and management. Semin Thromb Hemost 2002;28 (Suppl 2):3–13. doi:10.1055/s-2002–32312.
28. Geerts WH, Pineo GF, Heit JA et al. Prevention of venous thromboembolism: the seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest 2004;126:338S–400S. doi:10.1378/chest.126.3_suppl.338S.
29. Sue-Ling HM, Johnston D, McMahon MJ et al. Pre-operative identification of patients at high risk of deep venous thrombosis after elective major abdominal surgery. Lancet. 1986;1:1173–1176. doi:10.1016/S0140-6736(86)91158-X.
30. Flordal PA, Berggvist D, Burmark US et al. Risk factors for major thromboembolism and bleeding tendency after elective general surgical operations. The Fragmin Multicentre Study Group. Eur J Surg 1996;162:783–789.
31. Huber O, Bounameaux H, Borst F et al. Postoperative pulmonary embolism after hospital discharge. An underestimated risk. Arch Surg 1992;127:310–313.
32. Wille-Jorgensen P, Ott P. Predicting failure of low-dose prophylactic heparin in general surgical procedures. Surg Gynecol Obstet 1990;171:126–130.
33. Nicolaides A, Irving D, Pretzell M et al. The risk of deep-vein thrombosis in surgical patients. Br J Surg 1973;60:312.
34. Hendolin H, Mattila MA, Poikolainen E. The effect of lumbar epidural analgesia on the development of deep vein thrombosis of the legs after open prostatectomy. Acta Chir Scand 1981;147:425–429.
35. Sapala JA, Wood MH, Schuhknecht MP et al. Fatal pulmonary embolism after bariatric operations for morbid obesity: a 24-year retrospective analysis. Obes Surg. 2003;13:819–825. doi:10.1381/096089203322618588.
36. Rocha AT, de Vasconcellos AG, da Luz Neto ER et al. Risk of venous thromboembolism and efficacy of thromboprophylaxis in hospitalized obese medical patients and in obese patients undergoing bariatric surgery. Obes Surg. 2006;16:1645–1655. doi:10.1381/096089206779319383.
37. Wu EC, Barba CA. Current practices in the prophylaxis of venous thromboembolism in bariatric surgery. Obes Surg 2000;10:7–13. doi:10.1381/09608920060674021.
38. Nguyen NT, Hinojosa MW, Fayad C et al. Laparoscopic surgery is associated with a lower incidence of venous thromboembolism compared with open surgery. Ann Surg 2007;246:1021–1027.
39. Samama CM, Albaladejo P, Benhamou D et al. Venous thromboembolism prevention in surgery and obstetrics: clinical practice guidelines. Eur J Anaesthesiol 2006;23:95–116. doi:10.1017/S0265021505002164.
40. Torngren S. Pulmonary embolism and postoperative death. Acta Chir Scand 1983;149:269–271.
41. Cossu ML, Pilo L, Piseddu G et al. Prophylaxis of venous thromboembolism in bariatric surgery. Chir Ital 2007;59:331–335.
42. Frezza EE, Wachtel MS. A simple venous thromboembolism prophylaxis protocol for patients undergoing bariatric surgery. Obesity (Silver Spring) 2006;14:1961–1965. doi:10.1038/oby.2006.229.
43. Cohen AT, Tapson VF, Bergmann JF et al. Venous thromboembolism risk and prophylaxis in the acute hospital care setting (ENDORSE study): a multinational cross-sectional study. Lancet 2008;371:387–394. doi:10.1016/S0140–6736(08)60202–0.
44. Alizadeh K, Hyman N. Venous thromboembolism prophylaxis in colorectal surgery. Surg Technol Int 2005;14:165–170.
45. Beekman R, Crowther M, Farrokhyar F et al. Practice patterns for deep vein thrombosis prophylaxis in minimal-access surgery. Can J Surg 2006;49:197–202.
46. Wennberg JE. Physician uncertainty, specialty ideology, and a second opinion prior to tonsillectomy. Pediatrics 1977;59:952.
47. McPherson K, Wennberg JE, Hovind OB et al. Small-area variations in the use of common surgical procedures: an international comparison of New England, England, and Norway. N Engl J Med 1982;307:1310–1314.
48. Birkmeyer JD, Sharp SM, Finlayson SR et al. Variation profiles of common surgical procedures. Surgery 1998;124:917–923.
49. Caprini JA, Tapson VF, Hyers TM et al. Treatment of venous thromboembolism: adherence to guidelines and impact of physician knowledge, attitudes, and beliefs. J Vasc Surg 2005;42:726–733. doi:10.1016/j.jvs.2005.05.053.
50. Mommertz G, Sigala F, Glowka TR et al. Differences of venous thromboembolic risks in vascular general and trauma surgery patients. J Cardiovasc Surg (Torino) 2007;48:727–733.
51. Nicolaides AN, Irving D. Clinical factors and the risk of deep venous thrombosis. In Nicolaides AN, ed. Thromboembolism etiology: advances in prevention and management. Baltimore, MD: Thromboembolism etiology: advances in prevention and management, 1975 193–204.
52. Gillum RF. Pulmonary embolism and thrombophlebitis in the United States, 1970–1985. Am Heart J 1987;114:1262–1264. doi:10.1016/0002-8703(87)90212-2.
53. Gjores JE. The incidence of venous thrombosis and its sequelae in certain districts of Sweden. Acta Chir Scand Suppl. 1956;206:1–88.
54. Alcalay A, Wun T, Khatri V et al. Venous thromboembolism in patients with colorectal cancer: incidence and effect on survival. J Clin Oncol. 2006;24:1112–1118. doi:10.1200/JCO.2005.04.2150.
55. Proctor MC, Wainess RM, Henke PK et al. Venous thromboembolism: regional differences in the nationwide inpatient sample, 1993 to 2000. Vascular. 2004;12:374–380. doi:10.2310/6670.2004.00037.
56. Brasileiro AL, Miranda F Jr, Ettinger JE et al. Incidence of lower limbs deep vein thrombosis after open and laparoscopic gastric bypass: a prospective study. Obes Surg. 2008;18:52–57. doi:10.1007/s11695-007-9268-y.

J Gastrointest Surg (2008) 12:2023–2031
DOI 10.1007/s11605-008-0561-4

Surgical Outcomes of Patients with Gastrointestinal Stromal Tumors in the Era of Targeted Drug Therapy

Mehrdad Nikfarjam · Eric Kimchi · Serene Shereef · Niraj J. Gusani · Yixing Jiang · John Liang · Mandeep Sehmbey · Kevin F. Staveley-O'Carroll

Received: 2 March 2008 / Accepted: 2 May 2008 / Published online: 11 June 2008

Abstract
Background The discovery of the c-KIT mutation and the advent of targeted drug therapy with imatinib mesylate have revolutionized the management of gastrointestinal stromal tumors (GISTs). The outcome of patients with surgically treated GISTs treated in the era of targeted drug therapy was assessed and factors associated with adverse outcomes determined.
Materials and Methods Patients with GISTs requiring surgery at a tertiary care center from 2002 to 2007 were reviewed and prognostic factors determined.
Results Forty patients were surgically treated for GISTs. The median age at presentation was 59 years. The stomach (55%) was the main site of primary disease. The median tumor size was 7 cm. Eleven (28%) patients had metastatic disease at presentation. Surgery was undertaken in all patients with curative intent. Multi-organ resection was required in 10 (25%) patients. Imatinib mesylate was administered postoperatively in 68% of cases. Median follow-up was 24 months. There was a 40% recurrence rate with 63% undergoing repeat surgical resection. The peritoneum and liver were the main sites of recurrent disease. The 5-year disease-specific survival and disease-free survival (DFS) were 65% and 35%, respectively. High mitotic rate (P=0.017) and tumor size greater than 10 cm (P=0.009) were the only prognostically significant adverse factors of DFS on multivariate analysis, independent of imatinib mesylate treatment.
Conclusion Aggressive surgical treatment and follow-up of GISTs, combined with targeted drug therapy, leads to long-term DFS survival. Tumor recurrence is independently associated with a high tumor mitotic rate and size greater than 10 cm, despite the use of adjuvant targeted drug therapy.

Keywords Gastrointestinal stromal tumor · Recurrence · Disease-free survival · Mitotic rate · Size · Imitinab mesylate · Multivisceral resection · Targeted therapy

M. Nikfarjam · E. Kimchi · S. Shereef · N. J. Gusani · M. Sehmbey · K. F. Staveley-O'Carroll (✉)
Department of Surgery, Penn State College of Medicine,
Penn State Milton S. Hershey Medical Center,
H070, 500 University Drive, P.O. Box 850, Hershey,
PA 17033-0850, USA
e-mail: kstaveleyocarroll@hmc.psu.edu

M. Nikfarjam
e-mail: mnikfarjam@psu.edu

Y. Jiang
Department of Medicine,
Penn State Milton S. Hershey Medical Center,
Hershey, PA, USA

J. Liang
Department of Pathology,
Penn State Milton S. Hershey Medical Center,
Hershey, PA, USA

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. The reported annual incidence of GISTs is 11 to 14.5 cases per million population, which includes incidentally discovered GISTs and those found at autopsy.[1,2] It is estimated that 23% to 28% of patients are asymptomatic at presentation, with tumors found on abdominal imaging for non-specific complaints or at the time of surgery for other conditions.[3,4] GISTs most frequently occur in the stomach. Other common sites of occurrence include the small

intestine and colon. These tumors originate from the interstitial cells of Cajal, which are considered the pacemaker cells of the gastrointestinal tract.[5,6] Most characteristically express activation mutations of c-KIT, a tyrosine kinase, which forms the basis of targeted drug therapies.

The overall outcomes of patients with GISTs after surgical resection have traditionally been poor, as recurrences are very common and conventional chemotherapy is of limited benefit.[7–9] The discovery of activating receptor mutations and the effectiveness of the tyrosine kinase receptor inhibitor, imatinib mesylate, have dramatically improved treatment outcomes, although long-term reports are limited.[10,11] We present a single-institution series of patients surgically treated for GISTs in the era of targeted drug therapies to determine long-term outcomes and identify adverse prognostic factors.

Materials and Methods

Patient Population

All patients surgically treated for GISTs at Penn State Milton S. Hershey Medical Center from January 2002 to November 2007 were included in this study. Those with a diagnosis of GIST were identified from a prospective tumor registry database, with crosschecks of hospital admission records, discharge diagnosis, and pathology registries to ensure that all records were identified. The diagnosis of GIST was confirmed by histopathologic review of all cases and by immunohistochemical staining.

Preoperative Assessment

Demographic data, symptom duration and type, and preoperative investigations were recorded for all patients. The administration and duration of targeted drug therapies was recorded and response rates preoperatively graded according to response evaluation criteria in solid tumors (RECIST) criteria.[12]

Operative Procedures and Complications

Operative intervention and complications were recorded for each case. The presence of tumor rupture at the time of surgery was specifically noted. All patients underwent surgical resection with curative intent. A 2-cm clear margin was the aim when possible.

Pathological Findings

All specimens were available for analysis and were confirmed GISTs by immunohistochemistry for CD117, CD34, or both. The maximum tumor diameter and the mitotic rate per 50 high power fields (hpf) were recorded for each specimen. In addition, the cell type, the presence of necrosis, involved margins, and mucosal infiltration were recorded.

Follow-up

Follow-up was achieved through review of hospital and office medical records. The social security death index database was accessed when follow-up was not possible to determine survival status. Patients were followed every 3 months with computed tomography (CT) imaging of the abdomen and pelvis to assess for disease recurrence. In the event of disease recurrence, repeat surgical resection was undertaken with the aim of complete tumor clearance, when possible.

Statistical Analysis

Results were expressed as median (range) unless otherwise stated. Comparisons between categorical variables were determined by chi-square and Fisher's exact test. Non-categorical variables were assessed by the Mann–Whitney *U* test. Survival analysis was performed by the Kaplan–Meier limit method to determine disease-specific survival (DSS) and disease-free survival (DFS) from the time of initial surgery. Comparisons between survival curves were made by the log-rank test. Cox-proportional analysis by forward regression was undertaken to determine factors independently associated with DFS after initial resection. A statistical software package (SPSS Version 11.5, Chicago, IL, USA) was used for statistical analysis, with $P<0.05$ considered statistically significant.

Results

Patient Population and Symptoms

Forty patients had surgical resection of GISTs during the study period. Table 1 summarizes the demographic features, location of tumors, and presenting symptoms. The median age at presentation was 59 (27–82) years, with a slight female predominance. Primary gastric GISTs were diagnosed in 22 (55%) patients, making this the most common site of occurrence (55%). The small intestine and duodenum together accounted for eight (20%) cases; colonic GISTs (sigmoid and rectum) were found in six (15%) patients and esophageal in one patient (2.5%). In three (7.5%) patients, the mesentery was considered the primary site of disease. In total, 34 (85%) patients had one or more symptoms before presentation; however, in only 31 (78%)

Table 1 Characteristics of Patients with Gastrointestinal Stromal Tumors (n=40)

Characteristics	Values
Demographics	
Male/female	17/23 (43%/57%)
Age (range)	59 (27–82)
Ethnicity white	40 (100%)
Primary location	
Stomach	22(55%)
Small intestine	4 (10%)
Duodenum	4 (10%)
Colon	6(15%)
Esophagus	1 (2.5%)
Other	3 (7.5%)
Presentation	
Duration of symptoms(months)	0 (0–84)
Abdominal pain	17 (43%)
Gastrointestinal bleeding	11(28%)
Incidental imaging finding	5 (13%)
Abdominal mass	11(28%)
Weight loss	11 (28%)
Incidental surgical finding	4 (10%)

patients were symptoms considered related to GISTs. In five (13%) patients, GISTs were identified incidentally on imaging for other conditions, and in four (10%) cases, the diagnosis was made at the time of surgery. The most common presenting symptoms were abdominal pain (43%), self-detection of a mass (28%), weight loss (28%), and gastrointestinal bleeding (28%). Overall, the median duration of symptoms was less than 1 month, ranging from several hours in a patient with a perforated small bowel GIST, to 7 years of intermittent abdominal pain and gastrointestinal bleeding in a patient with a duodenal GIST. A history of other malignancy was noted in six (15%) patients.

Preoperative Diagnosis and Therapy

Imaging

CT detected a mass in 33 of 39 (85%) cases imaged. Endoscopy was performed on 25 patients and identified a GIST in 23 (92%) cases. Positron emission tomography scanning was performed in three patients to confirm suspected metastases noted on CT imaging. In 19 of 21 (90%) cases, biopsy confirmed the diagnosis of GIST preoperatively. Endoscopic ultrasound was utilized for preoperative assessment in five cases.

Preoperative Treatment

Preoperative blood transfusions were required in seven (18%) patients with a history of gastrointestinal bleeding. Imatinib mesylate was administered before surgery to five (13%) patients with metastatic disease. The median duration of treatment was 8 (3–24) months. Partial response was achieved in one case, disease remained stable in three cases, and progression was observed in one case.

Operative Procedures and Complications

Operative Procedures

Table 2 summarizes the operative procedures and their complications. In 11 (28%) patients, metastatic disease was recorded at the time of the operation. In five cases, peritoneal deposits were noted alone; in two cases, the liver was the only site of metastases; and in three cases, both liver and peritoneal metastases were noted. Tumor rupture was noted in four (10%) cases at the time of operation. Multi-organ resection was performed in 10 (25%) patients, involving combined resection of stomach, spleen, pancreas, and liver in five cases. Gastric resection was the most common procedure, being performed in 25 (63%) patients. Gastric resection alone was performed in 17 (43%) cases. Laparoscopic resection was performed in three patients with tumors less than 5 cm in maximum diameter and amenable to wedge resection. Endoscopic submucosal resection of a gastric GIST was performed in one patient, considered unfit for laparoscopic or open gastric resection. In three patients with liver metastases not amenable to surgical resection, radiofrequency ablation was performed to achieve complete tumor clearance.

Complications

There was no operative mortality in this series. The median length of postoperative stay was 7 (1–21) days. One or

Table 2 Operations and Complications

	Number (%)
Operations performed (n=40)	
Gastrectomy	17 (43%)
Small bowel/ duodenal resection	6(15%)
Colectomy	5 (13%)
Whipple's procedure	1 (3%)
Intrabdominal mass resection	1 (3%)
Multi-organ resection	10 (25%)
Complications	
Abscess/wound infection	3 (8%)
Deep venous thrombosis/pulmonary emboli	3 (8%)
Urinary tract infection	2 (5%)
Pneumonia	2 (5%)
Hemorrhage	2 (5%)
Other	5 (13%)
Total patients with complications	12 (30%)

more complications were noted in 12 (30%) patients. Infectious complications including wound infections and intra-abdominal abscesses requiring drainage were noted in three (8%) patients. Deep venous thrombosis occurred in two (5%) patients and pulmonary embolism in one (3%) case. One patient required reoperation due to postoperative hemorrhage, and one required reoperation for a small bowel obstruction. Blood transfusions were required during surgery or postoperatively in seven (18%) patients.

Pathologic Findings

All specimens were confirmed to have GIST by histological assessment and immunohistochemical staining for the CD117, CD34, or both. Table 3 summarizes the features of the tumors.

Type, Size, Necrosis, and Mitosis

The predominant cell type on histology was spindle cell in 30 (75%) cases, epitheliod in two (5%), and mixed cell type in the remaining eight (20%) cases. There was no significant difference between the type of cell and the primary site of disease. The median primary tumor diameter was 7 (0.7–24) cm. Fourteen (35%) patients had tumors measuring greater than 10 cm in maximum diameter. There was no significant difference in the size of gastric GISTs compared to other primary sites (7.5 vs 7 cm; P=0.355). Tumor necrosis was noted in 31 (78%) primary tumors. Gastric GISTs exhibited significantly less necrosis compared to tumors at other primary sites combined (63% vs 94%; P=0.027). A high mitotic rate of more than five mitotic cells per 50 hpf was noted in 34 (60%) cases. There

Table 3 Tumor Specific Features of Gastrointestinal Stromal Tumors and Impact on Survival (n=40)

	Number (%)	DSS (p value)	DFS (p value)
Metastases			
Present	11 (28%)	0.331	0.018*
Absent	29 (73%)		
Multi-organ involvement			
Yes	10 (25%)	0.949	0.252
No	30 (75%)		
Size			
≤5 cm	13 (33%)	0.394	0.025*
>5 cm	27 (68%)		
≤10 cm	26 (65%)	0.192	<0.001*
>10 cm	14 (35%)		
Mitosis			
≤5/50 hpf	14 (35%)	0.091	<0.001*
>5/50 hpf	16 (65%)		
Necrosis			
Present	31 (78%)	0.488	0.064
Absent	9 (23%)		
Nodal involvement			
Present	1 (3%)	0.393	0.687
Absent	39 (98%)		
Vascular involvement			
Present	2 (5%)	0.474	0.231
Absent	38 (95%)		
Positive margin			
Yes	5 (13%)	0.326	0.777
No	35 (88%)		
Tumor rupture			
Present	4 (10%)	0.914	0.268
Absent	36 (90%)		
Cell type			
Spindle	30 (75%)	0.832	0.194
Epitheliod	2 (5%)		
Mixed type	8 (20%)		
Postoperative imatinib			
Yes	13 (33%)	0.1748	0.01*
No	27 (68%)		

Hpf – high power filed
DSS – Disease specific survival DFS – Disease Free Survival
* P<0.005 (Log-Rank test)

was no significant difference in mitotic rate between gastric GISTs and other primary sites (P=0.435).

Margins, Mucosal, Nodal, and Vascular Involvement

Microscopically positive margins were noted in five (13%) cases. In 13 (33%) cases, mucosal infiltration by the primary tumor was noted. The incidence of mucosal involvement was not statistically different between gastric GISTs and other primary tumor types (P=0.51). Nodal involvement was noted overall in one (2%) case. Vascular invasion was identified in two (5%) cases.

Follow-up Therapy and Survival

Median follow-up in this study was 24 (1–74) months. Complete follow-up was possible in all 40 patients.

Postoperative Chemotherapy

Imatinib mesylate was administered postoperatively to 27 (68%) patients with high risk lesions and all patients with metastatic disease. The median duration of therapy was 21 (1–63) months, with 16 patients on therapy at the time of last follow-up. One or more side effects were reported in 11 of 27 (40%) patients receiving postoperative therapy. The most common adverse effects were edema, gastrointestinal upset, rash, and fatigue. Sunitinib malate was administered to four patients who were intolerant to or had disease progression on imatinib mesylate.

Postoperative Recurrences

Tumor recurrence was noted in 16 (40%) patients in this series after initial surgery. The median time from operation to detectable recurrences was 9 (1–55) months. The sites of recurrence were the peritoneum alone in seven (44%), liver alone in three (19%), liver and peritoneum combined in three (19%), and lymph node recurrences in two (13%) cases. There was one local recurrence in an elderly patient after esophagectomy, who had microscopically positive margins after his first operation.

Repeat Operation

Of the 16 patients with recurrent disease, 10 (63%) had one or more repeat operations with curative intent. Nine patients underwent resection of peritoneal deposits. In four such cases, resection also included a colectomy. In one case, a gastrectomy was performed. Three patients had a liver resection combined with resection of peritoneal deposits. One patient required excision of peritoneal deposits and a pancreaticoduodenectomy. One patient with a paraduodenal lymph node recurrence underwent a pancreaticoduodenectomy alone. Histology confirmed lymph node metastases. There was no operative mortality in patients who had repeat operations in this series. One or more complications were noted in four (40%) patients in this group.

Survival

There were 11 (28%) patients with evidence of disease at the end of follow-up. Six patients who had disease recurrence were clinically free of tumors after repeat surgery combined with targeted drug therapy. There were seven deaths in this series, with six related to recurrent GISTs. One patient treated for a colonic GIST died as result of recurrent lung cancer 6 months after colonic resection. The overall DSS at 5 years was 65%, and the DFS at 5 years after initial surgery was 35% (Fig. 1). The 5 year DSS of 16 patients with recurrent GISTs was 50%, all of whom received adjuvant drug therapy. In patients with metastatic GISTs at presentation, the 1- and 3-year DFS were 46% and 17%, respectively, after surgery, with a median DFS of 10 months. The DSS in this group at 5 years was 58%.

Prognostic Factors

All factors that could potentially influence disease recurrence were analyzed by univariate analysis. Demographic factors (age and gender), presenting complaints (specific symptoms and asymptomatic), operative variables (multi-visceral resection, gastric resection, rupture, and reoperations), preoperative therapy (blood transfusions and imatinib mesylate), postoperative treatment (imatinib mesylate and blood transfusions), and pathologic features (metastases at presentation, size, mitotic rate, mucosa infiltration, involved margins, lymph node status, and tumor location) were analyzed. High mitotic rate (P<0.001), tumor size greater than 5 cm (P=0.0246), tumor size greater than 10 cm (P<0.001), postoperative imatinib mesylate (P=0.01) and metastases at initial presentation (P=0.0182) were the only prognostically significant adverse factors associated with DFS (Fig. 2). Given the small number of deaths in this series, there were no statistically significant adverse factors associated with DSS (Fig. 2). Statistically significant factors in DFS were assessed by multivariate analysis as shown in Table 4, with high mitotic rate (P=0.017) and tumor size greater than 10 cm (P=0.009) as the only remaining significant factors. The median DFS of patients with tumors with a mitotic index of greater than 5 per 50 hpf was 13 months, with an 11% 5-year DFS. In patients with tumors greater than 10 cm, the median DFS was 13 months, with all patients developing recurrences within 3 years of their initial surgery. The 5-year DSS in this group was 50%.

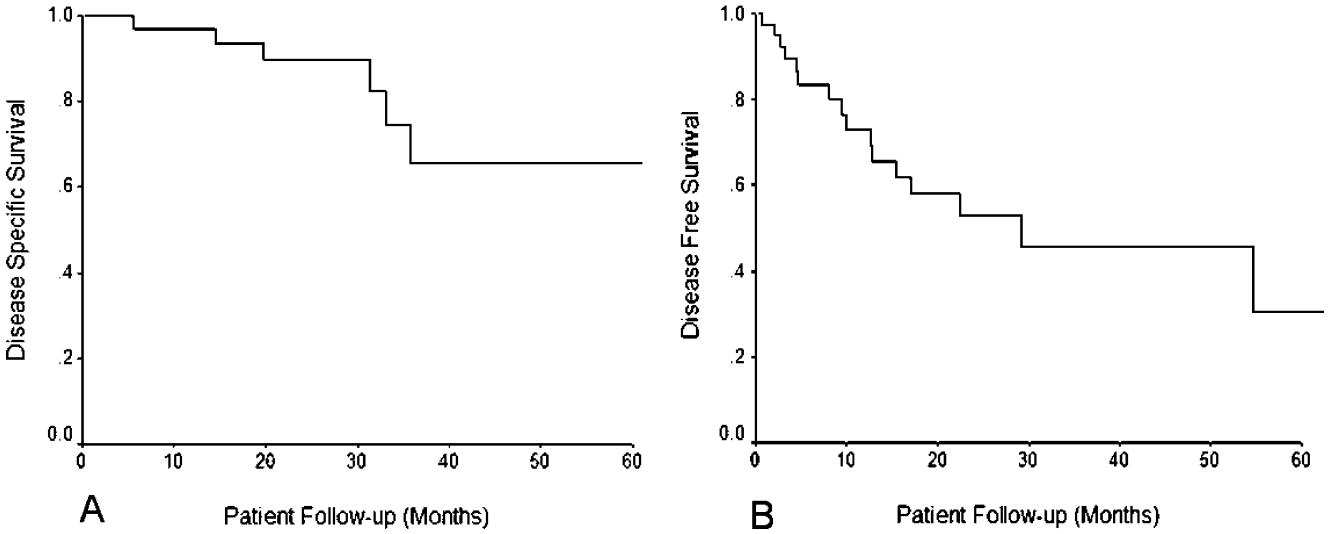

Figure 1 **A** Overall disease-specific survival (*DSS*) and **B** disease-free survival (*DFS*) of patients after initial surgery for gastrointestinal stromal tumors.

Discussion

Gastrointestinal stromal tumors are associated with a high rate of recurrence after surgical excision and considered poorly responsive to conventional chemotherapy. The discovery of mutations in these tumors, involving the cell surface receptor tyrosine kinase, c-KIT, and subsequent development of targeted tyrosine kinase inhibitors, has resulted in significant improvements in recurrence-free survival.[13] In 2002, imatinib mesylate was the first c-KIT receptor antagonist to be approved by the Federal Drug Administration (FDA) for the treatment of GISTs in the USA.[14,15] Recently, long-term outcomes of patients in the era of targeted drug therapies have been reported, requiring re-definition of prognostic factors that affect outcomes.

Surgical series before the era of targeted drug therapy report 5-year actuarial survival rates of approximately 50%.[16,17] The median DFS is 18 months, with 60% of recurrences occurring within 2 years of surgery.[7] In patients with metastatic GISTs at presentation, 5-year survival is approximately 25% after surgical resection.[18] In patients with more advanced GISTs, doxorubicin-based chemotherapy is associated with a median overall survival of 9 months.[17,19] Improvements in DFS have recently been noted in high-risk patients with GISTs, treated by surgery and adjuvant drug therapy with tyrosine kinase inhibitors.[13,20] Even in patients with advanced disease, the 2-year survival is currently 75% to 80% and approaches 100% in those most responsive to imatinab mesylate.[21–23] In a large series of 335 patients with resectable GISTs treated since 2002, the median DFS was 37 months and 5-year DFS was 38%, in which 30% of treated tumors were greater than 10 cm.[24] In series of patients with metastatic GISTs, the 2-year survival is improved by 20% in patients treated by surgery and imatinib mesylate compared to patients historically treated by surgery alone.[18] The overall DFS of 35% in our series is comparable to other recent studies of unselected patients with resectable GISTs.[17,24] In our study, 35% had tumors greater than 10 cm, and 28% had metastases at presentation. Multi-organ resection was required in 25% of cases. These features reflect the advanced nature of tumors treated in our series. In total, 68% of patients received postoperative imatinib mesylate. The recurrence rate of patients after surgery was 40% with a 5-year DSS of 65%. In 11 patients with metastatic GISTs at presentation, the 5-year DSS was 58%. One or more repeat surgical resections were performed in over half of patients with recurrent disease.

In our series, an aggressive surgical approach, multi-organ resection, re-operation for recurrence, and targeted drug therapy appeared to improve long-term survival compared to historic series, despite the advanced nature of GISTs treated. Recent population studies based on Surveillance, Epidemiology, and End Results (SEER) database also suggest improved survival of patients with GISTs treated in the era of imatinib mesylate.[25] However, radical surgery involving two or more organs was associated with worse survival in the SEER series. This may simply reflect the biology of the tumors treated, with outcomes appearing to somewhat improve from 2000. In our series, multi-organ resection for locally advanced tumors achieved complete tumor clearance in nine of 10 (90%) cases and was not associated with reduced DFS compared to single-organ resection. This is despite tumor size exceeding 10 cm in maximum diameter in eight cases.

The factors associated with disease recurrence after resection have been reported previously in large series before and after the introduction of imatinab mesylate.[17,19,21] The

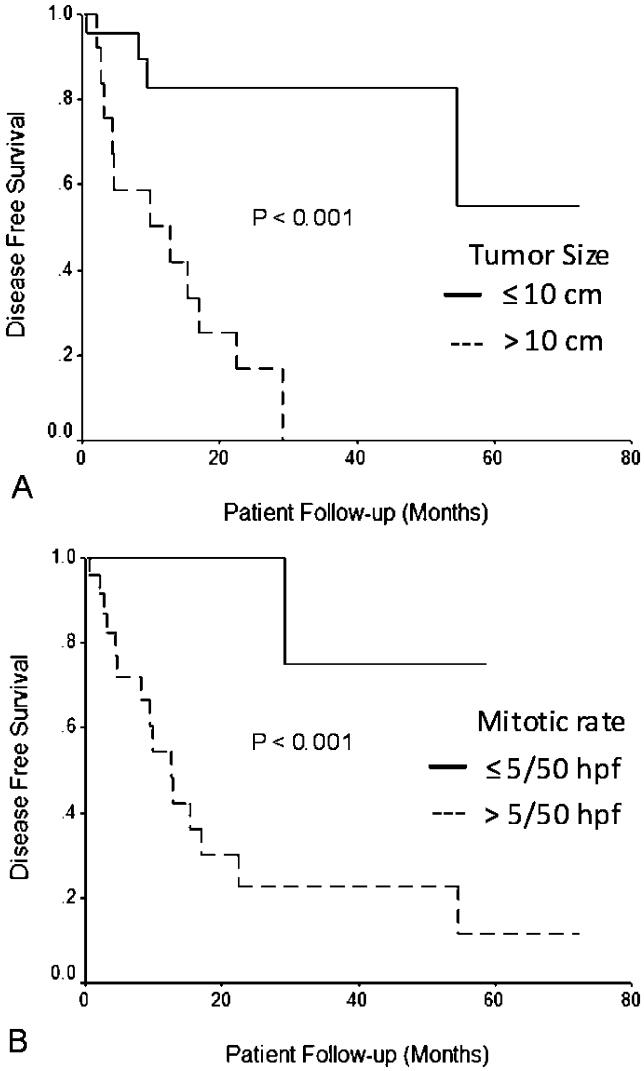

Figure 2 **A** Disease-free survival (*DFS*) with tumors equal to less than 10 cm compared to those greater than 10 cm and **B** tumors with a mitotic rate equal to less than 5/50 high power field (hpf) compared to those with greater than 5/50 hpf. Log-rank testing.

size of tumors and mitotic rate of GISTs have consistently been major factors associated with disease recurrence.[26] In our study, mitotic rate of more than five per 50 hpf, tumor size (5 and 10 cm), and metastases at presentation were significant adverse factors in DFS by univariate analysis. Postoperative imatinib mesylate was also an adverse factor on univariate analysis, but this is not unexpected given that it was generally given to patients considered high risk of recurrence. On multivariate analysis, only mitotic rate and tumor size greater than 10 cm were independent adverse risk factors for DFS. The 5-year DFS of patients with tumors with a high mitotic rate was 11%. All patients with tumors greater than 10 cm developed recurrences within 3 years of surgery, but the DSS at 5 years in this group was 50%, with most undergoing repeat surgical resections. DSS was not significantly influenced by mitotic rate and tumor size. This may simply reflect the small number of deaths in this series at follow-up, but it may equally relate to an aggressive surgical approach in the treatment of primary and recurrent GISTs and adjuvant drug therapy. Significant differences in DSS according to tumor size and mitotic rate may become evident with longer follow-up.

The impact of other factors on DFS is less well established. There are reports that the origin of a GIST is an important prognostic determinant.[24,27,28] Gastric GISTs (50%) and small bowel GISTs (25%) are the most commonly reported sites of primary origin.[13] Some series have reported that small bowel GISTs have a worse prognosis than other primary sites of similar size and mitotic activity.[26] In the series by Rutkowski et al.[24] of 355 resectable GISTs, the 5-year survival of 153 patients with gastric GISTs (60%) was significantly better that at other primary sites combined (24%), after a median follow-up of 31 months. In our series, we found no differences in survival between gastric GISTs and other locations combined. Whether this is related to a small sample size is unknown. In addition, small bowel GISTs constituted only

Table 4 Predictors of Disease-free Survival in 40 patients After Initial Resection of GISTs

Variable	Univariate analysis (log-rank test) (*P*)	Multivariate analysis (Cox-Proportional Hazard Regression) (*P*)	Risk ratio	95% CI (confidence interval)
Mitotic rate >5/50 hpf	<0.001	0.017	12.16	1.55–95.23
Tumor diameter >10 cm	<0.001	0.009	5.19	1.50–18.00
Tumor diameter >5 cm	0.025	0.164	132,630.1	0.00–1.59+261
Metastases at presentation	0.0182	0.333	1.18	0.04–3.49
Postoperative Imatinib	0.01	0.314	3.16	0.34–29.89

hpf High power field, *GIST* gastrointestinal stromal tumors

10% of primary tumors in our series. We found no difference in size and mitotic rate between gastric GISTs and those at other sites. We did note a lower rate of necrosis in gastric GISTs than in other sites combined, but this was not statistically an adverse prognostic factor. In the four cases of small intestine GISTs in our report, the rate of tumor rupture was 50%. Tumor rupture in previous studies was associated with a high incidence of tumor recurrence,[29] but this was not shown in our study. Other factors reported to be important in disease recurrence in other series include gender, cell type, and tumor necrosis.[24,30]

Incomplete surgical resection has also been associated with high disease recurrence in large series.[16,17,31,32] In such series, a positive microscopic resection margin is reported in 5% to 30% of cases.[16,17,31,32] Preoperative drug therapy with imatinab mesylate may aid the completeness of resection of advanced GISTs.[33] In our series, incomplete resection was noted in five (13%) cases but was not adversely associated with recurrence and survival. There was local recurrence in one patient with microscopically incomplete resection of an esophageal GIST. Two others with incomplete resection had distant recurrences. It is possible that targeted chemotherapy may control or treat microscopic or residual disease. However, the role for debulking surgery, in the era of targeted drug therapy, has not been determined. In all our cases, surgical resection was undertaken with curative intent. Given the long-term survival of patients and improved outcomes with targeted drug therapy, the role of debulking surgery needs to be reassessed.[33–35] Studies suggest that debulking surgery in patients with limited drug progression on imatinib mesylate may lead to prolonged survival.[35]

There is growing evidence of improved DFS with targeted drug therapy in patients with high risk GISTs after surgical resection.[23] In a preliminary report of a randomized controlled trial, imatinib mesylate administered for 1 year postoperatively reduced tumor recurrence compared to placebo in patients with tumors greater than 6 cm in maximum diameter.[20] Whether imatinib mesylate prevents or simply delays the onset of tumor recurrence is uncertain. Nilsson et al.[36] recently compared a series of 23 patients with advanced tumors, treated by surgery, followed by 12 months of imatinib mesylate to 48 patients treated by surgery alone, serving as historic controls. At 3-year follow-up, disease recurrence was noted in 4% in the adjuvant treatment group compared to 67% in the historic controls. The benefit of more prolonged therapy, in the face of possible drug resistance, is undetermined. In our series, the median duration of imatinib mesylate postoperatively was 21 months, with six patients treated for greater than 24 months with minimal side effects. Secondary resistance is reported to occur in patients at a median 24 months after the commencement of therapy and may be related to imatinib-resistant c-KIT mutations.[37,38] To minimize drug resistance, there may be theoretical benefits to limiting the duration of adjuvant therapy and then providing treatment at the first evidence of recurrence. However, in a randomized French study in patients with advanced metastatic GIST, cessation of imatinib mesylate after 1 year led to rapid disease progression when compared to continuous treatment.[39] The authors of this study recommended continuous treatment in those with advanced GISTs.

Sunitinib malate was given to three patients in our study with concerns of disease progression or side effects to imatinib mesylate. In randomized controlled trials, time-to-tumor progression in patients with advanced GISTs unresponsive to imatinib mesylate treated by sunitinib malate was 27 weeks compared to 6 weeks in those on placebo.[40] Sunitinib malate is now recommended for all patients who have disease progression on imatinib mesylate and those who experience significant side effects on imatinib mesylate therapy.[13]

An aggressive surgical approach to GISTs combined with targeted drug therapy appears to significantly improve overall survival of patients with GISTs compared to historic series. When recurrences occur, strong consideration should be given to repeat operations if all macroscopic disease can be removed. Repeat surgery is possible in the majority of patients, with low morbidity and mortality and may contribute to improvements in survival. Mitotic rate and tumor size greater than 10 cm remain independent prognostic factors in DFS, despite widespread use of targeted drug therapies postoperatively in these patients.

References

1. Nilsson B, Bumming P, Meis-Kindblom JM et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era—a population-based study in western Sweden. Cancer 2005;103(4):821–829.
2. Tryggvason G, Gislason HG, Magnusson MK, Jonasson JG. Gastrointestinal stromal tumors in Iceland, 1990–2003: the icelandic GIST study, a population-based incidence and pathologic risk stratification study. Int J Cancer 2005;117(2):289–293.
3. Hassan I, You YN, Shyyan R, et al. Surgically managed gastrointestinal stromal tumors: a comparative and prognostic analysis. Ann Surg Oncol 2008;15:4–6.
4. Bumming P, Ahlman H, Andersson J, Meis-Kindblom JM, Kindblom LG, Nilsson B. Population-based study of the diagnosis and treatment of gastrointestinal stromal tumours. Br J Surg 2006;93(7):836–843.
5. Mazur MT, Clark HB. Gastric stromal tumors. Reappraisal of histogenesis. Am J Surg Pathol 1983;7(6):507–519.
6. Corless CL, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. J Clin Oncol 2004;22(18):3813–3825.
7. Ng EH, Pollock RE, Romsdahl MM. Prognostic implications of patterns of failure for gastrointestinal leiomyosarcomas. Cancer 1992;69(6):1334–1341.

8. Shiu MH, Farr GH, Papachristou DN, Hajdu SI. Myosarcomas of the stomach: natural history, prognostic factors and management. Cancer 1982;49(1):177–187.
9. Casali PG, Picci P. Adjuvant chemotherapy for soft tissue sarcoma. Curr Opin Oncol 2005;17(4):361–365.
10. Blanke CD, Corless CL. State-of-the art therapy for gastrointestinal stromal tumors. Cancer Invest 2005;23(3):274–280.
11. De Giorgi U, Verweij J. Imatinib and gastrointestinal stromal tumors: where do we go from here? Mol Cancer Ther 2005;4 (3):495–501.
12. Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92(3):205–216.
13. Rubin BP, Heinrich MC, Corless CL. Gastrointestinal stromal tumour. Lancet 2007;369(9574):1731–1741.
14. Savage DG, Antman KH. Imatinib mesylate—a new oral targeted therapy. N Engl J Med 2002;346(9):683–693.
15. Gold JS, Dematteo RP. Combined surgical and molecular therapy: the gastrointestinal stromal tumor model. Ann Surg 2006;244 (2):176–184.
16. Pierie JP, Choudry U, Muzikansky A, Yeap BY, Souba WW, Ott MJ. The effect of surgery and grade on outcome of gastrointestinal stromal tumors. Arch Surg 2001;136(4):383–389.
17. DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM, Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg 2000;231(1):51–58.
18. Gold JS, van der Zwan SM, Gonen M et al. Outcome of metastatic GIST in the era before tyrosine kinase inhibitors. Ann Surg Oncol 2007;14(1):134–142.
19. DeMatteo RP, Heinrich MC, El-Rifai WM, Demetri G. Clinical management of gastrointestinal stromal tumors: before and after STI-571. Hum Pathol 2002;33(5):466–477.
20. DeMatteo RP, Maki R. Adjuvant imatinib mesylate increases recurrence free survival (RFS) in patients with completely resected localized primary gastrointestinal stromal tumor (GIST): North American Intergroup Phase III trial ACOSOG Z900. J Clin Oncol 2007;25:10079 (Abstract).
21. DeMatteo RP, Maki RG, Singer S, Gonen M, Brennan MF, Antonescu CR. Results of tyrosine kinase inhibitor therapy followed by surgical resection for metastatic gastrointestinal stromal tumor. Ann Surg 2007;245(3):347–352.
22. Demetri GD, von Mehren M, Blanke CD et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002;347(7):472–480.
23. Verweij J, Casali PG, Zalcberg J et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet 2004;364(9440):1127–1134.
24. Rutkowski P, Nowecki ZI, Michej W et al. Risk criteria and prognostic factors for predicting recurrences after resection of primary gastrointestinal stromal tumor. Ann Surg Oncol 2007;14 (7):2018–2027.
25. Perez EA, Gutierrez JC, Jin X et al. Surgical outcomes of gastrointestinal sarcoma including gastrointestinal stromal tumors: a population-based examination. J Gastrointest Surg 2007;11 (1):114–125.
26. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006;23 (2):70–83.
27. Emory TS, Sobin LH, Lukes L, Lee DH, O'Leary TJ. Prognosis of gastrointestinal smooth-muscle (stromal) tumors: dependence on anatomic site. Am J Surg Pathol 1999;23(1):82–87.
28. Ueyama T, Guo KJ, Hashimoto H, Daimaru Y, Enjoji M. A clinicopathologic and immunohistochemical study of gastrointestinal stromal tumors. Cancer 1992;69(4):947–955.
29. Ng EH, Pollock RE, Munsell MF, Atkinson EN, Romsdahl MM. Prognostic factors influencing survival in gastrointestinal leiomyosarcomas. Implications for surgical management and staging. Ann Surg 1992;215(1):68–77.
30. Novitsky YW, Kercher KW, Sing RF, Heniford BT. Long-term outcomes of laparoscopic resection of gastric gastrointestinal stromal tumors. Ann Surg 2006;243(6):738–745 (discussion 45–47).
31. Langer C, Gunawan B, Schuler P, Huber W, Fuzesi L, Becker H. Prognostic factors influencing surgical management and outcome of gastrointestinal stromal tumours. Br J Surg 2003;90(3):332–339.
32. Crosby JA, Catton CN, Davis A et al. Malignant gastrointestinal stromal tumors of the small intestine: a review of 50 cases from a prospective database. Ann Surg Oncol 2001;8(1):50–59.
33. Andtbacka RH, Ng CS, Scaife CL et al. Surgical resection of gastrointestinal stromal tumors after treatment with imatinib. Ann Surg Oncol 2007;14(1):14–24.
34. Blay JY, Bonvalot S, Casali P et al. Consensus meeting for the management of gastrointestinal stromal tumors. Report of the GIST Consensus Conference of 20–21 March 2004, under the auspices of ESMO. Ann Oncol 2005;16(4):566–578.
35. Raut CP, Posner M, Desai J et al. Surgical management of advanced gastrointestinal stromal tumors after treatment with targeted systemic therapy using kinase inhibitors. J Clin Oncol 2006;24(15):2325–2331.
36. Nilsson B, Sjolund K, Kindblom LG et al. Adjuvant imatinib treatment improves recurrence-free survival in patients with high-risk gastrointestinal stromal tumours (GIST). Br J Cancer 2007;96 (11):1656–1658.
37. Chen LL, Sabripour M, Andtbacka RH et al. Imatinib resistance in gastrointestinal stromal tumors. Curr Oncol Rep 2005;7(4):293–299.
38. Debiec-Rychter M, Cools J, Dumez H et al. Mechanisms of resistance to imatinib mesylate in gastrointestinal stromal tumors and activity of the PKC412 inhibitor against imatinib-resistant mutants. Gastroenterology 2005;128(2):270–279.
39. Blay JY, Le Cesne A, Ray-Coquard I et al. Prospective multicentric randomized phase III study of imatinib in patients with advanced gastrointestinal stromal tumors comparing interruption versus continuation of treatment beyond 1 year: the French Sarcoma Group. J Clin Oncol 2007;25(9):1107–1113.
40. Demetri GD, van Oosterom AT, Garrett CR et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006;368(9544):1329–1338.

J Gastrointest Surg (2008) 12:2032–2036
DOI 10.1007/s11605-008-0658-9

Indications and Results of Reversal of Vertical Banded Gastroplasty (VBG)

Rebecca Thoreson · Joseph J. Cullen

Received: 28 May 2008 / Accepted: 5 August 2008 / Published online: 3 September 2008

Abstract
Introduction Vertical banded gastroplasty (VBG) was initiated in 1980 as a weight loss operation that restricted oral intake.
Objective The aim of our study was to determine the results of patients who presented with complications of the VBG and wanted reversal of the VBG, not a conversion to another gastric weight loss operation.
Material and Methods From 1993 to 2008, 27 patients had reversal of a VBG. Of the patients, 85% were female and presented on average 13 years (range 2–27 years) after the VBG. Presenting symptoms included nausea/vomiting in 88%, reflux in 65%, stricture requiring endoscopic dilatation in 38%, while 7% of patients had upper gastrointestinal bleeding or required total parenteral nutrition. Patients were offered conversion to another weight loss operation but decided on reversal of the VBG alone. All reversals were performed in a similar manner by placing a linear stapler through a gastrotomy resulting in division of the polypropylene mesh band, and reversal of the VBG pouch.
Results No patients died from the procedure and morbidity included one wound infection and one wound seroma. Preoperative Visick score decreased significantly after reversal, while reflux symptoms resolved in 93% of patients.
Conclusion We conclude that reversal of a VBG results in symptomatic relief in the majority of patients.

Keywords Gastric surgery · Gastroplasty · Obesity · Reflux

Abbreviations
VBG Vertical banded gastroplasty

Presented at the Annual meeting of the Society for Surgery of the Alimentary Tract, San Diego, CA, May 17–22, 2008.

R. Thoreson · J. J. Cullen
Departments of Surgery,
University of Iowa Carver College of Medicine,
Iowa City, IA, USA

J. J. Cullen
Veterans Affairs Medical Center,
Iowa City, IA, USA

J. J. Cullen (✉)
University of Iowa Hospitals and Clinics,
4605 JCP, 200 Hawkins Drive,
Iowa City, IA 52242,, USA
e-mail: joseph-cullen@uiowa.edu

Introduction

Vertical banded gastroplasty (VBG) was initiated in 1980 as a weight loss operation that restricted oral intake.[1] A small volume pouch of 14–20 ml is created along the lesser curve and the outlet is reinforced with a band of polypropylene mesh or a silastic ring. Advantages of the VBG include a lack of malabsorption and no anastomosis or bypass as in other operations designed for weight loss. In a 10-year follow-up study, VBG was found to be successful (defined as a loss of at least 25% of preoperative excess weight) as a weight loss operation. After 1 year, the average percent excess weight lost was 52.3% and 64.3% in the super obese (more than 225% of ideal weight) and morbid obese (less than 225% of ideal weight) respectively. At 5 years, the average excess weight lost was 51.6% and 58.8%. In addition, morbidity and mortality was found to be low. Operative mortality was 0.24%, the risk of leakage and peritonitis was 0.6%, and the wound infection rate was 1.4%.[2]

The results in other centers have been variable with less than adequate long-term results with regard to weight loss or quality of life. A study of 35 patients who underwent a VBG showed that the operation was safe with minimal complications (early morbidity of 5.7% and late morbidity of 22.8%) and no mortality.[4] However, at 3-year follow-up there were 14 of 29 patients (48%) who were vomiting more than once a week.[4] Another 5-year follow-up study showed that of 100 patients who underwent a VBG, none of them were able to eat regular food without restriction and many patients required reoperation (25%) due to failure of the surgical procedure.[5] A 10-year follow-up of patients who underwent a VBG found that only 26% of patients maintained a weight loss of half of their excess body weight.[3] Frequent vomiting was also found to be a postoperative complication occurring in 21% of patients at least once a week, while gastroesophageal reflux disease (GERD) was found in 38% 3 years postoperatively.[3]

Gastric restrictive operations have late failure rates most commonly due to staple line disruption, enlargement of the gastric pouch, and enlargement of the stoma. Furthermore, stomal stenosis leads to food intolerance and recurrent vomiting and for these patients, weight loss remains satisfactory, but they suffer the sequelae of recurrent vomiting. Using a Kaplan–Meier analysis, Van Gemert and colleagues estimated that 56% of VBG patients and 12% of gastric bypass patients would need revisional surgery over a 12-year period.[6]

Patients who have had a VBG may require reoperation for conversion to other bariatric procedures or reversal due to a number of reasons including inadequate weight loss, vomiting, or gastroesophageal reflux. In some series,[7] GERD symptoms after VBG are relieved by conversion to a Roux-en-Y gastric bypass. Some patients do not desire to have a conversion to operation to induce weight loss for a variety of reasons. Reversal of a VBG is an option that may not lead to further weight loss but could potentially alleviate some of the symptoms associated with this operation. The aim of our study was to evaluate presenting symptomatology in patients who had a VBG reversal including the indications for reversal, any symptoms after reversal, and complications from the reversal procedure. Additionally, we wanted to determine any weight fluctuations after reversal of this gastric restrictive operation.

Material and Methods

Medical records for all patients who underwent reversal of a VBG were abstracted for details including symptoms (abdominal pain, reflux, nausea, vomiting), nutritional status, diet, requirement of endoscopic dilation of the pouch, or gastrointestinal bleeding. We also reviewed the pre- and postoperative weights, operative morbidity, and post-takedown outcomes. This study was approved by the University of Iowa Institutional Review Board for Human subjects on November 11, 2007.

There were 27 patients who underwent a reversal of a VBG by the senior author between 1993 and 2008 at the University of Iowa Hospitals and Clinics or Iowa City VA Medical Center. These patients presented with complications of their VBG and wished to have their VBG reversed. They were each offered a conversion to another gastric weight loss operation, which they declined.

There were 22 females (85%) and five males. They presented on average 13 years (range 2–27 years) after their initial VBG. The average age at the time of the VBG takedown was 52 (range 40–74). The presenting symptoms included nausea and/or vomiting in 89%, reflux in 67%, inability to tolerate solid foods in 48%, stricture requiring endoscopic dilation in 37%, while 7% presented with an upper GI bleed and 7% required supplemental nutrition (one with total parenteral nutrition and one required a gastrostomy tube).

Workup of these patients was very similar. Nearly 90% of the patients had upper gastrointestinal series with barium as an initial evaluation. Two thirds of patients had esophagogastroduodenoscopy (EGD) for diagnosis and potential therapeutic interventions. Half of the patients who had an EGD also had attempts at balloon dilatation to increase the size of the outlet.

Description of Procedure All VBG takedowns were performed in a similar manner. The previous upper midline incision is opened from the xiphoid to just superior to the umbilicus. Adhesions along the stomach and liver are taken down and the previous gastroplasty is identified. On the inferior portion of the stomach near the greater curvature a gastrotomy is created and a linear stapler is placed with one of the limbs within the lumen of the gastroplasty and the other within the gastric fundus. The stapler is fired resulting in an intraluminal, longitudinal side-to-side gastrogastrostomy (Fig. 1). The gastrotomy is then closed and then air is used to insufflate the stomach to evaluate for leak.

Results

Twenty-seven patients underwent a reversal of their vertical banded gastroplasty. There were no mortalities. Complications included one wound infection, one wound seroma, and one post-operative anemia. There were no gastric leaks. Figure 2 demonstrates a typical upper gastrointestinal series

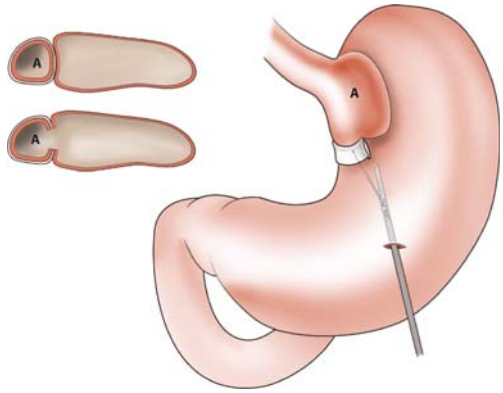

Figure 1 Technique of VBG reversal used in all 27 patients. Initially adhesions are taken down between the stomach, liver and colon. The anesthesiologists may place a large bore orogastric tube to aide the surgeon in delineating the anatomy. A gastrotomy is created near the inferior portion of the stomach. Intraluminal palpation of the outlet (which is sometimes severely stenosed) through the gastrotomy, is achieved to guide subsequent placement of a linear stapler. The linear stapler is placed with one of the limbs within the lumen of the gastroplasty (**A**) and the other within the gastric fundus. The stapler is fired resulting in an intraluminal, longitudinal side-to-side gastrogastrostomy. The gastrotomy is then closed and then air is used to insufflate the stomach to evaluate for leak.

in a patient who presented for reversal of their VBG due to severe reflux symptoms and sustained nausea and vomiting. Postoperatively, a repeat barium swallow was performed demonstrating reversal of the VBG and reestablishment of gastric anatomy (Fig. 2). Other complications were relative minor and did not extend the postoperative hospitalization. The patient with postoperative anemia required transfusion with three units of packed red blood cells during the postoperative hospital admission. The patient with the wound infection required the wound to be opened and packed. All patients were tolerating a solid food diet at the time of discharge postoperatively. All patients initially had relief of their presenting symptoms. However, on follow-up, 7/26 (27%) patients continued to have symptoms of some sort including heartburn, vomiting, and dysphagia. All of these patients had evaluations that included either esophagogastroduodenoscopy or upper gastrointestinal barium radiographs. In all of these patients, there was no obstruction demonstrated, but either reflux or esophagitis was seen. One patient was found to have severe esophageal dysmotility and no obstruction. One patient continued to have dysphagia but without abnormalities noted on EGD. All of the seven patients who continued to have symptoms after the VBG reversal were treated for GERD with improvement in symptoms.

To further quantify outcomes, Visick scores were determined pre- and post-VBG takedown. Although the Visick grading system was originally utilized in post-operative patients following gastric surgery for peptic ulcer

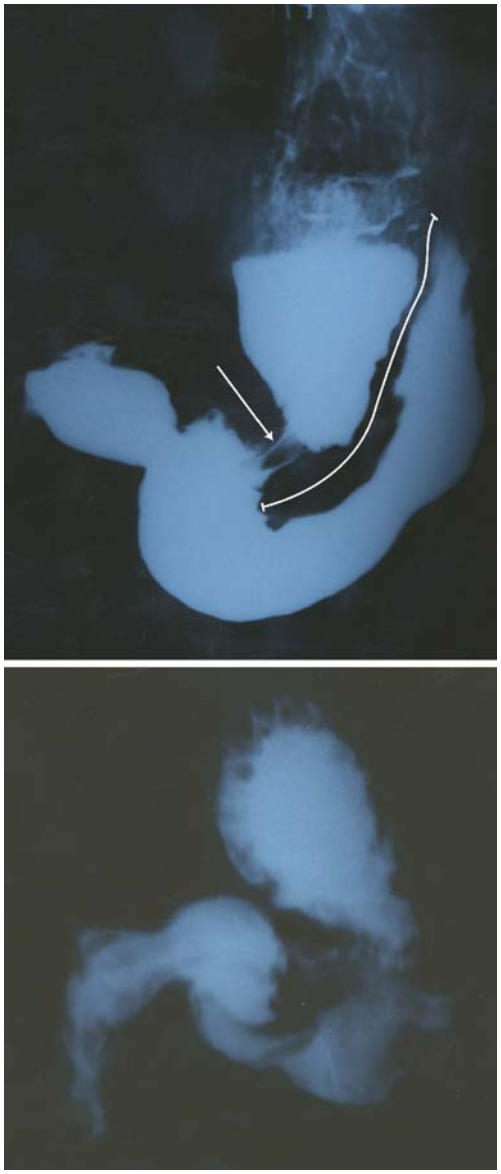

Figure 2 Upper gastrointestinal series before and after VBG reversal. Prior to reversal, a large, dilated gastroplasty pouch is seen, which correlated with the patient's frequent vomiting and severe GERD symptoms. Barium flow through the outlet was greatly diminished and reflux was also demonstrated. The *arrow* indicates the area of the marlex mesh band that was placed in for the outlet of the VBG. The line indicates the area of the vertical staple line, which is intact. Postoperatively, the patient had a repeat upper gastrointestinal series demonstrating free flow of contrast from the esophagus through the stomach and into the duodenum.

disease,[8] it has been used for various other gastric operations.[9] Grade 1 Visick scores are no symptoms; grade 2 include intermittent/mild symptoms, not affecting life-style; grade 3 are mild symptoms, but refractory to medical therapy; while grade 4 are severe symptoms, not improved (Table 1). The average pre-reversal Visick score was 2.8±

Table 1 Visick Grading System

Grade	Symptoms
Grade 1	No symptoms
Grade 2	Intermittent/mild symptoms, not affecting life-style
Grade 3	Mild symptoms, but refractory to medical therapy
Grade 4	Severe symptoms, not improved

0.1 and decreased significantly to 1.3±0.1 after the reversal ($P<0.001$). Of the 27 patients, 89% had improvement in their Visick scores and no patient had worsening of their Visick score after VBG reversal. Of the three patients who had no change in their Visick scores after reversal, their preoperative Visick scores were rated as 2 (Intermittent/mild symptoms, not affecting life-style). Of those patients, reflux symptoms were still present at follow-up, but not as severe as preoperatively.

Although follow-up was short, there was not a significant weight gain after reversal of the VBG. Prior to the reversal, patients had significant weight loss ($P<0.001$) after the initial VBG. The average weight prior to the VBG was 139 kg (range 105–182 kg) and the average weight at the time of the reversal was 96 kg (56–151 kg). There was not a significant amount of weight gained post-reversal ($P=0.3$). Post-reversal weight was 105 kg (range 63–157 kg). This was seen with a mean follow-up of 32 months (range 2–144 months) (Table 2).

Conclusions

This study showed that reversal of a vertical banded gastroplasty results in symptomatic relief in the majority of patients who present with nausea or vomiting, reflux symptoms, or inability to tolerate sold foods. This procedure can be done safely with minimal complications or mortality. All patients were tolerating solid foods in the immediate postoperative period. Only a few patients had return of their preoperative symptoms and the severity was decreased. Although follow-up was short, weight gain after the reversal was not significant. However, patients who desire a reversal of a VBG should also be instructed that weight gain may occur.

Table 2 Weight Changes Prior to VBG, Prior to Reversal, and Most Recent Weight

Pre-VBG weight (range)	Weight at reversal (range)	Weight after reversal (range)
139 kg (105–182)*	96 kg (56–151)	105 kg (63–157)

* $P<0.001$ vs. weight at reversal

To our knowledge, no previous studies have evaluated VBG reversals. Numerous studies have shown that some patients may develop symptoms after VBG.[1–5] A solution that is safe and effective is reversal of the VBG in the way described above. Other options, especially in patients extremely concerned about regaining the lost weight would be conversion to another weight loss procedure such as a Roux-en-Y gastric bypass. One study reviewed 25 patients with severe GERD after a VBG who subsequently underwent a conversion from a VBG to a Roux-en-Y gastric bypass.[7] In this study, 96% of the patients were nearly symptom free after the conversion from a VBG to a Roux-en-Y gastric bypass at a mean follow-up of 37 months.[7] There was also an average weight loss of 13 kg. This operation was also safe with no mortalities and six complications (24%). Both the reversal of the VBG and conversion to an alternative weight loss procedure have been shown to be safe and effective at relieving post-VBG symptoms.

The majority of the patients in our study had some degree of delayed VBG pouch emptying resulting in nausea, vomiting, and GERD symptoms. The delayed emptying of the VBG pouch may be explained by a stomal stenosis or stricture, or a dilated pouch leading to delayed emptying. The results of revisionary surgery for stomal stenosis are poor. In the study by Hunter and colleagues, 80% of revisionary operations were not successful in patients that had failure of a primary operation due to stomal stenosis.[10] In addition, nearly 50% of the patients operated for stomal stenosis required an additional revision and 33% had recurrent stenosis; 16% of the patients ended up with a complete reversal of the original bariatric procedure. Nearly 70% of the patients in this series had multiple endoscopic procedures including balloon dilatation following their revisional surgery. Thus, in patients with delayed pouch emptying due to stomal stenosis, revision of the stoma would not be recommended but instead a conversion to a gastric bypass or reversal of the VBG would be the procedures of choice.

The reasons for GERD after VBG are not well understood. Reflux symptoms may be related to a number of factors including stasis in the pouch secondary to outlet stenosis, inclusion of acid secreting parietal mucosa with the proximal pouch,[11] or operative damage to the lower esophageal sphincter. Mason has stated that the most common reason for GERD after VBG is the creation of the VBG pouch during the original operation that may have been created too large or without any measurements at all.[12] In our study, two thirds of patients had esophagogastroduodenoscopy (EGD) and half of these patients also had attempts at balloon dilatation to increase the size of the outlet. This may explain the reflux symptoms in these

patients may be due to stasis in the pouch secondary to outlet stenosis. Our findings are consistent with the observations of Mason[12] due to the fact that 60% of the patients who had an upper gastrointestinal series were noted to have a dilated pouch, abnormal pouch emptying, or reflux of barium, which also suggests that stasis in the pouch leads to GERD.

Our study has several limitations. Preoperative esophageal manometry or pH studies were not performed in these patients, which limits our ability to ascertain the reasons or the severity of GERD. However, manometry may not be beneficial in demonstrating the cause of GERD in patients with a dilated pouch. Follow-up was short at only 32 months (range 2–144 months). Although we did not see a significant weight gain in our study, we thoroughly counsel patients that significant weight gain may occur after VBG reversal. A possible reason for the lack of weight gain in these patients is a change in diet. Some investigators have demonstrated that many patients adapt to the food intolerances after a VBG by changing their diets to include semisolid food and/or high clear liquids, resulting an increase in caloric intake that is ingested, in turn resulting in an increase in the patient's weight and failure of the VBG (13). Although this is speculation, perhaps after ingesting the high caloric liquids instead of solid foods due to the gastroplasty outlet, patients who have a reversal may resume eating more solid foods instead of the high caloric liquids. Our study does not address this, and only further follow-up studies investigating eating patterns in this group of patients would be needed to support this theory.

In summary, in patients with a VBG who present with nausea, vomiting, reflux, outlet stenosis, or other symptoms of gastric outlet obstruction and who desire relief of their symptoms without a conversion to another weight loss operation, reversal of the VBG is a safe and effective option. There were no deaths in our series of patients and morbidity was low. Postoperative Visick scores decreased significantly after reversal while reflux symptoms resolved in 93% of patients. Due to the fact that follow-up was short in our present study, patients who desire a reversal of a VBG should also be instructed that weight gain may occur. We conclude that reversal of a VBG results in symptomatic relief in the majority of patients.

Acknowledgments The authors would like to thank Dr. Edward Mason for his helpful comments and review of the manuscript.

References

1. Mason E. Morbid obesity: use of vertical banded gastroplasty. Surg Clin North Am 1987;3:521–36.
2. Mason E, Maher JW, Scott DH, Rodriguez EM, Doherty C. Ten years of vertical banded gastroplasty for severe obesity. Probl Gen Surg 1992;9:280–9.
3. Balsiger B, Poggio JL, Mai J, Kelly KA, Sarr MG. Ten and more years after vertical banded gastroplasty as primary operation for morbid obesity. J Gastrointest Surg 2000;4:598–605. doi:10.1016/S1091-255X(00)80108-0.
4. Kalfarentzos F, Skroubis G, Kehagias I, Mead N, Vagenas K. Weight loss following vertical banded gastroplasty: intermediate results of a prospective study. Obes Surg 2001;11:265–70. doi:10.1381/09608920160558588.
5. Baltasar A, Bou R, Atlandis F, Martinez R, Serra C, Bengochea M, et al. Vertical banded gastroplasty at more than 5 years. Obes Surg 1998;8:29–34. doi:10.1381/096089298765555015.
6. van Gemert WG, van Wersch MD, Greve JWM, Soeters PB. Revisional surgery after failed vertical banded gastroplasty: restoration of vertical banded gastroplasty or conversion to gastric bypass. Obes Surg 1998;8:21–8. doi:10.1381/096089298765555006.
7. Balsiger B, Murr MM, Mai J, Sarr MG. Gastroesophageal reflux after intact vertical banded gastroplasty: correction by conversion to roux-en-y gastric bypass. J Gastrointest Surg 2000;4:276–81. doi:10.1016/S1091-255X(00)80076-1.
8. Visick A. Study of failures after gastrectomy; Hunterian lecture. Ann R Coll Surg Engl 1948;3:266–94.
9. Mon R, Cullen JJ. Standard roux-en-y gastrojejunostomy vs "uncut" roux-en-y gastrojejunostomy. J Gastrointest Surg 2000;4:298–303. doi:10.1016/S1091-255X(00)80079-7.
10. Hunter RA, Watts JM, Dunstan RE, Elmslie R, O'Brien P, Slavotinek A, et al. Revisional surgery for failed gastric restrictive procedures for morbid obesity. Obes Surg 1992;2:245–52. doi:10.1381/096089292765560123.
11. Jobe BA, Horvath KD, Swanstrom LL. Postoperative function following laparoscopic Collis gastroplasty for shortened esophagus. Arch Surg 1998;133:867–74. doi:10.1001/archsurg.133.8.867.
12. Nightengale ML, Sarr MG, Kelly KA, Jensen MD, Zinsmeister AR, Palumbo PJ. A prospective evaluation of vertical banded gastroplasty as the primary operation for morbid obesity. Mayo Clin Proc 1991;66:773–82.

J Gastrointest Surg (2008) 12:2037–2044
DOI 10.1007/s11605-008-0594-8

Mechanical Bowel Preparation in Intestinal Surgery: A Meta-Analysis and Review of the Literature

Carlos E. Pineda · Andrew A. Shelton · Tina Hernandez-Boussard · John M. Morton · Mark L. Welton

Received: 30 April 2008 / Accepted: 25 June 2008 / Published online: 12 July 2008

Abstract
Introduction Despite several meta-analyses and randomized controlled trials showing no benefit to patients, mechanical bowel preparation (MBP) remains the standard of practice for patients undergoing elective colorectal surgery.
Methods We performed a systematic review of the literature of trials that prospectively compared MBP with no MBP for patients undergoing elective colorectal resection. We searched MEDLINE, LILACS, and SCISEARCH, abstracts of pertinent scientific meetings and reference lists for each article found. Experts in the field were queried as to knowledge of additional reports. Outcomes abstracted were anastomotic leaks and wound infections. Meta-analysis was performed using Peto Odds ratio.
Results Of 4,601 patients (13 trials), 2,304 received MBP (Group 1) and 2,297 did not (Group 2). Anastomotic leaks occurred in 97(4.2%) patients in Group 1 and in 81(3.5%) patients in Group 2 (Peto OR=1.214, CI 95%:0.899–1.64, P=0.206). Wound infections occurred in 227(9.9%) patients in Group 1 and in 201(8.8%) patients in Group 2 (Peto OR=1.156, CI 95%:0.946–1.413, P=0.155).
Discussion This meta-analysis demonstrates that MBP provides no benefit to patients undergoing elective colorectal surgery, thus, supporting elimination of routine MBP in elective colorectal surgery.
Conclusion In conclusion, MBP is of no benefit to patients undergoing elective colorectal resection and need not be recommended to meet "standard of care."

Keywords Mechanical bowel preparation · Elective intestinal surgery · Colon and rectal surgery · Meta-analysis · Literature review · Intestinal preparation

Introduction

Mechanical bowel preparation (MBP) is the standard of practice for patients undergoing elective colorectal surgical resection despite growing evidence that it may not be of benefit to the patient. Several trials have been run to address this issue, including two large multicenter-randomized controlled trials performed in Europe. The aims of this paper are to review the history and advances made surrounding this common practice, review all the published prospective randomized controlled trials, and perform a meta-analysis to evaluate the impact of mechanical bowel preparation on anastomotic leak and wound infection rates.

History of Mechanical Bowel Preparation

When anesthesia and antisepsis permitted surgeons to safely enter the peritoneal cavity, more and more challenging procedures were performed, including operations on the biliary tract, urinary tract, and the gastrointestinal tract. At the beginning of the 20th Century, intestinal resections were

Paper presented at the 49th Meeting of the Society for Surgery of the Alimentary Tract, San Diego, CA, USA, May 21st.

Grant support and other assistance: none received.

C. E. Pineda (✉) · A. A. Shelton · T. Hernandez-Boussard · J. M. Morton · M. L. Welton
Department of Surgery, Stanford University School of Medicine, 300 Pasteur Drive, H3680, Stanford, CA 94305-5655, USA
e-mail: cepineda@stanford.edu

fraught with many infectious complications that resulted from contamination of the operating field, lack of antibiotics, and poor or nonexistent postoperative support. Surgeons started prescribing specialized "elemental diets" and laxatives in order to maintain an empty bowel. Fewer complications were noted in patients treated in this fashion, thus, starting the era of mechanical bowel preparation. With advances in pharmacotherapy, the use of antibiotics perioperatively for intestinal surgery became commonplace. The landmark studies regarding the use of antibiotics and MBP compared the use of preoperative oral and intravenous antibiotics combined with MBP to MBP alone. These studies showed a significant decrease in the rate of infectious complications.[1] Preoperative prophylactic antibiotics became a mainstay of therapy along with MBP. This combination of oral and intravenous antibiotics with mechanical bowel preparation continues to be the combination most commonly used by surgeons in the United States.[2] Currently, the correct and timely administration of antibiotics have become performance measures for quality improvement projects nationwide.[3] The role of mechanical bowel preparation in the era of prophylactic antibiotic administration has never been addressed separately and, thus, remains one of the cornerstones of safe colorectal surgery.[4]

Goals of Mechanical Bowel Preparation

The stated goal of MBP is to completely empty the bowel before surgery in order to decrease the risk of infectious complications. This is conventional wisdom and is theoretically accomplished by decreasing the bacterial load in the intestinal lumen and by decreasing the risk of spillage of feces in the operative field. MBP also purportedly makes manipulation of the bowel easier for the surgeon. However, existing evidence does not support these tenets.

When MBP is performed alone, the bacterial load does not decrease significantly in the lumen or in the bowel wall.[5–7] The intervention that affects changes in bacterial flora is the use of antibiotics, not the bowel preparation.[8] Mucosal-associated bacteria are still found within the bowel wall with an increasing gradient from the distal rectum to the proximal colon after MBP with polyethylene glycol solution (PEG).[9] Thus, the bacteriologic benefit of mechanical bowel preparation is not readily apparent.

The reduction in the risk of fecal spillage in the operative field is also questionable. In a chart review of 333 patients who underwent various colorectal procedures, spillage of bowel contents occurred in 26 (17%) patients who underwent MBP compared to 22 (12%) patients who underwent no MBP (p=0.21). Interestingly, patients who had spillage during surgery compared to those that did not have higher anastomotic leak rates and wound infection rates, 6.2% versus 3.8% (p=0.39) and 12.5% versus 6.7% (p=0.23), respectively.[10] These differences did not reach statistical significance, but a trend that favored no MBP was apparent. Sometimes, MBP does not completely empty the bowel, and the remaining liquid effluent is harder to control, thus, potentially increasing the risk of spillage. Poor MBP has already been shown to increase the rate of anastomotic leak compared to patients with adequate MBP.[11] Lastly, it is logical to assume that an empty bowel is easier to manipulate than a full one. However, a recent single-blind randomized trial that compared MBP to no MBP in women undergoing laparoscopic gynecologic surgery found no difference in ease of bowel handling or differences in operative field visualization.[12]

Complications of Mechanical Bowel Preparation

MBP is not an innocuous procedure. There are many choices for preparation of the bowel before elective surgery, which include various preparations of PEG, bisacodyl tablets, aqueous and tablet sodium diphosphate (NaP), and saline laxatives.[13] However, the most popular among surgeons in the United States are PEG and NaP.[14] Traditional PEG is given to patients as a 4-L solution. Those patients unable to drink the solution are admitted the night prior to surgery and are given the PEG solution per nasogastric tube, thus, adding the discomfort associated with tube placement and the potential risk of aspiration.[15] NaP is more convenient for patients, as it is given as a 90-mL solution. Patients have less difficulty drinking the solution, have less gastrointestinal symptoms (pain and bloating), and less fatigue.[16,17] However, NaP is associated with more electrolyte disturbances, including changes in sodium, potassium, calcium, and phosphorus. Changes in calcium and phosphorous levels are markedly increased in patients 60 years or older, leading some to suggest that NaP not be provided without a prescription.[17] There have also been case reports of near-fatal and fatal complications associated with the use of NaP.[18–20]

On a survey of 105 patients who underwent elective colorectal resection, 65 underwent MBP and 45 underwent no MBP. The authors found that patients would prefer not to undergo MBP. The time to first bowel movement was shorter in the no MBP group (p=0.04). However, this group had more discomfort on postoperative day 4.[21] They attributed this difference in discomfort (pain was not different) to the decreased time to the first bowel movement.

Effects of Mechanical Bowel Preparation on Intestinal Mucosa

At the histologic level, MBP is associated with certain architectural changes, including loss of superficial mucus

and epithelial cells, inflammatory changes, and polymorphonuclear cell infiltration.[22] Other changes, such as aphtoid-like lesions, have been reported with NaP.[23] The clinical significance of these histologic changes is unknown and requires further investigation but suggests possible changes in bowel wall homeostasis that may impact anastomotic structural integrity.

Initial Experience Without Mechanical Bowel Preparation

Challenges to the use of MBP arose in the 1960s from surgeons who started performing primary repair of injuries to the colon in trauma, with good results in selected cases.[24] This, then, led to a flurry of single-institution or single-surgeon series in which MBP was omitted. These authors consistently found rates of wound infections and anastomotic leaks comparable to the literature that used MBP leading to the conclusion that the benefits of MBP might be overstated.[25]

Initial Randomized Controlled Trials

The first randomized controlled trials comparing MBP to no MBP were performed in Europe and South America in the early 1990s.[26–29] Since then, several trials have been performed.[30–37] All studies are slightly different in their methodology, with some studies including patients who also underwent procedures in which intestinal continuity was not restored, and others including procedures in both the right and left colon. Anastomotic leak rates for all studies are summarized in Table 1. The difficulty in interpretation and application in practice derives from the variability in methodology in these studies. For example, anastomotic leak rates range from 0.6% to 20.8% in patients who underwent MBP. Wound infection rates for all studies are summarized in Table 2.

Cochrane Review

Given the small number of patients in the aforementioned randomized controlled trials and the variability among these, several meta-analyses have been performed, including a Cochrane Review.[38,39] The latest iteration of the Cochrane Review included nine trials with a total of 1,592 patients. Anastomotic leaks were significantly higher in the MBP group (6.2% versus 3.2%, Peto OR 2.03, 95% CI:1.276–3.26, p=0.003). However, when subgroup analysis was performed for leakage for low anterior resection and leakage for colonic surgery (only four studies could be included), the analysis still favored no MBP, but the statistical significance was lost. The authors found a statistically significant difference favoring no MBP for a decrease in the rate of peritonitis. Elimination of MBP was associated with a statistically significant decreased anastomotic leak rate when sensitivity analyses for studies that were completed and papers published (abstracts excluded), studies that only included adults (children excluded), and in studies that only included creation of an anastomosis. No MBP was also favored in all other analyses (decreased mortality, decreased rate of reoperation, decreased rate of wound infection, decreased noninfectious extra-abdominal complications, and decreased rate of surgical site infections), but these differences did not reach statistical significance. These analyses are limited by the small number of studies that could be included. The authors concluded that MBP before colorectal surgery does not add any value for patients and that it might lead to an increase in anastomotic leak rate.[39]

Results of Latest Randomized Controlled Trials

In light of the Cochrane Review findings, two large multicenter-randomized controlled trials were performed and the results published in the past year; one was performed in Sweden and another in the Netherlands.[40,41] The Swedish trial randomized 686 patients to MBP and 657 to no MBP.[40] Patients in the MBP arm were prepped with PEG (47.2%), NaP (48.5%), or enemas (4.3%). Antibiotic prophylaxis was appropriate for colorectal surgery and similar in both arms. The indications for surgery, patient demographics, type of anastomosis (site and technique) were similar for both groups. The results showed no statistically significant difference in cardiovascular complication rates, general infectious rates, or surgical site infection rates. Anastomotic dehiscence occurred in 13 (2.3%) patients in the MBP arm and in 17 (2.6%) patients in the no MBP arm (p=0.46). No mid- to low-anterior resections were performed in either group.

The study from the Netherlands randomly assigned 670 patients to mechanical bowel preparation and 684 to no mechanical bowel preparation for elective bowel resection.[41] The authors found that those patients that did not undergo MBP had an anastomotic leak rate of 5.4% compared to 4.8% in those that did undergo MBP, but the difference was not statistically significant (p=0.69). However, in the group of patients who did not undergo MBP, there was a statistically significant increased risk for anastomotic leak associated with a pelvic abscess (p= 0.001). The authors did not explicitly state the complications for each type of anastomosis for each group. However, multivariate analysis did show that type of

Table 1 Randomized Controlled Trials that Compare Mechanical Bowel Preparation to No Mechanical Bowel Preparation—Anastomotic Leaks

Study	Procedures performed	Type of MBP	Total number of patients enrolled	Anastomotic leaks[a] MBP n/N (%)	Anastomotic leaks[a] No MBP n/N (%)	*P* value[b]
Brownson 1992[26]	Elective colorectal (not specified)	PEG	179	8/67 (11.9)	1/67 (1.5)	0.03
Burke 1994[27]	Elective left colectomy and anterior resection with primary anastomosis	Sodium picosulfate	169	3/82 (3.7)	4/87 (4.6)	1
Santos 1994[28]	Elective colon and rectal surgery (includes abdominoperineal resection and pediatric surgery)	Mineral oil, agar and phenolphthalein; enema; mannitol (3-day regimen)	149	7/67 (10.4)	4/75 (5.3)	0.34
Fillmann 1995[29]	Elective left and right-sided resections, rectal resections (including APR and total proctocolectomy)	Mannitol	60	2/23 (8.7)	1/23 (4.3)	1
Miettinen 2000[30]	Elective colon and rectal resections, colostomy closure, APR, ileal-pouch anal anastomosis	PEG	267	5/131 (3.8)	3/120 (2.5)	0.72
Tabusso 2002[31]	Elective colon and rectal resections, Hartmann reversal	Mannitol or PEG	47	5/24 (20.8)	0/23 (0)	0.04
Bucher 2005[33]	Elective left-sided colorectal surgery with primary colocolonic or colorectal anastomosis	PEG	153	5/78 (6.4)	1/75 (1.3)	0.21
Fa-Si-Oen 2005[34]	Elective colonic resections and restoration of Hartmann, excluding ileocecal resections and resections below peritoneal reflection	PEG	250	7/125 (5.6)	6/125 (4.8)	0.78
Ram 2005[35]	Elective colon and rectal resections (including APR)	NaP	329	1/146 (0.6)	2/149 (1.3)	1.0
Zmora 2006[36]	Left-sided colonic resections, rectal resection and Hartmann closure	PEG	249	5/120 (4.2)	3/129 (2.3)	0.48
Pena-Soria 2007[37]	Elective colorectal procedure with primary intraperitoneal anastomosis	PEG	97	4/48 (8.3)	2/49 (4.1)	0.05
Jung 2007[40]	Elective colonic resections with primary anastomosis (mid-, low anterior resection excluded)	PEG, NaP, Enema	1343	13/686 (1.9)	17/657 (2.6)	0.46
Contant 2008[41]	Elective colorectal surgery with primary anastomosis	PEG + Bisacodyl or NaP	1354	32/670 (4.8)	37/684 (5.4)	0.69

MBP Mechanical bowel preparation, *PEG* polyethylene glycol, *NaP* sodium phosphate, *APR* abdominoperineal resection
[a] Rates based on patients who underwent resection with primary anastomosis
[b] Fisher's exact test

anastomosis (ileocolic, colocolic, and colorectal), ASA classification, and intraoperative blood-loss correlated with an increase in anastomotic leaks in general.

Meta-analysis

Methods

We performed a systematic review of the literature of all trials that prospectively compared mechanical bowel preparation with no mechanical bowel preparation for patients undergoing elective colorectal surgical resection. We performed a search in MEDLINE using the following search terms: (1) "Surgical Procedures, Elective" [Mesh] AND "Colorectal Surgery" [Mesh] AND mechanical bowel preparation; (2) mechanical bowel preparation AND elective AND surgery; (3) mechanical bowel preparation AND surgery AND colon AND rectum. We also performed a search in LILACS and SCISEARCH using the following terms: mechanical bowel preparation AND elective surgery. This was followed by a manual search of the reference lists for each article found, as well as abstracts of pertinent scientific meetings. Experts in the field were queried as to knowledge of additional reported trials. There were no limits on dates or language and all searches were performed up to January 2008. Studies had to be prospective, have two groups (one with mechanical bowel preparation and one

Table 2 Randomized Controlled Trials that Compare Mechanical Bowel Preparation to No Mechanical Bowel Preparation—Wound Infections

Study	Total number of patients enrolled	Wound infections MBP n/N (%)	Wound infections no MBP n/N (%)	*P* value[a]
Brownson 1992[26]	179	5/86 (5.8)	7/93 (7.5)	0.77
Burke 1994[27]	169	4/82 (4.9)	3/87 (3.4)	0.71
Santos 1994[28]	149	17/72 (23.6)	9/77 (11.7)	0.08
Fillmann 1995[29]	60	1/30 (3.3)	2/30 (6.7)	1
Miettinen 2000[30]	267	5/138 (3.6)	3/129 (2.3)	0.72
Tabusso 2002[31]	47	2/24 (8.3)	0/23 (0)	0.49
Bucher 2005[33]	153	10/78 (12.8)	3/75 (4)	0.07
Fa-Si-Oen 2005[34]	250	9/125 (7.2)	7/125 (5.6)	0.79
Ram 2005[35]	329	16/164 (9.8)	10/165 (6.1)	0.22
Zmora 2006[36]	249	8/120 (6.7)	13/129 (10.1)	0.36
Pena-Soria 2007[37]	97	6/48 (12.5)	6/49 (12.2)	1
Jung 2007[40]	1343	54/686 (7.9)	42/657 (6.4)	0.34
Contant 2008[41]	1354	90/670 (13.4)	96/684 (14.0)	0.75

MBP Mechanical bowel preparation
[a] Fisher's exact test

without mechanical bowel preparation), and have the two outcomes of interest clearly stated in their results section. The outcomes we abstracted were anastomotic leaks and wound infections. Retrospective studies and studies that only evaluated either mechanical bowel preparation or no mechanical bowel preparation were excluded from meta-analysis. Meta-analysis was performed using Comprehensive Meta-Analysis version 2 (Englewood, NJ, 2005, USA) applying the Peto-Odds ratio (fixed effects model). We also ran a test of statistical heterogeneity for each category.

Results

Of a total of 4,601 patients (13 trials), 2,304 were allocated to mechanical bowel preparation (Group 1) and 2,297 were allocated to no mechanical bowel preparation (Group 2). Anastomotic leaks (Table 1) occurred in 97 (4.2%) patients in Group 1 and in 81 (3.5%) patients in Group 2 (Peto OR= 1.214, CI 95%:0.899–1.64, P=0.206). Wound infections (Table 2) occurred in 227 (9.9%) patients in Group 1, and in 201 (8.8%) patients in Group 2 (Peto OR=1.156, CI 95%:0.946–1.413, P=0.155). Forest plots for anastomotic leaks and wound infections are shown in Figs. 1 and 2, respectively.

Discussion

Initial challenges to mandatory MBP first arose in the 1960s surrounding primary colon repairs in traumatic injuries to the colon. This led to single-institution and single-surgeon series where MBP was eliminated and ultimately to prospective randomized controlled trials comparing MBP to no MBP. A Cochrane review in 2005 suggested that MBP does not add value, but the number of patients evaluable were still small. Two more large trials have been performed since the Cochrane analysis, and now a total of 4,601 patients have been studied in a prospective fashion. Our meta-analysis suggests that MBP is of no benefit to patients undergoing elective colon and rectal surgery.

Based on the earlier small trials and Cochrane review many surgeons have abandoned routine MBP for elective "right-sided" surgeries, where the proximal extent of the resection will involve the small bowel and, therefore, theoretically be associated with a decreased risk for anastomotic and wound complications. More recently, some have questioned the need for MBP where a colocolonic or colorectal anastomosis is anticipated. Because of continued concerns for the role of MBP in rectal surgery and the exclusion of this population from most of the prospective trials, a retrospective review was performed on 144 patients who underwent anterior resection for cancer without MBP or a diverting stoma demonstrated an excellent anastomotic leak rate of only 4.9%.[42] In a French case-control study of an unselected group of patients with rectal cancer, the authors found an increased morbidity associated with MBP and no difference in the anastomotic leak rates.[43]

However, even with the growing body of evidence that suggests that mechanical bowel preparation should be abandoned, many groups have yet to change their practice. One of the main reasons is that even with several randomized controlled trials and meta-analyses, many practitioners feel that the right question has not been asked and, thus, the right trial has not been run. The ideal trial would recruit the number of patients necessary to show a difference in outcome. Power calculations by our statistics department resulted in over 2,400 patients, thus, requiring

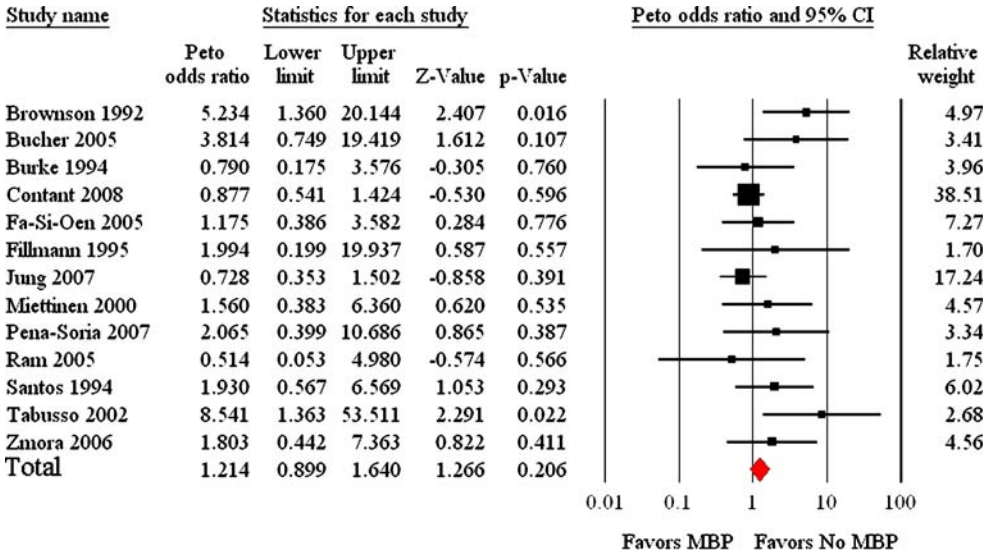

Figure 1 Forest Plot—Mechanical bowel preparation versus no mechanical bowel preparation for anastomotic leaks. Test for heterogeneity: Q=16.818, df=12, p=0.157, I^2=28.649. Test for overall effect: Z=1.266, p=0.206.

collaboration among many institutions. Because the rate of anastomotic leak is low in ileocolic anastomoses, these should be excluded from the study, allowing a focus on colocolonic and colorectal anastomoses. The study should compare the same type of anastomosis, report the height of anastomosis, and use a similar operative technique. More importantly, the endpoints (anastomotic leaks and wound infections) must be unambiguously defined. These requirements become difficult as it is hard to minimize variability in studies that require participation of various surgeons and centers. Other possible reasons why a change in practice has not taken place include the influence of training programs on practice patterns, the inability to work "comfortably" with a bowel filled with feces, and the persistent yet unrealized fear of increased risk of fecal spillage during surgery when MBP is eliminated.

In modern surgical practice, the use of prophylactic antibiotics and the rate of surgical site wound infections have become, for better or worse, performance measures used to rank, reward, and penalize institutions and physicians as part of national and institutional quality improvement projects.[3] Since MBP may or may not increase the rate of infectious complications, it will become imperative to define its place in clinical practice in order to justify its continued use. MBP should not be completely abandoned, as it is necessary for those procedures in which intraoperative colonoscopy is necessary. Even though the ideal study has not yet been performed, this meta-analysis does point to the fact that MBP is not a prerequisite of safe colorectal surgery, as suggested by others. Some of our European counterparts have embraced these findings and changed their practice patterns, yet we remain static, either as cautious observers or as laggards.

As individual-practicing surgeons, one can argue to remain cautious. In fact, the individual-practicing surgeon relies on national societies to provide guidelines that are

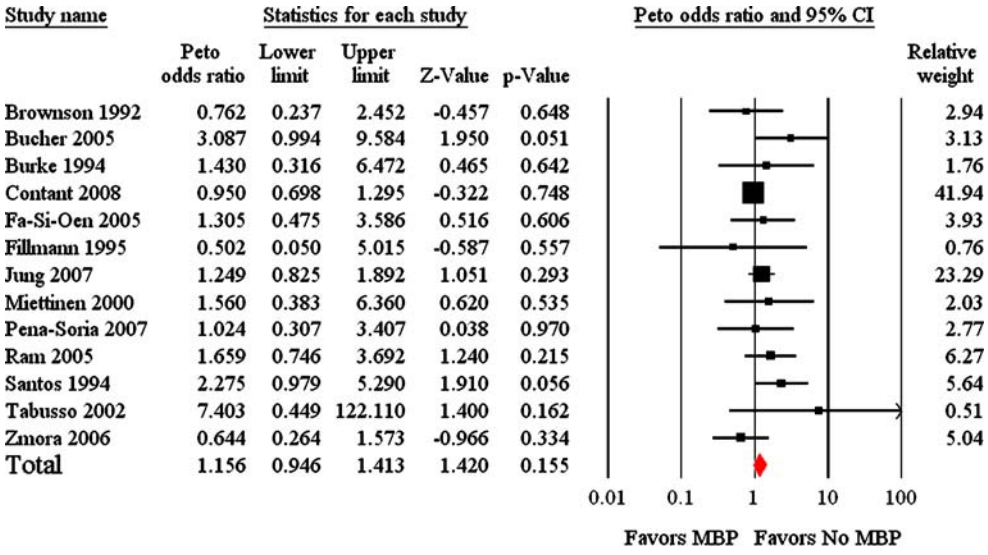

Figure 2 Forest Plot—Mechanical bowel preparation versus no mechanical bowel preparation for wound infections. Test for heterogeneity: Q=12.492, df=12, p=0.407, I^2=3.937. Test for overall effect: Z=1.42, p=0.155.

based on best available evidence.[44] This is also true for medicolegal proceedings, where practice guidelines serve as key elements that establish the standard of care.[45] As thought leaders, however, we should have the courage to expose unsubstantiated dogmas and encourage discontinuation of unfounded practices. Thus, our meta-analysis represents an opportunity for respected national societies, like the Society for Surgery of the Alimentary Tract, to lead by publicly endorsing the abandonment of routine MBP in elective colon and rectal surgery.

Conclusion

MBP has remained a dogmatic practice in surgery of the alimentary tract. This updated meta-analysis demonstrates that MBP is of no benefit to patients undergoing elective colon and rectal surgery, thus, supporting elimination of routine MBP. It should not be considered as a prerequisite to meet the "standard of care."

References

1. Nichols RL, Broido P, Condon RE, Gorbach SL, Nyhus LM. Effect of preoperative neomycin-erythromycin intestinal preparation on the incidence of infectious complications following colon surgery. Am Surg 1973;178:453–62. doi:10.1097/00000658-197310000-00008.
2. Zmora O, Wexner SD, Hajjar L, Park T, Efron JE, Noqueras JJ, Weiss EG. Trends in preparation for colorectal surgery: survey of the members of the American Society of Colon and Rectal Surgeons. Am Surg 2003;69:150–4.
3. McCahill LE, Ahern JW, Gruppi LA, Limanek J, Dion GA, Sussman JA, McCaffrey CB, Leary DB, Lesaqe MB, Single RM. Enhancing compliance with Medicare guidelines for surgical infection prevention: experience with a cross-disciplinary quality improvement team. Arch Surg 2007;142:355–61. doi:10.1001/archsurg.142.4.355.
4. Nichols RL, Choe EU, Weldon CB. Mechanical and antibacterial bowel preparation in colon and rectal surgery. Chemotherapy 2005;51(Suppl 1):115–21. doi:10.1159/000081998.
5. Nichols RL, Gorbach SL, Condon RE. Alteration of intestinal microflora following preoperative mechanical preparation of the colon. Dis Colon Rectum 1971;14:123–7. doi:10.1007/BF02560057.
6. Lindsey JT, Smith JW, McClugage SG Jr, Nichols RL. Effects of commonly used bowel preparations on the large bowel mucosal-associated and luminal microflora in the rat model. Dis Colon Rectum 1990;33:554–60. doi:10.1007/BF02052206.
7. Smith MB, Baliga P, Sartor WM, Goradia VK, Holmes JW, Nichols RL. Intraoperative colonic lavage: failure to decrease mucosal microflora. South Med J 1991;84:38–42. doi:10.1097/00007611-199104000-00017.
8. Bornside GH, Cohn I Jr. Intestinal antisepsis. Stability of fecal flora during mechanical cleansing. Gastroenterology 1969;57:569–573.
9. Bleday R, Braidt J, Ruoff K, Shellito PC, Ackroyd FW. Quantitative cultures of the mucosal-associated bacteria in the mechanically prepared colon and rectum. Dis Colon Rectum 1993;36:844–9. doi:10.1007/BF02047381.
10. Mahajna A, Krausz M, Rosin D, Shabtai M, Hershko D, Ayalon A, Zmora O. Bowel preparation is associated with spillage of bowel contents in colorectal surgery. Dis Colon Rectum 2005;48:1626–31. doi:10.1007/s10350-005-0073-1.
11. Irvin TT, Goligher JC. Aetiology of disruption of intestinal anastomoses. Br J Surg 1973;60:461–4. doi:10.1002/bjs.1800600612.
12. Muzii L, Bellati F, Zullo MA, Manci N, Angioli R, Panici PB. Mechanical bowel preparation before gynecologic laparoscopy: a randomized, single-blind, controlled trial. Fertil Steril 2006;85:689–93. doi:10.1016/j.fertnstert.2005.08.049.
13. Wexner SD, Beck DE, Baron TH, Fanelli RD, Hyman N, Shen B, Wasco KE. A consensus document on bowel preparation before colonoscopy: prepared by a task force from the American Society of Colon and Rectal Surgeons (ASCRS), the American Society for Gastrointestinal Endoscopy (ASGE), and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES). Surg Endosc 2006;20:1147–60. doi:10.1007/s00464-006-0152-y.
14. Nichols RL, Smith JW, Garcia RY, Waterman RS, Holmes JW. Current practices of preoperative bowel preparation among North American colorectal surgeons. Clin Infect Dis 1997;24:609–19.
15. de Graaf P, Slagt C, de Graaf JL, Loffeld RJ. Fatal aspiration of polyethylene glycol solution. Neth J Med 2006;64:196–8.
16. Oliveira L, Wexner SD, Daniel N, DeMarta D, Weiss EG, Noqueras JJ, Bernstein M. Mechanical bowel preparation for elective colorectal surgery. A prospective, randomized, surgeon-blinded trial comparing sodium phosphate and polyethylene glycol-based oral lavage solutions. Dis Colon Rectum 1997;40:585–91. doi:10.1007/BF02055384.
17. Mathus-Vliegen EM, Kemble UM. A prospective randomized blinded comparison of sodium phosphate and polyethylene glycol-electrolyte solution for safe bowel cleansing. Aliment Pharmacol Ther 2006;23:543–52. doi:10.1111/j.1365-2036.2006.02777.x.
18. Gonlusen G, Akgun H, Ertan A, Olivero J, Truong LD. Renal failure and nephrocalcinosis associated with oral sodium phosphate bowel cleansing: clinical patterns and renal biopsy findings. Arch Pathol Lab Med 2006;130:101–6.
19. Ullah N, Yeh R, Ehrinpreis M. Fatal hyperphosphatemia from a phosphosoda bowel preparation. J Clin Gastroenterol 2002;34:457–8. doi:10.1097/00004836-200204000-00017.
20. Aydogan T, Kanbay M, Uz B, Kaya A, Isik A, Bozalan R, Erkman M, Akcay A. Fatal hyperphosphatemia secondary to a phosphosoda bowel preparation in a geriatric patient with normal renal function. J Clin Gastroenterol 2006;40:177. doi:10.1097/01.mcg.0000196408.60851.cf.
21. Jung B, Lannerstad O, Pahlman L, Arodell M, Unosson M, Nilsson E. Preoperative mechanical preparation of the colon: the patient's experience. BMC Surg 2007;7:5. doi:10.1186/1471-2482-7-5.
22. Bucher P, Gervaz P, Egger JF, Soravia C, Morel P. Morphologic alterations associated with mechanical bowel preparation before elective colorectal surgery: a randomized trial. Dis Colon Rectum 2006;49:109–12. doi:10.1007/s10350-005-0215-5.
23. Zwas FR, Cirillo NW, El-Serag HB, Eisen RN. Colonic mucosal abnormalities associated with oral sodium phosphate solution. Gastrointest Endosc 1996;43:463–6.
24. LoCicero J 3rd, Tajima T, Drapanas T. A half-century of experience in the management of colon injuries: changing concepts. J Trauma 1975;15:575–9. doi:10.1097/00005373-197507000-00003.
25. Duthie GS, Foster ME, Price-Thomas JM, Leaper DJ. Bowel preparation or not for elective colorectal surgery. J R Coll Surg Edinb 1990;35:169–71.

26. Brownson P, Jenkins SA, Nott D, Ellenbogen S. Mechanical bowel preparation before colorectal surgery: results of a prospective randomized trial. Br J Surg 1992;79:461–2.
27. Burke P, Mealy K, Gillen P, Joyce W, Traynor O, Hyland J. Requirement for bowel preparation in colorectal surgery. Br J Surg 1994;81:907–10. doi:10.1002/bjs.1800810639.
28. Santos JC Jr, Batista J, Sirimarco MT, Guimaraes AS, Levy CE. Prospective randomized trial of mechanical bowel preparation in patients undergoing elective colorectal surgery. Br J Surg 1994;81:1673–6. doi:10.1002/bjs.1800811139.
29. Fillmann EEP, Fillmann HS, Fillmann LS. Elective colorectal surgery without prepare [Cirugia colorretal eletiva sem preparo]. Rev Bras Colo-Proct 1995;15:70–1.
30. Miettinen RP, Laitinen ST, Makela JT, Paakkonen ME. Bowel preparation with oral polyethylene glycol electrolyte solution vs. no preparation in elective open colorectal surgery: prospective, randomized study. Dis Colon Rectum 2000;43:669–75. discussion 75–77. doi:10.1007/BF02235585.
31. Tabusso FY, Zapata JC, Espinoza FB, Meza EP, Figueroa ER. Mechanical preparation in elective colorectal surgery, a useful practice or need. Rev Gastroenterol Peru 2002;22:152–8. Preparación mecánica en cirugía electiva colo-rectal ¿Costumbre o necesidad?
32. Zmora O, Mahajna A, Bar-Zakai B, Rosin D, Hershko D, Shabtai M, Krausz MM, Ayalon A. Colon and rectal surgery without mechanical bowel preparation: a randomized prospective trial. Ann Surg 2003;237:363–7. doi:10.1097/00000658-200303000-00010.
33. Bucher P, Gervaz P, Soravia C, Mermillod B, Erne M, Morel P. Randomized clinical trial of mechanical bowel preparation versus no preparation before elective left-sided colorectal surgery. Br J Surg 2005;92:409–14. doi:10.1002/bjs.4900.
34. Fa-Si-Oen P, Roumen R, Buitenweg J, van de Velde C, van Geldere D, Putter H, Verwaest C, Verhoef L, de Waard JW, Swank D, D'Hoore A, Croiset van Uchelen F. Mechanical bowel preparation or not? Outcome of a multicenter, randomized trial in elective open colon surgery. Dis Colon Rectum 2005;48:1509–16. doi:10.1007/s10350-005-0068-y.
35. Ram E, Sherman Y, Weil R, Vishne T, Kravarusic D, Dreznik Z. Is mechanical bowel preparation mandatory for elective colon surgery? A prospective randomized study. Arch Surg 2005;140:285–8. doi:10.1001/archsurg.140.3.285.
36. Zmora O, Mahajna A, Bar-Zakai B, Hershko D, Shabtai M, Krausz MM, Ayalon A. Is mechanical bowel preparation mandatory for left-sided colonic anastomosis? Results of a prospective randomized trial. Tech Coloproctol 2006;10:131–5. doi:10.1007/s10151-006-0266-1.
37. Pena-Soria MJ, Mayol JM, Anula-Fernandez R, Arbeo-Escolar A, Fernandez-Represa JA. Mechanical bowel preparation for elective colorectal surgery with primary intraperitoneal anastomosis by a single surgeon: interim analysis of a prospective single-blinded randomized trial. J Gastrointest Surg 2007;11:562–7. doi:10.1007/s11605-007-0139-6.
38. Bucher P, Mermillod B, Gervaz P, Morel P. Mechanical bowel preparation for elective colorectal surgery: a meta-analysis. Arch Surg 2004;139:1359–64. discussion 65. doi:10.1001/archsurg.139.12.1359.
39. Guenaga KF, Matos D, Castro AA, Atallah AN, Wille-Jorgensen P. Mechanical bowel preparation for elective colorectal surgery. Cochrane Database Syst Rev 2005, CD001544.
40. Jung B, Pahlman L, Nystrom PO, Nilsson E. Multicentre randomized clinical trial of mechanical bowel preparation in elective colonic resection. Br J Surg 2007;94:689–95. doi:10.1002/bjs.5816.
41. Contant CM, Hop WC, van't Sant HP, Oostvoqel HJ, Smeets HJ, Stassen LP, Neijenhuis PA, Idenburg FJ, Dijkhuis CM, Heres P, van Tets WF, Gerritsen JJ, Weidema FF. Mechanical bowel preparation for elective colorectal surgery: a multicentre randomised trial. Lancet 2007;370:2112–7. doi:10.1016/S0140-6736(07)61905-9.
42. Vlot EA, Zeebregts CJ, Gerritsen JJ, Mulder HJ, Mastboom WJ, Klaase JM. Anterior resection of rectal cancer without bowel preparation and diverting stoma. Surg Today 2005;35:629–33. doi:10.1007/s00595-005-2999-2.
43. Bretagnol F, Alves A, Ricci A, Valleur P, Panis Y. Rectal cancer surgery without mechanical bowel preparation. Br J Surg 2007;94:1266–71. doi:10.1002/bjs.5524.
44. Eagle KA, Garson AJ Jr, Beller GA, Sennett C. Closing the gap between science and practice: the need for professional leadership. Health Aff (Millwood) 2003;22:196–201. doi:10.1377/hlthaff.22.2.196.
45. Feld AD. Medicolegal implications of colon cancer screening. Gastrointest Endosc Clin N Am 2002;12:171–9. doi:10.1016/S1052-5157(03)00065-5.

J Gastrointest Surg (2008) 12:2045–2050
DOI 10.1007/s11605-008-0598-4

Enteral Stents for Malignancy: A Report of 46 Consecutive Cases over 10 years, with Critical Review of Complications

Melissa S. Phillips · Sonia Gosain · Hugo Bonatti · Charles M. Friel · Kristi Ellen · Patrick G. Northup · Michel Kahaleh

Received: 22 May 2008 / Accepted: 25 June 2008 / Published online: 22 July 2008

Abstract
Background Current management of malignant gastric outlet obstruction (GOO) includes surgical diversion or enteral stent placement for unresectable cancer. We analyzed the long-term results, predictive factors of outcomes, and complications associated with enteral stents with focus on their management.
Methods Between 1997 and 2007, 46 patients with malignant GOO underwent placement of self-expandable metal stents (SEMS) for palliation. Patients were captured prospectively after 2001 and followed until complication or death. Patency, management of complications, and long-term survival were analyzed.
Results Forty-six patients had a mean survival of 152±235 days and a mean SEMS patency rate of 111±220 days. SEMS patency rates of 98%, 74%, and 57% at 1, 3, and 6 months were seen. Thirteen patients presented with obstruction and included two SEMS migration, two early occlusion, one fracture, four malignant ingrowth, and four with delayed clinical failure. Interventions included seven endoscopic revisions with three SEMS replacements. Six had percutaneous endoscopic gastrostomy with jejunal arm placed. Two patients eventually underwent surgical bypass. Two patients required surgery for complications including delayed duodenal perforation and aortoenteric fistula.
Conclusions SEMS effectively palliate gastric outlet obstructions that result from upper gastrointestinal malignancies. Their benefits offset potential complications or malfunctions, when a pluridisciplinary approach is adopted.

Keywords Enteral stent · Malignant gastric outlet obstruction · Unresectable cancer · Self-expandable metal stent

Presented at Digestive Disease Week/SSAT, May 2008, San Diego, California.

M. S. Phillips · H. Bonatti · C. M. Friel
Surgery, University of Virginia Health System, Charlottesville, VA, USA

S. Gosain · K. Ellen · P. G. Northup · M. Kahaleh (✉)
Digestive Health Center, University of Virginia Health System, Box 800708, Charlottesville, VA 22908-0708, USA
e-mail: mk5ke@virginia.edu

Introduction

In patients presenting with gastric outlet obstruction, upper gastrointestinal (GI) malignancies are the source in up to 39% of cases.[1] Surgical resection with curative intent is the standard of care in patients who lack significant comorbidities.[2] In unresectable patients, gastrojejunostomy remains the standard of care if a surgical intervention is to be undertaken. In those patients with significant comorbidities, the morbidity rate approaches 40%,[3] encouraging alternatives to surgery. In patients who are not surgical candidates, enteral stenting offers an attractive option.[4] Self-expandable metal stents (SEMS) have proven themselves to be a safe[5] and relatively cost-effective[6] alternative to surgical palliation allowing the patient to be discharged

and start PO intake earlier.[7–8] However, most series are retrospective and underscore the magnitude of potential complications. Our aim is to analyze our 10-year experience using enteral stents and pluridisciplinary management of all possible complications or malfunctions.

Materials and Methods

Patients

Between 1997 and 2007, 46 patients with malignant gastric outlet obstruction (GOO) underwent SEMS placement (Table 1). All patients were not surgical candidates for curative resection based on staging or comorbidities. Twelve patients had previously undergone attempted curative resection with disease recurrence. Follow-up 24 h post-procedure included phone contact by an endoscopy nurse. The patients were evaluated in clinic when enrolled in a chemo-radiation protocol with laboratories, performed every 2 months until death. Clinical response to SEMS placement, procedure-related morbidity, and overall patient survival were captured. Data were collected prospectively (43 patients) starting in 2001. Patients before this date (three patients) were captured retrospectively. The study was approved by our Institutional Review Board; all patients provided written consent for their procedures.

Table 1 Patient Characteristics

Characteristics	Number
Number of patients	46
Gender (male/female)	32/14
Mean age (range; year)	65 (24–88)
Chemoradiation administered (yes/no)	27/19
Serum albumin (mean [SD], mg/dl) (range)	3.19 [0.69] (1.70–4.80)
Primary malignancy	
Pancreatic cancer	23
Gastric cancer	8
Cholangiocarcinoma	5
Esophageal cancer	2
Duodenal cancer	1
Gallbladder cancer	1
Lymphoma	1
Metastatic colon cancer	1
Metastatic endometrial cancer	1
Metastatic ovarian cancer	1
Neuroendocrine tumor	1
Sarcoma	1

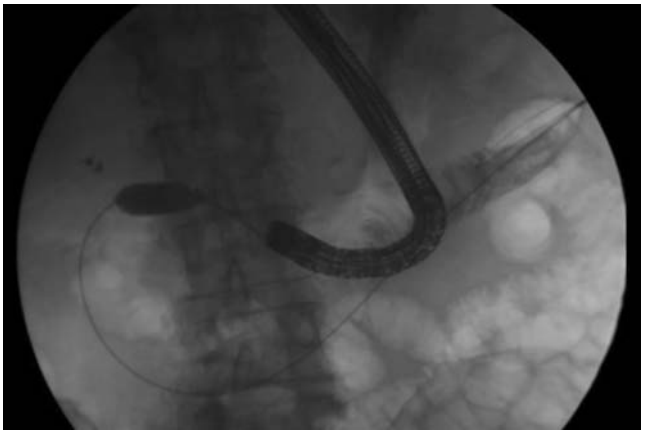

Figure 1 Balloon dilation of the malignant enteral stricture.

Enteral Stent Insertion and Deployment

After endoscopic access was obtained proximal to the stricture, using fluoroscopy the length of each stricture was determined, and balloon dilation was performed at the discretion of the operator (Fig. 1). The SEMS delivery system was advanced proximal to the stricture over a guidewire where the SEMS was partially deployed (Figs. 2 and 3) and centered across the stricture before full expansion (Figs. 4). In case a biliary stent needed to be placed, this was typically inserted before the deployment of the enteral stent. All procedures were performed by dedicated pancreatico-biliary endoscopists.

Forty patients (87%) had a Wallstent (Boston Scientific, Natick, MA, USA) placed. Four had an Alimaxx (Alveolus, Charlotte, NC, USA), and two had a Bard (Bard, Tempe, AZ, USA) stent placed.

Indication for SEMS Placement

Indication for SEMS insertion included obstructive symptoms in the setting of unresectable or recurrent malignancy.

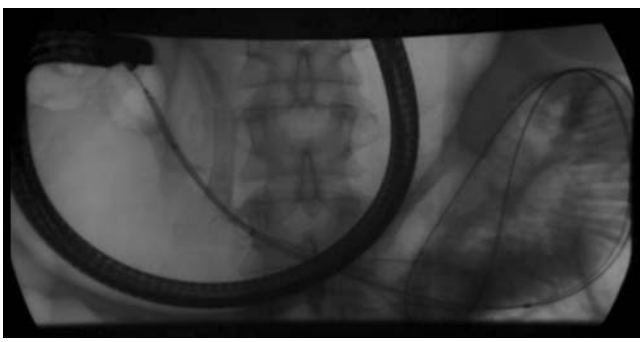

Figure 2 Partial deployment of the SEMS across the malignant stricture.

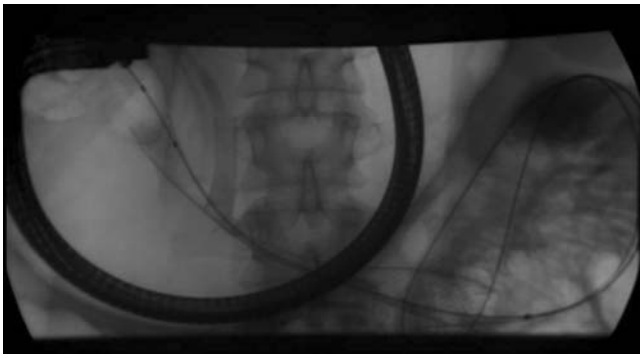

Figure 3 Progressive deployment of the SEMS over a wire.

The majority of patients had pancreatic adenocarcinoma (23 patients, 50%) or gastric cancer (eight patients, 17%; Table 1). Poor generalized medical status was defined as an American Society of Anesthesiologist score of 3 or greater and was present in 84%.

Serum albumin was used as a marker of patient's nutritional status, with a mean of 3.2±0.7 mg/dl.

Definition of Events

Successful SEMS placement was defined as deployment of the SEMS across the stricture with patency visualized both endoscopically and fluoroscopically. Clinical success was defined as relief of obstructive symptoms and ability to take oral intake within 24 h of SEMS placement independent of SEMS patency on imaging or endoscopic evaluation.

Complications were stratified as early (occurring ≤30 days of SEMS placement) and late (occurring >30 days following SEMS placement). Patency was defined as the period of time between SEMS insertion and repeat intervention or death. Repeat intervention was defined as any procedure to improve obstructive symptoms after initial SEMS placement. This included balloon dilation, placement of additional SEMS, percutaneous endoscopic gastrostomy with jejunal arm (PEGJ), or surgical intervention. Patients who had a PEGJ placed prior to or concurrently with stent placement were not defined as post-procedure complications.

Statistical Methods

The composite primary end point was stent malfunction requiring reintervention or death. Patient survival and SEMS patency were calculated using Kaplan–Meier estimates with censoring at end of follow-up. Univariate and multivariate logistic regression were used to determine if there were independent variables predicting combined mortality or stent failure using the method of maximum likelihood estimates. Factors were included in the multivariate analysis if they were established risk factors for mortality based on the literature or were significant in the univariate analysis to a level of 0.20. Data manipulation and analyses were performed with SAS©, version 9.1 (Cary, NC, USA) and Graphpad Prism©, version 4.0 (San Diego, CA, USA). The level of type 1 error for statistical significance was assumed to be less than or equal to 0.05. All statistical tests were two-sided.

Results

SEMS were successfully placed in all patients. No patient died as a direct result of SEMS placement, and all causes of death were related to progression of disease. There were no occurrences of perforation at stent placement. Forty-two patients (91%) had a clinical response to SEMS placement. Four patients failed to resolve their obstructive symptoms despite confirmed endoscopic patency; these patients were treated with PEGJ placement. In patients with an initial clinical response, a total of seven complications were recorded, five early and two late. Four patients (9%) had local tumor ingrowth through the mesh of the stent leading to secondary obstruction that was treated with either endoscopic intervention (three patients) or surgery (one patient). These were not included as complications, since they were resultant from progression of the primary disease.

Patients with Previous Surgical Interventions

Twelve patients who underwent attempts at curative surgical resection were treated with SEMS after tumor recurrence or progression. An additional four patients had laparoscopic evaluation for potential resection aborted in the setting of metastatic disease. Thirty patients did not undergo attempts at primary resection or surgical staging

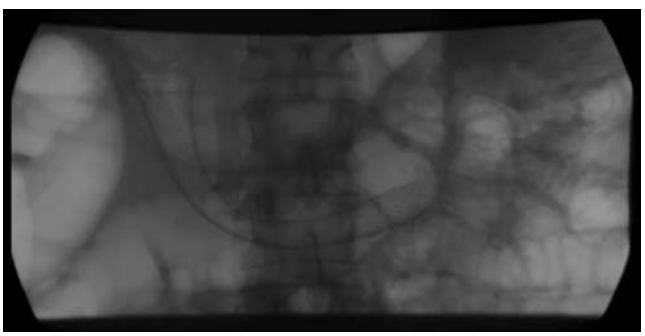

Figure 4 Successful SEMS placement after removal of the delivery system.

secondary to either medical comorbidities or tumor burden. Five patients included in this study had jejunal SEMS placement after previous pancreaticoduodenectomy (two patients) or gastrectomy (three patients).

Chemotherapy and Radiation

All patients were offered chemoradiation, with a total of 27 patients (57%) enrolled in an institution-specific protocol, based on their oncologist's recommendation for their specific tumor type.

Early Complications (≤30 days)

Early complications related to SEMS placement included stent migration in two patients, managed by removal of the original SEMS and replacement with a new SEMS. Two patients who had initially responded to SEMS placement developed delayed-onset obstructive symptoms with endoscopically patent SEMS. Each was managed by PEGJ placement for decompression with the presumption that disease distal to the SEMS, in the setting of carcinomatosis, was the etiology. One patient developed stent fracture managed by stent removal with dilation (Table 2).

Long-Term Complications (>30 days)

There were no migrated or fractured SEMS beyond 30 days. Long-term complications include duodenal perforation 35 days after stenting, requiring emergent surgical repair with closure and Graham patch. One patient who had previously undergone a pancreaticoduodenectomy developed an aortoenteric fistula from stent erosion that presented as an upper GI bleed 12 months after initial stent placement. She was treated with an endovascular aortic stent followed by interval resection with definitive repair (Table 2).

Local Tumor Recurrence

Four patients were found to have occluded SEMS at 14, 62, 64, and 75 days post-stenting. These obstructions were consistent with local tumor ingrowth and progression of the primary disease process. These were treated, respectively, with repeat SEMS placement, argon plasma coagulation application, balloon dilation, and surgical bypass.

Stent Patency, Multivariate Analysis, and Patient Survival

Mean survival was 152 days (range, 13–1,411 days). Mean stent patency was 111 days (range, 3–1,411 days). Kaplan–Meier survival analysis showed a patency rate of 98%, 74%, 57%, and 58% at 1, 3, 6, and 12 months, respectively (Fig. 5).

Multivariate analysis failed to identify any factor predictive of survival. Factors analyzed included age, gender, serum albumin as a marker for nutritional status, or treatment with chemoradiation. (Table 3)

Overall, if migration, fracture, tumor ingrowth, erosion, and perforation are taken into account, the global long-term patency rate obtained is 76%. This rate does not include the four patients (9%) that did not gain a clinical response from SEMS placement despite the stent being patent endoscopically and radiographically.

Table 2 Complications of SEMS, Final Treatment, and Total Follow-up Time

Case #	Complication	Days to Reintervention	Intervention	Days to Follow-up
1	Clinical failure	2	PEGJ followed by gastrojejunostomy	63
2	Clinical failure	3	PEGJ	95
3	Clinical failure	3	PEGJ	74
4	Clinical failure	6	PEGJ	13
5	SEMS migration	4	SEMS replacement	51
6	SEMS migration	13	SEMS replacement	67
7	Delayed clinical failure	7	PEGJ	78
8	Delayed clinical failure	21	PEGJ	604
9	SEMS fracture	27	SEMS removal, serial dilation	601
10	Duodenal perforation	35	Surgical primary repair, Graham patch	117
11	Aortoenteric fistula	375	Endovascular stent then surgical repair	471
12	Tumor ingrowth	14	SEMS Replacement	35
13	Tumor ingrowth	62	Balloon dilation, APC	121
14	Tumor ingrowth	64	Balloon dilation	64
15	Tumor ingrowth	75	Gastrojejunostomy	105

APC Argon plasma coagulation, *SEMS* self-expandable metal stent, *PEGJ* percutaneous endoscopic gastrostomy with jejunal arm

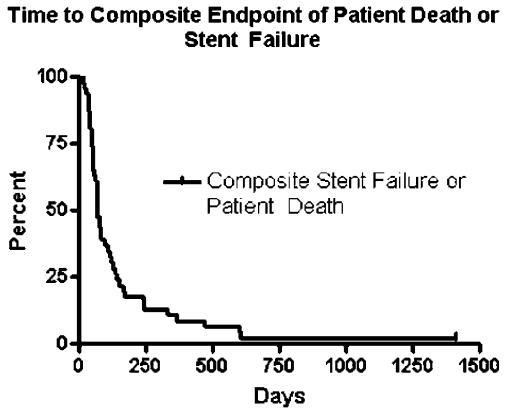

Figure 5 Kaplan–Meier analysis of SEMS patency rate and survival.

Discussion

Gastric outlet obstruction is a common cause of preterminal morbidity, leading to a progressive deterioration in quality of life in patients with advanced upper GI malignancies. Up to 39% of patients with GOO will have a malignant etiology, commonly unresectable pancreatic cancer.[1] Surgical palliation has been the accepted standard for treatment of these patients for many years.[2] Singh et al.[9] describe a retrospective review of 340 patients undergoing either curative resection, palliative surgery, or neither for pancreatic adenocarcinoma. Seventy patients underwent gastrojejunostomy, 20 prophylactically and 50 therapeutically for GOO. Of those who did not undergo bypass, 25% required a later repeat surgical intervention for gastrojejunostomy. They report morbidity rates greater than 30% in this patient population. Patient comorbidities and time to recovery/discharge after palliative surgery have promoted tertiary-care centers proficient in interventional endoscopy to use enteral stenting as an alternative. For over a decade, SEMS has been used as a minimally invasive technique for palliative treatment of patients with malignant gastric outlet obstruction.[10–11]

A comprehensive review of 32 case series, including 606 patients unable to take oral intake, reported successful stent deployment in 97% of patient and oral intake possible in all cases, with 87% of cases capable of eating at least a soft mechanical diet.[12] Well-described complications of enteral stent placement include tumor overgrowth, obstruction, and stent migration.[13] Graber et al.[14] have published results from a prospective multicenter trial demonstrating a mortality rate of 9.8% due to stent complications with 25% developing SEMS occlusion secondary to local tumor ingrowth and disease progression with a subpopulation requiring surgical intervention for hemorrhage and perforation.

Our study confirms previous data in the literature. We show a 100% success rate in SEMS deployment with a 91% clinical success rate. Four patients had lack of improvement within the first week after stent placement. In these patients, peritoneal carcinomatosis with multi-level obstruction or autonomic infiltration with dysmotility was presumed responsible for symptoms persistence.

In our study population, seven patients (14%) had a PEGJ placed prior to SEMS insertion, and an additional four patients (9%) had a PEGJ placed concomitantly with SEMS placement for malnutrition. These patients had no additional evidence of stent dysfunction.

The data for this study were collected in a prospective manner starting in 2001 (43 patients, 93%) with the establishment of an enteral stent database; therefore, we were able to collect known complications more accurately compared to retrospective studies. Our data shows that seven (17%) of 42 patients with clinical response to SEMS placement had a complication related to enteral stenting. This rate does not include the four patients (9%) that developed local tumor recurrence requiring reintervention. In this setting, the reported complication rate is less than those of other published studies likely because all stent placement and treatment were performed at a tertiary-care center by dedicated interventional endoscopists. This trend of specialists having a lower complication rate has been reported in other fields,[15] and a similar trend would be predicted in our study.

SEMS placement has become a preferred palliative tool in most tertiary-care centers since it is more cost effective than palliative surgery[6] and permits earlier discharge, with faster return to PO intake and less postoperative recovery time.[16]

In our case series, we reviewed the long-term results and complications associated with enteral stents with special consideration given to their management, outlining the excellent collaboration between the GI and surgical communities. It also shows no statistically significant correlation between survival and any of our independent variables including age, gender, albumin, and chemoradiation therapy.

Table 3 Multivariate Analysis of Independent Factors Predicting Outcome

	p value	OR	95% CI
Age (>65 years old)	0.18	8.4	0.4–192.0
Gender (male)	0.16	6.8	0.5–100.7
Chemoradiation	0.22	5.6	0.4–85.0
Albumin (<3.0)	0.46	0.4	0.0–4.7

Conclusions

In conclusion, SEMS offer an efficacious palliation of malignant gastric outlet obstruction in patients. Our series underlines the need to establish a pluridisciplinary approach involving interventional radiologists, endoscopists, and surgeons alike in order to successfully manage any complications or failures associated with SEMS.

References

1. Awan A, Johnston DE, Jamal MM. Gastric outlet obstruction with benign endoscopic biopsy should be further explored for malignancy. Gastrointest Endosc 1998;48(5):497–500.
2. Fisher WE, Andersen DK, Bell RH Jr, Saluja AK, Brunicardi FC. Chapter 32: The Pancreas. Schwartz's Principles of Surgery. Eighth edition, (October 14, 2004).
3. Medina-Franco H, Abarca-Pérez L, España-Gómez N, Salgado-Nesme N, Ortiz-López LJ, García-Alvarez MN. Morbidity-associated factors after gastrojejunostomy for malignant gastric outlet obstruction. Am Surg. 2007;73(9):871–875.
4. Graber I, Dumas R, Filoche B, Boyer J, Coumaros D, Lamouliatte H, Legoux JL, Napoleon B, Ponchon T, Societe Francaise d'Endoscopie Digestive. The efficacy and safety of duodenal stenting: a prospective multicenter study. Endoscopy 2007;39 (9):784–787.
5. Maetani I, Tada T, Ukita T et al. Comparison of duodenal stent placement with surgical gastrojejunostomy for palliation in patients with duodenal obstructions caused by pancreaticobiliary malignancies. Endoscopy 2004;36:73–78.
6. Johnsson E, Thune A, Liedman B. Palliation of malignant gastroduodenal obstruction with open surgical bypass or endoscopic stenting: clinical outcome and health economic evaluation. World J Surg 2004;28:812–817.
7. Jeurnink SM, van Eijck CH, Steyerberg EW, Kuipers EJ, Siersema PD. Stent versus gastrojejunostomy for the palliation of gastric outlet obstruction: a systematic review. BMC Gastroenterol 2007;7:18.
8. Espinel J, Sanz O, Vivas S, Jorquera F, Muñoz F, Olcoz JL, Pinedo E. Malignant gastrointestinal obstruction: endoscopic stenting versus surgical palliation. Surg Endosc 2006;20(7):1083–1087.
9. Singh SM, Longmire WP Jr, Reber HA. Surgical palliation for pancreatic cancer. The UCLA experience. Ann Surg 1990;212 (2):132–139.
10. Baron TH. Expandable metal stents for the treatment of cancerous obstruction of the gastrointestinal tract. N Engl J Med 2001;344: 1681–1687.
11. Baron TH, Harewood GC. Enteral self-expandable stents. Gastrointest Endosc 2003;58:421–433.
12. Dormann A, Meisner S, Verin N et al. Self expainding metal stents for gastroduodenal malignancies: systemic review of their clinical effectiveness. Endoscopy 2004;36:543–550.
13. Mauro MA, Koecher RE, Baron TH. Advances in gastrointestinal intervention. The treatment of gastroduodenal and colorectal obstructions with metallic stents. Radiology 2000;215:659–669.
14. Graber L, Dumas R, Foliche B et al. The efficacy and safety of duodenal stenting: a prospective multicenter study. Endoscopy 2007;39:784–787.
15. Beecherl EE, Shires GT, Shires GT. Treatment of Post-pancreaticoduodenectomy Complications. Curr Treat Options Gastroenterol 2004;7(5):365–370.
16. Mittal A, Windsor J, Woodfield J et al. Matched study of three methods for palliation of malignant pyloroduodenal obstruction. Br J Surg 2004;91:205–209.