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2008 SSAT QUICKSHOT PRESENTATION

Leukocyte Depletion in Allogeneic Blood Transfusion Does Not Change the Negative Influence on Survival Following Transthoracic Resection for Esophageal Cancer

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Abstract
Background Perioperative transfusion of allogeneic blood has been hypothesized to have an immunomodulatory effect and influence survival in several cancer types. This study evaluates the association between receipt of leucocyte-depleted and non-depleted allogeneic blood and survival following esophagectomy for cancer.
Methods A retrospective analysis was performed including 291 patients with esophageal cancers who underwent transthoracic en bloc esophagectomy and extended mediastinal lymphadenectomy. Neoadjuvant chemoradiation was administered in 152 (52.2%) patients. Perioperative blood transfusions were quantified and the potential prognostic cutoff for transfused units was calculated according to LeBlanc.
Results The median number of perioperative blood transfusions was 2 (0–24), and 106 patients (36.4%) received no transfusions. Patients with one or less blood transfusion showed a significantly improved survival compared to patients receiving more than one unit ($p<0.009$). In multivariate analysis, blood transfusion categories showed significance ($p<0.015$) next to pT, pN, pM category, and residual tumor categories (R-categories). Separate analysis of 183 patients treated after the mandatory introduction of leukocyte-depleted blood transfusions detected a strong tendency, but no significant difference in survival for patients getting one or less or more than one transfusion ($p=0.056$). Receipt of leukocyte-depleted versus non-depleted units, however, had no influence on survival ($p=0.766$).
Conclusions The need for perioperative allogeneic blood transfusions is significantly associated with poorer survival following resection for esophageal cancer by univariate and multivariate analysis. Our data suggest that the reduction of leukocytes in allogeneic transfusions is not sufficient to overcome the negative influence on survival.

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Keywords Esophageal carcinoma · Allogeneic blood transfusion · Leukocytes-depleted blood transfusion · Survival

Introduction

Since the 1970s, perioperative blood transfusion has been thought to have an immunomodulatory effect. Though beneficial in transplantation surgery, it was postulated to be associated with decreased survival rates in various tumor types including esophageal cancer.[1]

The cause of this phenomenon is still unclear. Some authors assumed decreased survival with perioperative blood transfusion to be rather a reflection of circumstances

necessitating transfusion.[2,3] Others demonstrated a significantly independent relationship by multivariate analysis.[4–6]

Studies exploring underlying mechanisms showed a decreasing number of circulating T lymphocytes with a decreased ratio of helper-to-suppressor T lymphocytes. Natural killer cell function was reduced like the interleukin-2 production, whereas the number of suppressor T lymphocytes and production of prostaglandin-E was increased. In summary, allogeneic blood transfusion decreases T-cell-based immune response, an important mechanism to remove tumor cells from the body. Furthermore, macrophage migration was found to be impaired preventing antigen presentation.[1]

In animal models, allogeneic blood transfusion was associated with increased tumor growth and frequency of metastases.[7] These effects could possibly be abolished through depleting donor blood of leukocytes.[8,9] In patients undergoing colorectal surgery receiving leukocyte-depleted transfusions, postoperative infections decreased significantly despite impaired natural killer cell function.[10]

Previous studies dealing with blood transfusion in esophageal surgery did not deal with leukocyte-depleted transfusions.[2–6,11] After the mandatory introduction in Germany in 2001, pre-storage leukocyte-depleted products are used without exception, with an amount of contaminating leukocytes of less than 1×10^6/unit according to the European consensus.[12]

In this retrospective analysis, we evaluated the prognostic influence of perioperative allogeneic blood transfusions in patients with esophagectomy for esophageal cancer. Comparisons were made between patients treated with leukocyte-depleted versus non-depleted units of blood.

Material and Methods

A retrospective study was performed with 305 patients who underwent esophagectomy between January 1997 and October 2006 in the Department of Visceral and Vascular Surgery, University of Cologne, Germany. To exclude the effects of surgery-related postoperative complications, 14 patients (4.8%) dying within 90 days after the operation were excluded.

From 291 study patients, there were 234 men (80.4%) and 57 women (19.6%) with a median age of 62 years (range, 18.9 to 83.2 years).

Histopathological examination of the resected specimens revealed squamous cell cancer in 137 patients (47.1%), adenocarcinoma in 148 cases (50.9%), and other rare entities in six patients (2.1%).

Because of locally advanced disease, 152 patients (52.2%) received standardized neoadjuvant chemoradiation with cisplatin, 5-fluorouracil, and 36 Gy as described in detail.[13] Four to five weeks after completion of chemoradiation, transthoracic en bloc esophagectomy with two-field lymphadenectomy was performed. Relevant clinical and histopathological data are summarized in Table 1.

To determine the number of perioperative blood transfusions, an observation period of 30 days after operation was chosen. One unit equals approximately 280-ml (250–310 ml) suspension of packed red blood cells.

An Edict of the Paul-Ehrlich-Institute allowed only the use of leukocyte-depleted blood transfusions after October 1, 2001 in Germany. Pre-storage depletion achieves an amount of contaminating leukocytes of less than 1×10^6/unit according to the European consensus.[12]

Statistical Analysis

The median follow-up was 4.9 years (range, 1.1–11 years). All living patients had a follow-up of more than 12 months.

Table 1 Patient Characteristics

Parameter	Number of patients (%)
Median age, 62.0 years (range, 18.9–83.2 years)	
Gender	*n*=291
Male	234 (80.4%)
Female	57 (19.6%)
Histology	*n*=291
Squamous cell cancer	137 (47.1%9
Adenocarcinoma	148 (50.9%)
Others	6 (2.1%)
Neoadjuvant treatment	*n*=291
No	139 (47.8%)
Yes	152 (52.2%)
T category	*n*=291
pT0	27 (9.3%)
pT1	68 (23.4%)
pT2	58 (19.9%)
pT3	136 (46.7%)
pT4	2 (0.7%)
N category	*n*=291
pN0	149 (51.2%)
pN1	142 (48.8%)
M category	*n*=291
cpM0	249 (85.6%)
cpM1	42 (14.4%)
Grading	*n*=291
G1	5 (1.7%)
G2	148 (50.9%)
G3	135 (46.4%)
G4	3 (1%)
R category	*n*=291
R0	276 (94.8%)
R1/2	15 (5.2%)

pT local invasiveness, *pN* lymph node metastases, *c/pM* distant metastases (categories according to UICC), *y* neoadjuvant therapy, *n* number of patients

We analyzed the best cutoff value for number of blood transfusions (ec) as a prognostic variable by simulating the log-rank test for groups defined by (ec < c) and (ec > c) for observed values of the covariate for the entire data set. This tree-based method for prognostic stratification was described by LeBlanc.[14]

Kaplan–Meier plots were used to describe survival distribution.[15] The log-rank test was used to evaluate for survival differences.[16] For multiple comparisons, the Holm–Sidak method was used. In addition, 95% confidence intervals (95% CI) for the different survival curves were calculated. Cox regression analysis was applied to identify independent prognostic variables. The level of significance was set to $p<0.05$.

All statistical tests were performed using the Software Package SPSS for Windows, version 14.0, Chicago, IL, USA.

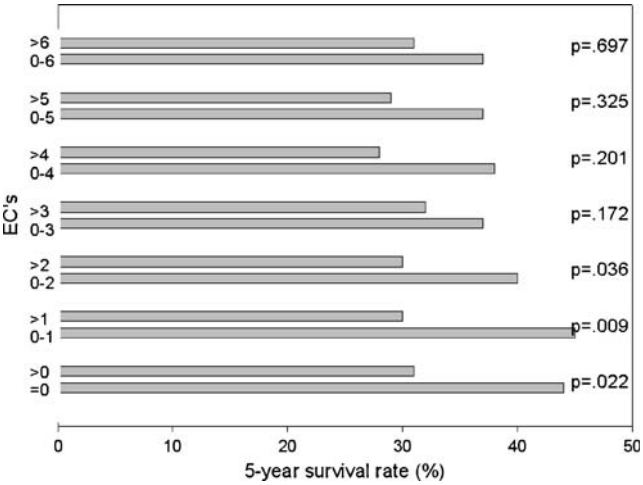

Figure 1 Analysis of the best cutoff value for number of blood transfusions (ec) as a prognostic variable by simulating the log-rank test for groups defined by (ec < c) and (ec > c) for observed values of the covariate for the entire data set.[14]

Results

Transfused Allogeneic Blood Units

Transfusion demand ranged from 0 to 24 U of blood. Median was 2 U and mean value was 3.5±4.5 U. One hundred six patients (36.4%) received no allogeneic blood transfusions, five patients only one unit (1.7%).

There were 108 cases before October 1, 2001, whereas after introduction of leukocyte-depleted blood, 183 patients were analyzed. In the first period, 18 patients (16.7%) were not transfused, and one person received a single unit (0.9%). In the second period, 88 patients (48.1%) were operated without allogeneic blood and four patients with a single unit (2.2%). The median number of blood transfusions decreased significantly from 4 to 1 U ($p<0.001$).

Survival Analysis

The 5-year survival rate for all patients was 35±3%. A significant cutoff value was identified between 0–1 and >1 U of transfused blood (Fig. 1). Five-year survival rates for patients with 0–1 U transfused blood was 46±7% compared to 29±4% for patients with >1 U [median survival 3.52 (0.99–6.04) vs. 2.1 years (1.66–2.54), $p<0.009$] (Fig. 2).

Currently, 126 patients are alive, 158 died, and seven patients were lost to follow-up.

In a subgroup analysis of 183 patients treated after the mandatory introduction of leukocyte-depleted blood transfusions in October 2001, no significant difference in survival ($p=0.056$, Fig. 3) was found for patients getting one or less or more than one transfusion [5-year survival rates, 39±9% compared to 29±7%; median survival was 3.24 (1.51–4.98) vs. 2.25 (1.66–2.84) years].

The comparison of transfused patients before and after October 2001 failed to show a significant difference ($p=0.766$) between non-depleted units (5-year survival, 30±5%) versus leukocyte-depleted units (5-year survival, 30±7%) on survival (Fig. 4) [median survival was 1.96 (1.33–2.60) vs. 2.34 years (1.65–3.03)].

Multivariate Analysis

Cox regression analysis for all patients including pT, pN, c/pM categories, resection categories, histology, neoadjuvant therapy, and blood transfusion categories showed significance for pT [$p<0.002$, HR 2.9 (1.5–5.6) (pT3–pT1)], pN [$p<0.0001$, HR 2.0 (1.4–3.1)], pM [$p<0.011$, HR 1.7 (1.1–2.5)], residual tumor categories (R-categories) [$p<0.005$, HR 2.4 (1.3–4.5)], and blood transfusion categories [$p<0.015$, HR 1.6 (1.1–2.3)].

Discussion

In the present study, patients receiving none or 1 U of allogeneic blood had a significantly better 5-year survival rate than patients getting more than 1 U by univariate analysis. In multivariate analysis, transfusion category remained independently associated with survival like pT, pN, c/pM, and resection categories.

In the literature, several studies dealing with blood transfusion and survival in patients with esophageal carcinoma are published, most of them with mixed histological types.

Langley et al.[4] demonstrated transfusion of more than 3 U to be an independent negative predictor for survival by

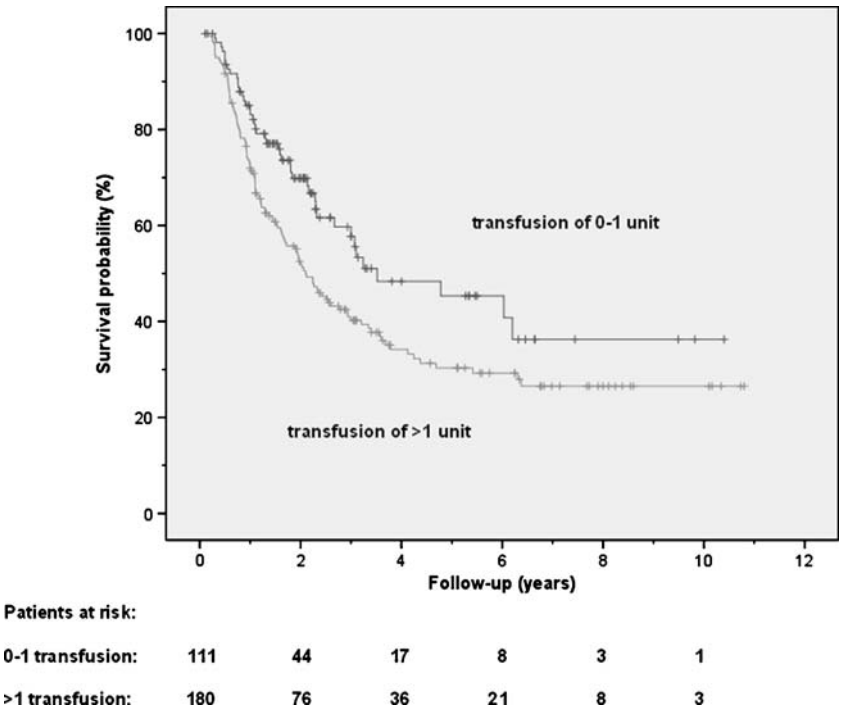

Figure 2 Kaplan–Meier curves based on blood transfusions (≤1 versus >1; cutoff according to LeBlanc, log-rank, $p<0.009$). Overall survival rate at 5 years for all patients was 35±3%.

multivariate analysis. This observation is supported by Tachibana et al.[5] who identified more than 2 U as independent prognostic factor in squamous cell cancer patients. As in our study, they excluded all patients dying within 90 days after the operation to exclude effects of surgery-related postoperative complications. Dresner et al.[6] confirmed transfusion of more than 4 U as independent factor in esophageal cancer patients.

In contrast, Swisher et al.[2] demonstrated blood transfusion of more than 8 U to be associated with decreased long-term survival by univariate analysis. This, however, was due to an increased number of postoperative complications which then eliminated significance in multivariate analysis. The authors suggest that complications that necessitate transfusions were responsible for this observation because no increase in local or distant tumor recurrences were

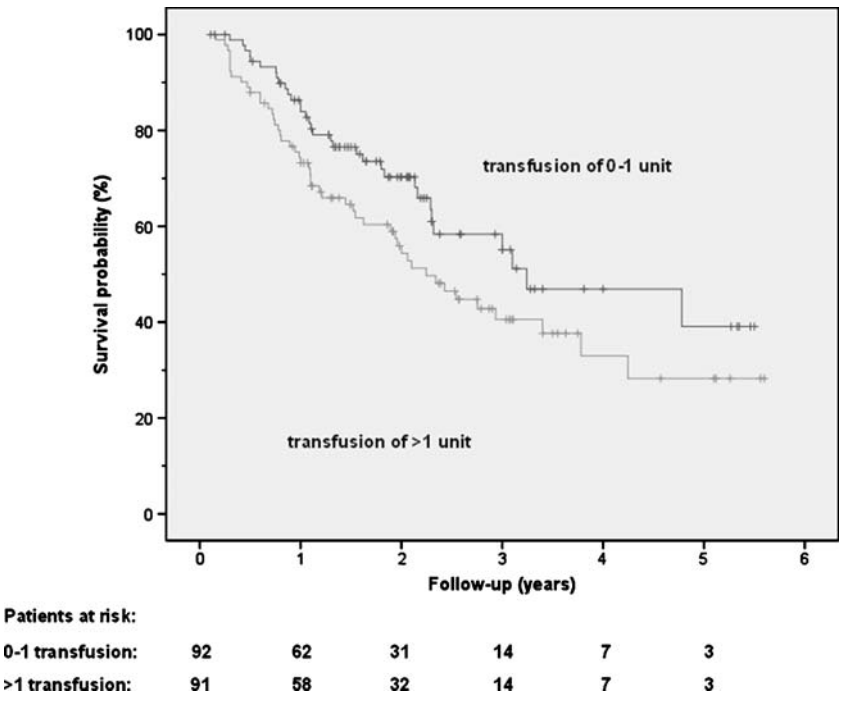

Figure 3 Kaplan–Meier curves based on blood transfusions (≤1 versus >1; cutoff according to LeBlanc) for the subgroup of 183 patients treated after the mandatory introduction of leukocyte-depleted blood transfusions in October 2001. Log-rank failed level of significance ($p=0.056$) for patients getting more than one transfusion (5-year survival, 29±7%) versus ≤1 (5-year survival 39±9%).

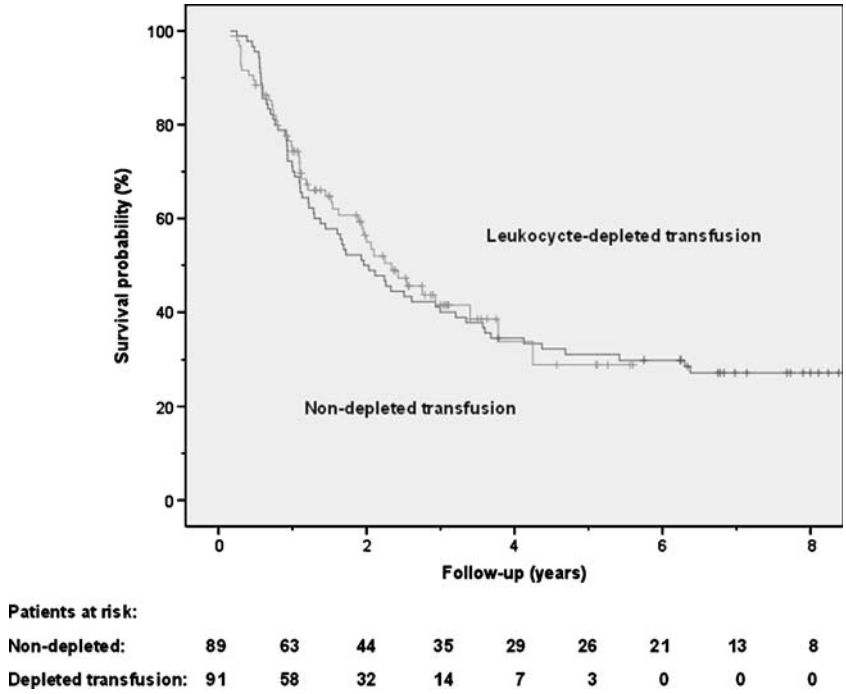

Figure 4 Kaplan–Meier curves for patients receiving non-depleted (5-year survival, 30±5%) versus leukocyte-depleted transfusions (5-year survival, 30±7%), log-rank, $p=0.766$.

identified. Nozoe et al.[3] also found that the occurrence of postoperative complications was a prognostic factor, whereas perioperative allogeneic blood transfusions were not in patients with squamous cell cancer.

Craig et al.[11] identified that blood transfusion is only associated with reduced short-term survival for patients in advanced stage III. They hypothesized that occult micrometastases progressed in this subgroup due to transfusion-induced immunomodulatory effects.

This is in line with a study by Motoyama et al.[17] comparing autologous with allogeneic blood transfusions. Differences were seen in prolonged disease-free survival for patients getting autologous blood, but not for recurrence rates or survival times following recurrence. Takemura et al.[18] demonstrated that patients with nodal involvement and T3/4 tumors had a significantly improved survival after autologous compared to allogeneic transfusion.

Because contaminating donor leukocytes could be responsible for this effect, we sub-analyzed our data for operations pre- and post-introduction of leukocyte-depleted blood transfusions (less than 1×10^6 leukocytes/unit according to the European consensus).[12] The comparison of transfused patients failed to show an association between non-depleted versus leukocyte-depleted units on survival. The different follow-up time periods for these groups represent a potential bias, but analysis of Kaplan–Meier curves showed a similarity within the first years of follow-up. The shorter follow-up in the population of leukocyte-depleted blood transfusion might also be the reason for the strong tendency but missing significance of the amount of transfused units towards reduced survival.

In colorectal surgery, Jensen et al.[19] found after transfusion with whole blood an increase in postoperative infectious complications accompanied by elevated IL-2R and IL-6 levels and decreased lymphocyte proliferation and CD4/CD8 ratio in leukocyte-depleted blood only slight and transient changes similar to non-transfused patients. In comparison between buffy-coat-poor and leukocyte-depleted blood transfusion, differences in wound infections and abscesses could be also noticed; however, the mortality rate was not different,[20] even after 7 years of follow-up in contrast to non-transfused patients.[21]

Also, in colorectal cancer, Houbiers et al.[22] found no difference in disease-free survival, cancer recurrence rate, or overall infections between patients receiving buffy-coat-poor or leukocyte-depleted blood. In contrast to non-transfused patients, both groups had a reduced survival and higher infection rate. The effect of blood transfusion on survival might therefore not be mediated by allogeneic leukocytes alone, but also cellular and humoral components could be able to alter the immune potential.[23]

In summary, the need for perioperative allogeneic blood transfusions is associated with poorer survival following resection by transthoracic en bloc esophagectomy for esophageal carcinomas by univariate and multivariate analysis. Our data suggest that either the reduction of leukocytes is not sufficient or that besides leukocytes other cellular or humoral elements may also influence survival after blood transfusion.

References

1. Fields RC, Meyers BF. The effects of perioperative blood transfusion on morbidity and mortality after esophagectomy. Thorac Surg Clin 2006;16:75–86. doi:10.1016/j.thorsurg.2006.01.005.
2. Swisher SG, Holmes EC, Hunt KK, Gornbein JA, Zinner MJ, McFadden DW. Perioperative blood transfusions and decreased long-term survival in esophageal cancer. J Thorac Cardiovasc Surg 1996;112:341–348. doi:10.1016/S0022-5223(96)70260-X.
3. Nozoe T, Miyazaki M, Saeki H, Ohga T, Sugimachi K. Significance of allogenic blood transfusion on decreased survival in patients with esophageal carcinoma. Cancer 2001;92:1913–1918. doi:10.1002/1097-0142(20011001)92:7<1913::AID-CNCR1709>3.0.CO;2-8.
4. Langley SM, Alexiou C, Bailey DH, Weeden DF. The influence of perioperative blood transfusion on survival after esophageal resection for carcinoma. Ann Thorac Surg 2002;73:1704–1709. doi:10.1016/S0003-4975(02)03508-7.
5. Tachibana M, Tabara H, Kotoh T, Kinugasa S, Dhar DK, Hishikawa Y, Masunaga R, Kubota H, Nagasue N. Prognostic significance of perioperative blood transfusions in resectable thoracic esophageal cancer. AJG 1999;94:759–765.
6. Dresner SM, Lamb PJ, Shenfine J, Hayes N, Griffin SM. Prognostic significance of perioperative blood transfusion following radical resection for oesophageal carcinoma. Eur J Surg Oncol 2000;26:492–497. doi:10.1053/ejso.1999.0929.
7. Francis DM, Clunie GJ. Influence of the timing of blood transfusion on experimental tumor growth. J Surg Res 1993;54:237–241. doi:10.1006/jsre.1993.1037.
8. Bordin JO, Bardossy L, Blajchman MA. Growth enhancement of established tumors by allogeneic blood transfusion in experimental animals and its amelioration by leukodepletion: The importance of the timing of the leukodepletion. Blood 1994;84:344–348.
9. Blajchman MA, Bardossy L, Carmen R, Sastry A, Singal DP. Allogeneic blood transfusion-induced enhancement of tumor growth: Two animal models showing amelioration by leukodepletion and passive transfer using spleen cells. Blood 1993;81:1880–1882.
10. Jensen LS, Andersen AJ, Christiansen PM, Hokland P, Juhl CO, Madsen G, Mortensen J, Möller-Nielsen C, Hanberg-Sörensen F, Hokland M. Postoperative infection and natural killer cell function following blood transfusion in patients undergoing elective colorectal surgery. Br J Surg 1992;79:513–516. doi:10.1002/bjs.1800790613.
11. Craig SR, Adam DJ, Yap PL, Leaver HA, Elton RA, Cameron EWJ, Snag CTM, Walker WS. Effect of blood transfusion on survival after esophagogastrectomy for carcinoma. Ann Thorac Surg. 1998;66:356–361. doi:10.1016/S0003-4975(98)00460-3.
12. Council of Europe. Guide to the preparation, use and quality assurance of blood components. 13th edn. Strassbourg, France: Council of Europe Publishing, 2007.
13. Schneider PM, Baldus SE, Metzger R, Kocher M, Bongartz R, Bollschweiler E, Schaefer H, Thiele J, Dienes HP, Mueller RP, Hoelscher AH. Histomorphologic tumor regression and lymph node metastases determine prognosis following neoadjuvant radiochemotherapy for esophageal cancer: implications for response classification. Ann Surg. 2005;242:684–692. doi:10.1097/01.sla.0000186170.38348.7b.
14. LeBlanc M. Tree-based methods for prognostic stratification. In Crowley J, ed. Handbook of statistics in clinical oncology 2001. New York: Marcel Decker, 2001, pp 457–471.
15. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–481. doi:10.2307/2281868.
16. Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: Good practice and pitfalls. Lancet 2002;359:1686–1689. doi:10.1016/S0140-6736(02)08594-X.
17. Motoyama S, Okuyama M, Kitamura M, Saito R, Kamata S, Murata K, Ogawa JI. Use of autologous instead of allogeneic blood transfusion during esophagectomy prolongs disease-free survival among patients with recurrent esophageal cancer. J Surg Oncol 2004;87:26–31. doi:10.1002/jso.20064.
18. Takemura M, Osugi H, Higashino M, Takada N, Lee S, Kinoshita H. Effects of substituting allogenic blood transfusion with autologous blood transfusion on outcomes after radical oesophagectomy for cancer. Ann Thorac Cardiovasc Surg 2005;11:293–300.
19. Jensen LS, Hokland M, Nielsen HJ. A randomized controlled study of the effect of bedside leucocyte depletion on the imunosuppressive effect of whole blood transfusion in patients undergoing elective colorectal surgery. Br J Surg 1996;83:973–977. doi:10.1002/bjs.1800830727.
20. Jensen LS, Kissmeyer-Nielsen P, Wolff B, Qvist N. Randomised comparison of leucocyte-depleted versus buffy-coat-poor blood transfusion and complications after colorectal surgery. Lancet 1996;348:841–845. doi:10.1016/S0140-6736(96)06168-5.
21. Jensen LS, Puho E, Pedersen L, Mortensen FV, Sorensen HT. Long-term survival after colorectal surgery associated with buffy-coat-poor and leucocyte-depleted blood transfusion: a follow-up study. Lancet 2005;365:681–682.
22. Houbiers JGA, Brand A, van de Watering LMG, Hermans J, Verwey PJM, Bijnen AB, Pahlplatz P, Eeftinck Schattenkerk M, Wobbes T, de Vries JE, Klementschitsch P, van de Maas AHM, van de Velde CJH. Randomised controlled trial comparing transfusion of leucocyte-depleted or buffy-coat-depleted blood in surgery for colorectal cancer. Lancet 1994;344:573–578. doi:10.1016/S0140-6736(94)91965-8.
23. Nielsen HJ. Detrimental effects of perioperative blood transfusion. Br J Surg 1995;82:582–587. doi:10.1002/bjs.1800820505.

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2008 SSAT POSTER PRESENTATION

Hemorrhage-Induced Hepatic Injury and Hypoperfusion can be Prevented by Direct Peritoneal Resuscitation

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Abstract
Background Crystalloid fluid resuscitation after hemorrhagic shock (HS) that restores/maintains central hemodynamics often culminates in multi-system organ failure and death due to persistent/progressive splanchnic hypoperfusion and end-organ damage. Adjunctive direct peritoneal resuscitation (DPR) using peritoneal dialysis solution reverses HS-induced splanchnic hypoperfusion and improves survival. We examined HS-mediated hepatic perfusion (galactose clearance), tissue injury (histopathology), and dysfunction (liver enzymes).

Methods Anesthetized rats were randomly assigned (n=8/group): (1) sham (no HS); (2) HS (40% mean arterial pressure for 60 min) plus conventional i.v. fluid resuscitation (CR; shed blood + 2 volumes saline); (3) HS + CR + 30 mL intraperitoneal (IP) DPR; or (4) HS + CR + 30 mL IP saline. Hemodynamics and hepatic blood flow were measured for 2 h after CR completion. In duplicate animals, liver and splanchnic tissues were harvested for histopathology (blinded, graded), hepatocellular function (liver enzymes), and tissue edema (wet–dry ratio).

Results Group 2 decreased liver blood flow, caused liver injuries (focal to submassive necrosis, zones 2 and 3) and tissue edema, and elevated liver enzymes (alanine aminotransferase (ALT), 149±28 μg/mL and aspartate aminotransferase (AST), 234±24 μg/mL; $p<0.05$) compared to group 1 (73±9 and 119±10 μg/mL, respectively). Minimal/no injuries were observed in group 3; enzymes were normalized (ALT 89±9 μg/mL and AST 150±17 μg/mL), and tissue edema was similar to sham.

Conclusions CR from HS restored and maintained central hemodynamics but did not restore or maintain liver perfusion and was associated with significant hepatocellular injury and dysfunction. DPR added to conventional resuscitation (blood and crystalloid) restored and maintained liver perfusion, prevented hepatocellular injury and edema, and preserved liver function.

Keywords Hemorrhagic shock · Direct peritoneal resuscitation · Liver blood flow · Liver injury

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No conflicts of interest exist.

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Introduction

Despite advances in treatment and therapies, hemorrhagic shock remains a major cause of morbidity and mortality following trauma.[1] Management of hemorrhagic shock comprises bleeding control and correction of the vascular volume deficit with intravenous fluid replacement. The resuscitation process is clinically assessed by the restoration and maintenance of central hemodynamics. Recent evidence suggests that despite return of central hemodynamics by aggressive fluid resuscitation, the gut and liver experience a progressive vasoconstriction and hypoperfusion.[2–4] This end-organ tissue hypoperfusion is linked to several mechanistic factors including endothelial cell dysfunction, compounding tissue hypoxia, compromised capillary filling and fluid exchange, deranged electrolyte handling, and the release of mediators that produce an exaggerated systemic inflammatory response.[2,5–9] These factors result in cellular and end-organ tissue injury that translate clinically into organ dysfunction and, potentially, organ failure. The complexity of the pathogenesis of shock-induced end-organ tissue damage and multi-system organ failure necessitates a continued search for treatment modalities to prevent the course of hemorrhagic shock pathophysiology, alleviate end-organ damage, and improve survival in trauma patients.

Recent studies have shown that topical exposure on the small intestine with commercially available peritoneal dialysis solution during resuscitation from hemorrhagic shock, termed direct peritoneal resuscitation, can prevent or reverse the vasoconstriction and hypoperfusion commonly associated with conventional resuscitation.[10] In those experimental studies, direct peritoneal resuscitation produced a rapid and sustained vasodilation and hyperperfusion of the gut regardless of the timing of direct peritoneal resuscitation (i.e., at the time of or delayed for 4 h after conventional volume replacement).[10,11] Other studies have examined the effects of adjunctive direct peritoneal resuscitation by analyzing whole-organ blood flow distribution (colorimetric microsphere technique); the exaggerated systemic inflammatory cytokine response often associated with resuscitated hemorrhagic shock (cytokine enzyme-linked immunosorbent assays) and survival.[12,13] Adjunctive peritoneal resuscitation caused splanchnic hyperperfusion that was associated with increased lung blood flow (>100% increase). These changes in organ blood flow distribution were associated with down-regulation of the systemic inflammatory response and increased survival compared to conventional resuscitation therapies.[12,13] Hepatic artery blood flow was constant in those studies, in large part due to the dual liver blood supply which does not allow for the measurement of total liver blood flow. Microspheres are cleared from the arterial circulation via the gastrointestinal microvasculature, and thus the contribution of portal vein blood flow from the gastrointestinal circulation cannot be determined by the microsphere technique. The purpose of the current study was to focus on the effects of adjunctive direct peritoneal resuscitation from hemorrhagic shock on total effective liver blood flow as measured by galactose clearance, hepatocellular function, histopathology, and organ edema formation. We hypothesized that direct peritoneal resuscitation exposure in the peritoneal cavity would stabilize liver blood flow and prevent liver injury, in much the same manner that had been previously seen with direct peritoneal resuscitation-mediated protection of gut perfusion during resuscitated hemorrhagic shock.

Materials and Methods

Animals were maintained in a facility approved by the American Association for the Accreditation of Laboratory Animal Care. The research protocol was approved by the Institutional Animal Care and Use Committee and Biohazard Safety Committee at the Louisville Veterans Administration Medical Center. Male Sprague–Dawley rats (200–220 g) were acclimated for 1–2 weeks prior to experimental use during which time the animals received standard rat chow (20 g/day) and water ad libitum. Animal weights were recorded daily to ensure positive weight gain.

Surgery and Animal Preparation All animal and experimental interventions were performed under aseptic conditions. Anesthesia was induced with intraperitoneal pentobarbital (50 mg/kg), and supplemental subcutaneous injections (25% of the original dose) were given as needed to maintain a surgical plane of anesthesia throughout the experimental protocol. After induction of anesthesia, 2 mL of normal saline was injected subcutaneously to maintain body fluid homeostasis during surgery and equilibration. Body temperature was maintained at 37±1°C with a rectal probe and a servo-controlled heating pad. Surgery was carried out after the loss of blink and withdrawal reflexes. A tracheotomy was performed (Intramedic PE-240 polyethylene tubing, Clay Adams Division of Becton Dickinson & Company, Parsipanny, NJ, USA), and animals were allowed to spontaneously breathe room air. The right femoral artery and vein and the left femoral artery were cannulated with PE-50 catheters for blood pressure measurement, blood withdrawal, and resuscitation. Animals were allowed to equilibrate for 45–60 min following the completion of surgery. Mean arterial pressure (MAP) and heart rate (HR) were continuously monitored and recorded every 15 min throughout the experimental protocol (Digi-Med Signal Analyzers, Louisville, KY, USA). All animals had repeated baseline MAP and HR values within 10% prior to initiation of shock protocol.

After equilibration, animals were randomly assigned to undergo hemorrhage and resuscitation or sham protocol as outlined in the experimental groups. The end point for all groups was 2 h after completion of resuscitation. Two sets of animals for each experimental group were completed, one set (n=8/group) for liver blood flow determination by galactose clearance and a second set (n=6/group) for the measurement of liver enzymes, histopathology, and tissue edema. At the 2-h post-resuscitation (RES) time point in the second set of animals, serum was obtained from arterial blood samples for liver function tests (i.e., aspartate aminotransferase (AST) and alanine aminotransferase, (ALT)) using commercially available kits (Sigma Chemical Company, St. Louis, MO, USA). Tissue samples of liver, lung, and abdominal muscle were harvested, immediately weighed (wet weight), and then dried in an oven at 50°C until constant weight was obtained (dry weight). Tissue wet weight to dry weight ratio was calculated to serve as an index of total tissue water. Separate liver specimens were collected for histopathological staining (hematoxylin and eosin (H&E)). Each tissue sample was processed in triplicate for later blinded analysis.

Hemorrhagic Shock Model The standard model of resuscitated hemorrhagic shock we utilized has been previously described.[2] Briefly, hemorrhagic shock was achieved with blood withdrawal (1 mL/min) from the femoral artery into a syringe pre-rinsed with heparin until 40% of baseline MAP was attained. Hypovolemia was maintained for 60 min with blood withdrawal or return to maintain the 40% MAP. On average, the hemorrhage volume required to maintain the target MAP was 6.11 mL. Conventional resuscitation was initiated with the return of the shed blood via the femoral vein over 5 min, followed by normal saline infusion of two times the volume of shed blood over the next 25 min. Adjunctive direct peritoneal resuscitation was initiated at the start of intravenous fluid resuscitation with intraperitoneal injection of 30 mL of 2.5% glucose-based clinical peritoneal dialysis solution (Delflex®, Fresenius USA, Inc. Ogden, UT, USA) that contained 5.67 g/L sodium chloride, 3.92 g/L sodium lactate, 0.257 g/L calcium chloride, 0.152 g/L magnesium chloride at a pH of 5.5, and osmolality of 398 mOsm/L. As a volume control for adjunctive direct peritoneal resuscitation, 30 mL of normal saline was injected intraperitoneally immediately following the initiation of intravenous fluid resuscitation in a separate group of animals. All peritoneal resuscitation solutions were pre-warmed to 37°C prior to injection.

Animal Groups As already mentioned, two sets of experiments were performed in each of the following groups: group 1, sham animals which underwent surgical cannulations but no hemorrhagic shock or resuscitation; group 2, hemorrhagic shock plus conventional i.v. fluid resuscitation; group 3, hemorrhagic shock plus conventional i.v. fluid resuscitation and 30 mL of peritoneal dialysis solution injected intraperitoneally; and group 4, hemorrhagic shock plus conventional i.v. fluid resuscitation and 30 mL of normal saline injected intraperitoneally. All animals in groups 3 and 4 were checked at the end of the experimental protocol for peritoneal bleeding, which was an exclusion criterion for the study.

Liver Blood Flow Determination The galactose clearance method has been used to assess effective hepatic blood flow in both experimental animals and humans.[23] The assumptions inherent in this technique are that systemic galactose is solely metabolized and thus cleared from the plasma by the liver, and therefore, the steady-state galactose clearance accurately measures liver blood flow. To measure effective hepatic blood flow (EHBF), a steady-state galactose concentration was obtained by the bolus infusion of galactose (2.6 mg/1 mL/5 min) via the femoral vein catheter followed by a constant infusion of galactose (13 mg/mL/h). Steady-state systemic galactose concentration was achieved in 30–40 min after the initial bolus, verified with two successive blood samples (0.2 mL each) collected at 40 and 55 min after bolus. When the variation between samples was less than 10%, the experimental protocol was initiated. No rats were excluded due to unstable steady-state galactose concentrations. EHBF was determined every 30 min throughout the protocol by blood galactose determination in triplicate. EHBF was calculated by measuring low steady-state galactose concentration (GCss) at a known infusion rate (I) as described by the equation EHBF=I/GCss.

Histology Scoring H&E-stained liver specimens were evaluated for signs of liver injury according to a predetermined tissue injury score based on previously published injury score criteria in blinded fashion.[14,15] Specimens with no or minimal injury were scored 0, focal necrosis scored 1, centrilobular necrosis (zone 3) scored 2, submassive necrosis (zone 2 and 3) scored 3, and massive necrosis scored 4. Each sample was identified only by number such that the pathologists were blinded to the experimental protocol and animal groups. Two pathologists (M.E.C. and J.R.P) evaluated each tissue specimen independently and scored the tissue using the scoring system.

Statistical Analysis Data are expressed as mean±standard error of the mean, and differences between groups were determined by two-way analysis of variance (ANOVA). The null hypothesis was rejected a priori at $P<0.05$. When differences were found using ANOVA, one of the following post hoc tests was performed (as indicated in the figure

legends): Tukey–Kramer honestly significant different test, Bonferroni's test, or repeated measures ANOVA and Dunnett's test.

Results

Figure 1 shows that there were no differences between groups in mean arterial blood pressure or pulse rate during the post-resuscitation period. In the hemorrhagic shock groups, mean arterial pressure was held at 40% of baseline during the 60-min hypovolemic period per the experimental protocol. Conventional resuscitation restored and maintained mean arterial pressure at baseline levels for all hemorrhagic shock groups without additional fluid infusion. Heart rate was decreased during in all hemorrhage groups during hypovolemia, which was completely reversed by resuscitation in groups 2–4.

There were no differences between groups in baseline liver blood flow (Fig. 2). During the period of hypovolemia, effective hepatic blood flow was reduced approximately 40–45% compared to group baseline values in the three hemorrhage groups: conventional resuscitation (3.39±0.29 mL/min/100 g; −43%), saline (3.29±0.17; −44%), and direct peritoneal resuscitation (3.54±0.30, −41%), and these levels were also significantly lower than sham animals (5.70±0.29 mL/min/100 g). All resuscitation protocols restored effective hepatic blood flow to baseline levels at the completion of resuscitation. However, the conventional resuscitation (group 2) and IP saline (group 4) rats displayed a slow, progressive decline in effective hepatic blood flow that was not observed in the direct peritoneal resuscitation group (group 3). Direct peritoneal resuscitation rats had normalized effective hepatic blood flow throughout the 2-h post-resuscitation period. At the 30-min end point of resuscitation, effective hepatic blood flow (mL/min/100 g) was 4.35±0.21 in conventional resuscitation ($p<0.05$ versus direct peritoneal resuscitation), 4.52±0.30 in IP saline ($p<0.05$ versus direct peritoneal resuscitation), 5.74±0.26 in direct peritoneal resuscitation, and 5.20±0.27 in sham animals.

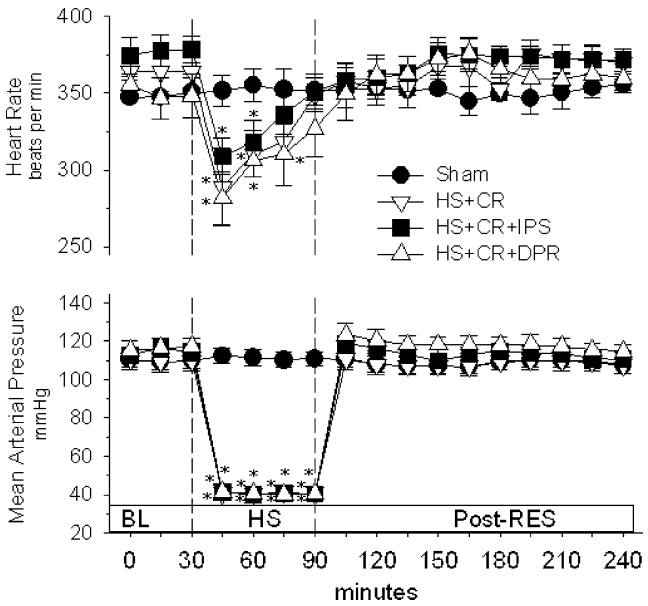

Figure 1 Heart rate and mean arterial pressure. *BL* baseline; groups: *Sham* surgical cannulations but no hemorrhage shock or resuscitation; *HS + CR* hemorrhagic shock plus conventional intravenous fluid resuscitation; *HS + CR + DPR* hemorrhagic shock and resuscitation plus 30 mL of clinical peritoneal dialysis solution (Delflex™) intraperitoneally at the time of resuscitation; *HS + CR + IPS* hemorrhagic shock and resuscitation plus 30 mL of normal saline intraperitoneally at the time of resuscitation. *$p<0.01$ versus corresponding baseline by repeated measures ANOVA and Dunnett's post-test.

Histopathologic scoring of the sham (group 1) liver specimens revealed no/minimal injury. Fifty percent (three of six) of IP saline (group 4) liver specimens were scored as having focal or centrilobular necrosis. Similarly, the conventional resuscitation rats (group 2) had 50% (3/6) of livers scored as having focal, centrilobular, or submassive necrosis. The direct peritoneal resuscitation group (group 3) had a decreased incidence of microscopic liver injury compared to the other hemorrhagic shock groups. In the direct peritoneal resuscitation liver specimens, only one in six was scored as having focal necrosis, the remaining specimens (5/6) were scored as no/minimal injury. Representative liver micrographs are depicted in Fig. 3. As seen in the micrographs, liver architectural pattern was lost in the conventional resuscitation and IP saline groups due to near obliteration of the sinusoids, presumably due to edema in endothelial cells and hepatocytes. Multiple areas of focal necrosis (zones 2 and 3) along with stasis and red blood cell aggregation in central veins were seen in the conventional resuscitation (group 2) and IP saline (group 4) specimens.

Direct peritoneal resuscitation-mediated histopathological changes in conventional resuscitation and IP saline groups correlated with impaired hepatocellular function as assessed by liver enzyme assays at 120 min post-RES (Fig. 4). Conventional resuscitation liver enzyme levels (μg/mL) were significantly elevated (ALT 149±28 and AST 234±24) compared to sham rats (73±9 and 119±10, respectively). Adjunct peritoneal resuscitation restored liver enzyme levels to near sham control levels (ALT 89±9 and AST 150±17). However, peritoneal saline installation in the IP saline rats did not improve liver enzymes (ALT 149±27 and AST 212±25).

Finally, tissue edema (total tissue water) was assessed by wet–dry ratios (Fig. 5) at the 120-min resuscitation end point. Total tissue water of all organs investigated was significantly greater in the conventional fluid resuscitation

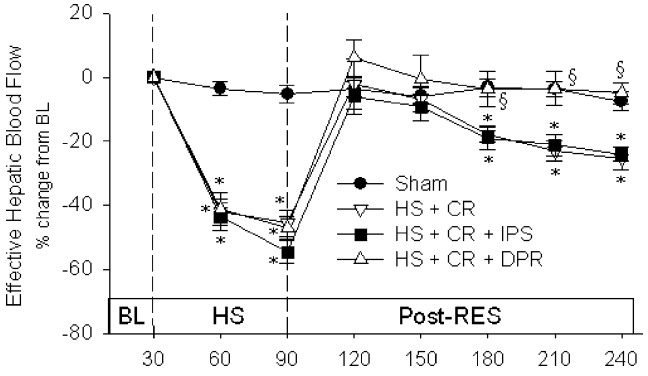

Figure 2 Effective hepatic blood flow. Groups: *Sham* surgical cannulations but no hemorrhage shock or resuscitation; *HS + CR* hemorrhagic shock plus conventional intravenous fluid resuscitation; *HS + CR + DPR* hemorrhagic shock and resuscitation plus 30 mL of clinical peritoneal dialysis solution (Delflex™) intraperitoneally at the time of resuscitation; *HS + CR +IPS* hemorrhagic shock and resuscitation plus 30 mL of normal saline intraperitoneally at the time of resuscitation. Baseline values in mL/min/100 g body weight were: Sham, 5.6±0.3; HS + CR, 6.3±0.5; HS + CR + IPS, 5.9±0.4; and HS + CR + DPR, 6.1±0.4. *$p<0.01$ versus corresponding baseline by repeated-measures ANOVA and Dunnett's post-test. *Section sign* $p<0.01$ versus the HS + CR group by two-way ANOVA and Bonferroni post-test.

(group 2) and IP saline (group 4) rats compared to the peritoneal resuscitation (group 3) or sham control (group 1), suggesting significant compartmental fluid shifts and total water sequestration in the conventional resuscitation and IP saline groups compared to shams, which was prevented in the direct peritoneal resuscitation rats.

Discussion

Liver dysfunction and failure associated with resuscitated hemorrhagic shock is a significant clinical problem that is driven by ischemic stress. This ischemic stress is thought to be mediated by multiple factors including pro-inflammatory cytokines and chemokines, reactive oxygen species, and eicosanoids, which in combination cause hepatic microcirculatory dysfunction, leukocyte infiltration, damage to cell membranes, development of fibrosis, and stasis of biliary flow. It is proposed that three major pathophysiological events occur during intravenous volume resuscitated hemorrhagic shock: (1) persistent liver and gut vasoconstriction and hypoperfusion despite restoration of central hemodynamic variables; (2) a liver- and gut-derived inflammatory response; and (3) tissue fluid sequestration and failure of early fluid mobilization within the intestinal fluid compartment. The addition of adjunctive direct peritoneal resuscitation with glucose-based peritoneal dialysis solutions to a volume replacement resuscitation strategy has been shown to improve or prevent these changes in the gut[8–10,17,18] and perhaps the liver.

Liver injury and dysfunction constitute a driving component of multi-system organ failure following resuscitation from hemorrhagic shock. Hepatocellular and sinusoidal endothelial cell dysfunction occurs early during hemorrhage and persists despite adequate fluid resuscitation.[16–21] The pathogenesis of end-organ damage appears to be initiated and maintained by a cascade of events

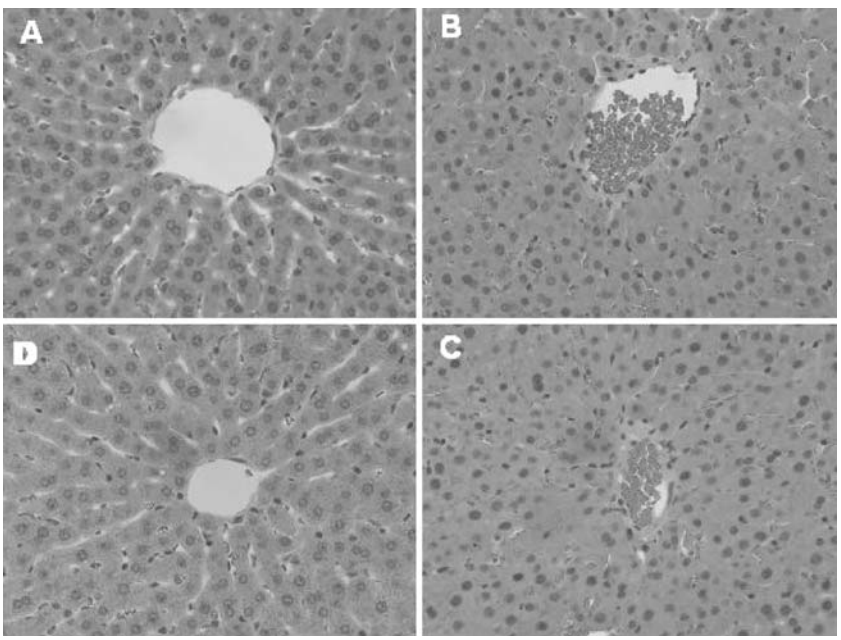

Figure 3 Liver histopathology (blinded scoring). **a** Sham; **b** HS + CR; **c** HS + CR + IPS; **d** HS + CR + DPR. *HS* hemorrhagic shock, *CR* conventional intravascular fluid resuscitation, *IPS* intraperitoneal saline (30 mL) at time of the fluid resuscitation, *DPR* adjunct direct peritoneal resuscitation (30 mL Delflex™ with 2.5% glucose) at the time of the fluid resuscitation.

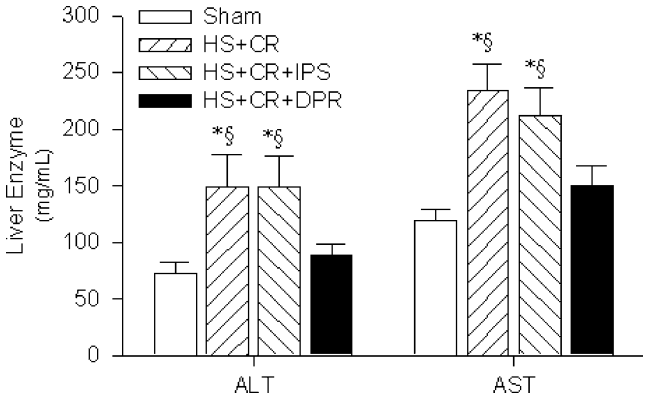

Figure 4 Liver function test. Groups: *Sham* surgical cannulations but no hemorrhage shock or resuscitation; *HS + CR* hemorrhagic shock plus conventional intravenous fluid resuscitation; *HS + CR + DPR* hemorrhagic shock and resuscitation plus 30 mL of clinical peritoneal dialysis solution (Delflex™) intraperitoneally at the time of resuscitation; *HS + CR + IPS* hemorrhagic shock and resuscitation plus 30 mL of normal saline intraperitoneally at the time of resuscitation. *$p<0.01$ versus Sham control by one-way ANOVA and Bonferroni post-test. *Section sign* $p<0.01$ versus the HS + CR group by two-way ANOVA and Bonferroni post-test.

involving multiple mediators and pathways (i.e., pro-inflammatory cytokines, reactive oxygen radicals, lipooxygenase derivatives, intracellular Ca^{2+} signaling, and hypoxia). A central event that could initiate such interactions might be compromised hepatic nutritive blood flow during hemorrhage and resuscitation. The current study supports this idea because restoration of hepatic blood flow by adjunctive direct peritoneal resuscitation was associated with improved hepatocellular function, tissue edema, and histopathological tissue injury score. Post-resuscitation splanchnic hypoperfusion occurs following correction of the intravascular volume deficit and accounts for the portal component of the deficit in nutrient hepatic flow.[22–26] In addition, endothelial cell dysfunction appears to play a role in gut hypoperfusion since protection of endothelial cell function through pharmacologic means either before or during resuscitation was associated with normal end-organ blood flow.[22,27–31] Thus, direct peritoneal resuscitation appears to maintain hepatic nutrient blood flow through mechanisms that preserve gut perfusion and subsequent portal flow.

Direct peritoneal resuscitation is a nonpharmacologic adjunctive resuscitation strategy to reverse splanchnic end-organ hypoperfusion by endothelium-dependent mechanisms. In the intestinal microvasculature, these mechanisms are thought to include activation of glibenclamide-sensitive K^+ channels (K_{ATP}), adenosine A1 receptor activation, and nitric oxide release.[32] Additional therapeutic benefits of adjunctive peritoneal resuscitation that would preserve hepatic perfusion and function include early fluid mobilization of gut tissue edema, prevention of endothelial cell swelling, and the down-regulation of the gut-associated systemic inflammatory response.[12,33,34] Of particular significance to end-organ tissue perfusion and function is hemorrhage-induced endothelial cell swelling and interstitial edema.[33] Endothelial cell swelling appears to occur early during hemorrhagic shock by activation of amiloride-sensitive

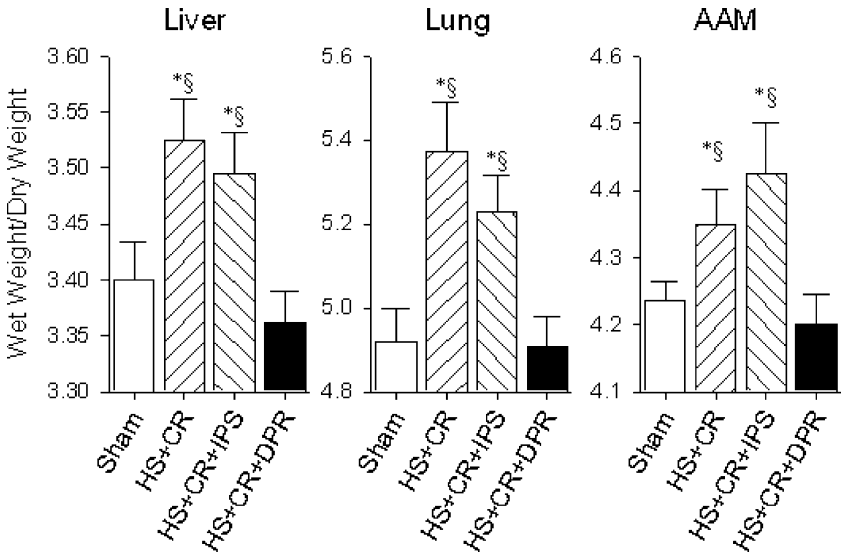

Figure 5 Total tissue water. *AAM* anterior abdominal muscle; Groups: *Sham* surgical cannulations but no hemorrhage shock or resuscitation; *HS + CR* hemorrhagic shock plus conventional intravenous fluid resuscitation; *HS + CR + DPR* hemorrhagic shock and resuscitation plus 30 mL of clinical peritoneal dialysis solution (Delflex™) intraperitoneally at the time of resuscitation; *HS + CR + IPS* hemorrhagic shock and resuscitation plus 30 mL of normal saline intraperitoneally at the time of resuscitation. *$p<0.01$ versus Sham control by one-way ANOVA and Bonferroni post-test. *Section sign* $p<0.01$ versus the HS + CR group by two-way ANOVA and Bonferroni post-test.

(Na^+/H^+ channels) and the rapid exchange of intracellular H^+ for extracellular Na^+ and water.[33,35] The resultant narrowing of the end-organ tissue capillaries in the gut and presumably in the sinusoids could physically impede filling and compromise liver nutritive perfusion.

The mechanism of hepatic injury after hemorrhage and resuscitation is not fully understood but has been extrapolated from ischemia-reperfusion models.[36] It has been proposed that, during ischemia-reperfusion injury, neutrophil hepatotoxicity causes liver injury and dysfunction.[37] Neutrophil-mediated injury involves chemokine-mediated neutrophil extravasation and subsequent interstitial degranulation. Our studies have demonstrated that liver myeloperoxidase levels, an index of neutrophil sequestration, remained low during the first 24 h following resuscitation from hemorrhagic shock.[34] These studies did not address mechanisms of neutrophil-mediated hepatocellular injury but suggest that neutrophil hepatotoxicity is not the predominant mechanism of liver injury in this model of hemorrhage resuscitation.

The gut and liver have been implicated as the primary source of cytokines following hemorrhagic shock.[38–41] Pro-inflammatory cytokines (TNF-α, IL-1, IL-6, IFN-γ) are released following trauma and shock and activate the cellular immune response, while anti-inflammatory cytokines (IL-4, IL-10) appear to modulate this pro-inflammatory response. The degree of activation of the systemic inflammatory response syndrome response and subsequent immunocompetence depends on the balance of the two processes and the pattern of cytokine expression. Direct peritoneal resuscitation has been shown to down-regulate the pro-inflammatory response noted in the liver and gut with volume resuscitation alone by decreasing IL-6 and TNF-α 24 h after hemorrhagic shock.[12] At the same time, IL-10 levels were significantly increased with direct peritoneal resuscitation. In this study, mortality correlated with the cytokine patterns ranging from 10% to 40% in the resuscitated groups versus 100% survival in the direct peritoneal resuscitation animals. The mechanisms behind the cytokine pattern presumably relate to persistent ischemic changes in the gut which lead to loss of mucosal barrier integrity and the release of pro-inflammatory cytokines. direct peritoneal resuscitation down-regulates the pro-inflammatory response as a result of maintaining perfusion of the liver and gut during resuscitation.

In conclusion, the present data demonstrate that conventional volume resuscitation from hemorrhagic shock that restores and maintains central hemodynamics does not restore or maintain effective hepatic blood flow and is associated with significant hepatocellular injury and dysfunction. Adjunctive direct peritoneal resuscitation initiated during resuscitation maintains effective hepatic blood flow, prevents hepatocellular injury, and improves liver function.

References

1. Hassoun HT, Kone BC, Mercer DW, Moody FG, Weisbrodt NW, Moore FA. Post-injury multiple organ failure: the role of the gut. Shock 2001;15:1–10.
2. Fruchterman TM, Spain DA, Wilson MA, Harris PD, Garrison RN. Selective microvascular endothelial cell dysfunction in the small intestine following resuscitated hemorrhagic shock. Shock 1998;10:417–422. doi:10.1097/00024382-199812000-00007.
3. Wang P, Hauptman JG, Chaudry IH. Hemorrhage produces depression in microvascular blood flow which persists despite fluid resuscitation. Circ Shock 1990;32:307–318.
4. Zakaria ER, Spain DA, Harris PD, Garrison RN. Resuscitation regimens for hemorrhagic shock must contain blood. Shock 2002;18:567–573. doi:10.1097/00024382-200212000-00014.
5. Deitch EA, Xu D, Franko L, Ayala A, Chaudry IH. Evidence favoring the role of the gut as a cytokine-generating organ in rats subjected to hemorrhagic shock. Shock 1994;1:141–145.
6. Wang P, Hauptman JG, Chaudry IH. Hepatocellular dysfunction occurs early after hemorrhage and persists despite fluid resuscitation. J Surg Res 1990;48:464–470.
7. Wang P, Ba ZF, Chaudry IH. Endothelial cell dysfunction occurs very early following trauma-hemorrhage and persists despite fluid resuscitation. Am J Physiol 1993;265:H973–H979.
8. Zakaria ER, Garrison RN, Spain DA, Harris PD. Impairment of endothelium-dependent dilation response after resuscitation from hemorrhagic shock involved postreceptor mechanisms. Shock 2004;21:175–181. doi:10.1097/00024382-200402000-00014.
9. Zweifach BW. Mechanisms of blood flow and fluid exchange in microvessels: hemorrhagic hypotension model. Anesthesiology 1974;41:157–168. doi:10.1097/00000542-197408000-00006.
10. Zakaria ER, Garrison RN, Spain DA, Matheson PJ, Harris PD, Richardson JD. Intraperitoneal resuscitation improves intestinal blood flow following hemorrhagic shock. Ann Surg 2003;237:704–711. doi:10.1097/00000658-200305000-00013.
11. Zakaria ER, Garrison RN, Kawabe T, Harris PD. Direct peritoneal resuscitation from hemorrhagic shock: effect of time delay in therapy initiation. J Trauma 2005;58:499–506. doi:10.1097/01.TA.0000152892.24841.54.
12. Garrison RN, Conn AA, Harris PD, Zakaria ER. Direct peritoneal resuscitation as adjunct to conventional resuscitation from hemorrhagic shock: a better outcome. Surgery 2004;136:900–908. doi:10.1016/j.surg.2004.06.027.
13. Zakaria ER, Hurt RT, Matheson PJ, Garrison RN. A novel method of peritoneal resuscitation improves organ perfusion after hemorrhagic shock. Am J Surg 2003;186:443–448. doi:10.1016/j.amjsurg.2003.07.006.
14. Chojkier M, Fierer J. D-Galactosamine hepatotoxicity is associated with endotoxin sensitivity and mediated by lymphoreticular cells in mice. Gastroenterology 1985;88:115–121.
15. Shiratori Y, Kawase T, Shiina S, Okano K, Sugimoto T, Teraoka H, Matano S, Matsumoto K, Kamii K. Modulation of hepatotoxicity by macrophages in the liver. Hepatology 1988;8:815–821. doi:10.1002/hep.1840080420.
16. Wang P, Ba ZF, Biondo A, Chaudry I. Liver endothelial cell dysfunction occurs early following hemorrhagic shock and persists despite crystalloid resuscitation. J Surg Res 1996;63:241–247. doi:10.1006/jsre.1996.0255.
17. Bauer M, Marzi I, Ziegenfuss T, Seeck G, Buhren V, Larsen R. Comparative effects of crystalloid and small volume hypertonic hyperoncotic fluid resuscitation on hepatic microcirculation after hemorrhagic shock. Circ Shock 1993;40:187–193.
18. Corso CO, Okamoto S, Leiderer R, Messmer K. Resuscitation with hypertonic saline dextran reduces endothelial cell swelling and improves hepatic microvascular perfusion and function after

hemorrhagic shock. J Surg Res 1998;80:210–220. doi:10.1006/jsre.1998.5426.
19. Dart RC, Liebler DC, Sipes IG. Hepatic injury and lipid peroxidation during hemorrhagic shock and resuscitation. Life Sci 1993;53:1685–1690. doi:10.1016/0024-3205(93)90205-H.
20. Holliday RL, Illner HP, Shires GT. Liver cell membrane alterations during hemorrhagic shock in the rat. J Surg Res 1981;31:506–515. doi:10.1016/0022-4804(81)90189-X.
21. Jarrar D, Wang P, Cioffi WG, Bland KI, Chaudry IH. Critical role of oxygen radicals in the initiation of hepatic depression after trauma hemorrhage. J Trauma 2000;49:879–885. doi:10.1097/00005373-200011000-00015.
22. Flynn WJ, Cryer HG, Garrison RN. Pentoxifylline restores intestinal microvascular blood flow during resuscitated hemorrhagic shock. Surgery 1991;110:350–356.
23. Flynn WJ, Cryer HG, Garrison RN. Pentoxifylline but not saralasin restores hepatic blood flow after resuscitation from hemorrhagic shock. J Surg Res 1991;50:616–621. doi:10.1016/0022-4804(91)90051-M.
24. Fruchterman TM, Spain DA, Wilson MA, Harris PD, Garrison RN. Selective microvascular endothelial cell dysfunction in the small intestine following resuscitated hemorrhagic shock. Shock 1998;10:417–422. doi:10.1097/00024382-199812000-00007.
25. Wang P, Hauptman JG, Chaudry IH. Hemorrhage produces depression in microvascular blood flow which persists despite fluid resuscitation. Circ Shock 1990;32:307–318.
26. Zakaria ER, Spain DA, Harris PD, Garrison RN. Resuscitation regimens for hemorrhagic shock must contain blood. Shock 2002;18:567–573. doi:10.1097/00024382-200212000-00014.
27. Flynn WJ Jr, Gosche JR, Garrison RN. Intestinal blood flow is restored with glutamine or glucose suffusion after hemorrhage. J Surg Res 1992;52:499–504. doi:10.1016/0022-4804(92)90318-T.
28. Flynn WJ Jr, Pilati D, Hoover EL. Effect of allopurinol on venous endothelial dysfunction after resuscitated hemorrhagic shock. Int J Surg Investig 1999;1:11–18.
29. Fruchterman TM, Spain DA, Wilson MA, Harris PD, Garrison RN. Complement inhibition prevents gut ischemia and endothelial cell dysfunction after hemorrhage/resuscitation. Surgery 1998;124:782–791. doi:10.1067/msy.1998.91489.
30. Wang P, Ba ZF, Chaudry IH. Endothelial cell dysfunction occurs after hemorrhage in nonheparinized but not in preheparinized models. J Surg Res 1993;54:499–506. doi:10.1006/jsre.1993.1077.
31. Watkins JM, Spain DA, Krysztopik RJ, Downard PJ, Wilson MA, Garrison RN. Heparan preserves intestinal perfusion after hemorrhage and resuscitation. J Surg Res 1996;66:154–158. doi:10.1006/jsre.1996.0388.
32. Zakaria ER, Li N, Garrison RN. Mechanisms of direct peritoneal resuscitation-mediated splanchnic hyperperfusion following hemorrhagic shock. Shock 2007;27:436–442. doi:10.1097/01.shk.0000245017.86117.4e.
33. Zakaria ER, Li N, Matheson PJ, Garrison RN. Cellular edema regulates tissue capillary perfusion after hemorrhage resuscitation. Surgery 2007;142:487–496. doi:10.1016/j.surg.2007.08.007.
34. Zakaria ER, Campbell JE, Peyton JC, Garrison RN. Postresuscitation tissue neutrophil infiltration is time-dependent and organ-specific. J Surg Res 2007;143:119–125. doi:10.1016/j.jss.2007.04.008.
35. Mazzoni MC, Intaglietta M, Cragoe EJ Jr, Arfors KE. Amiloride-sensitive Na+ pathways in capillary endothelial cell swelling during hemorrhagic shock. J Appl Physiol 1992;73:1467–1473.
36. Chang JX, Chen S, Ma LP, Jiang LY, Chen JW, Chang RM, Wen LQ, Wu W, Jiang ZP, Huang ZT. Functional and morphological changes of the gut barrier during the restitution process after hemorrhagic shock. World J Gastroenterol 2005;11:5485–5491.
37. Jaeschke H. Mechanisms of Liver Injury. II. Mechanisms of neutrophil-induced liver cell injury during hepatic ischemia-reperfusion and other acute inflammatory conditions. Am J Physiol Gastrointest Liver Physiol 2006;290:G1083–G1088. doi:10.1152/ajpgi.00568.2005.
38. Chang TW. Improvement of survival from hemorrhagic shock by enterectomy in rats: finding to implicate the role of the gut for irreversibility of hemorrhagic shock. J Trauma 1997;42:223–230. doi:10.1097/00005373-199702000-00007.
39. Martin C, Boisson C, Haccoun M, Thomachot L, Mege JL. Patterns of cytokine evolution (tumor necrosis factor-alpha and interleukin-6) after septic shock, hemorrhagic shock, and severe trauma. Crit Care Med 1997;25:1813–1819. doi:10.1097/00003246-199711000-00018.
40. Matsutani T, Kang SC, Miyashita M, Sasajima K, Choudhry MA, Bland KI, Chaudry IH. Liver cytokine production and ICAM-1 expression following bone fracture, tissue trauma, and hemorrhage in middle-aged mice. Am J Physiol Gastrointest Liver Physiol 2007;292:G268–G274. doi:10.1152/ajpgi.00313.2006.
41. Roumen RM, Hendriks T, Van der Ven-Jongekrijg J, Nieuwenhuijzen GA, Sauerwein RW, van der Meer JW, Goris RJ. Cytokine patterns in patients after major vascular surgery, hemorrhagic shock, and severe blunt trauma. Relation with subsequent adult respiratory distress syndrome and multiple organ failure. Ann Surg 1993;218:769–776. doi:10.1097/00000658-199312000-00011.

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2008 SSAT POSTER PRESENTATION

Hepatic Metastasectomy for Testicular Germ Cell Tumors: Is it worth it?

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Abstract
Background Chemotherapy is highly effective for metastatic germ cell tumor (GCT), but experience with resection of hepatic metastases from GCT is limited.
Methods Fifteen patients with GCT metastatic to the liver underwent 16 hepatic operations (1975–2002). Pre-resection therapy, surgical pathology, and operative outcomes were reviewed. All patients were followed to death or last contact for survival and disease status.
Results Patients underwent biopsy (three), wedge resection (nine), bisegmentectomy (two), and major lobectomy (two). Hepatic histology included: necrosis (33%), viable tumor (27%), mature teratoma (13%), and benign histology (27%). Concomitant resection of extrahepatic disease (14 patients, 93%) found necrosis (53%), mature teratoma (27%), and viable tumor (13%). Operative mortality was 0% and morbidity was 40%. At 8.2 years (mean) from resection, 11 patients (73%) were alive: five with no evidence of disease, two with elevated tumor marker only, and four with gross disease. Four patients (27%) died. The 10-year overall survival was 62% from diagnosis.
Conclusion Resection of post-chemotherapy hepatic disease is safe, even when combined with resection of extrahepatic residual disease. The varied histologic findings, lack of reliable predictors, and prolonged survival achieved support a multidisciplinary approach which includes surgical resection of hepatic metastases.

Keywords Germ cell tumor · Hepatic metastases · Testicular cancer · Liver resection

Introduction

Testicular germ cell tumors (GCTs) constitute the most common solid organ malignancy afflicting young adult men with peak incidences ranging between 25 and 35 years of age. A recent report from the Surveillance, Epidemiology, and End Results Program revealed that its incidence has increased by 44% between 1973 and 1998, including a 24% rise in the incidence of nonseminomas and a 64% rise in seminomas.[1] Fortunately, GCT is highly responsive to platinum-based chemotherapy and complete remission can be observed in 70–80% of the patients with advanced GCT.[2]

Long-term survival, however, is significantly worse when patients present with non-pulmonary metastases, including those in the liver, bone, or brain. According to the International Germ Cell Cancer Collaborative Group, "poor-risk" nonseminomas (defined as those with non-pulmonary metastases, arising from the mediastinum, or are associated with marked elevation of tumor markers) carry a 5-year overall survival of only 48% when compared to 80–92% in "good"- to "intermediate"-risk cohorts. Similarly, seminomas with non-pulmonary metastases carry a 5-year overall survival of 72% when compared to over 86% for those without such metastases.[3]

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While aggressive surgery to resect residual radiographic disease after systemic chemotherapy has become well integrated into the multidisciplinary care of patients with advanced GCT[4, 5], the role of surgical resection in patients with hepatic metastases from GCT remains poorly defined.[6, 7] Recent literature reported calculated 5-year survivals of 62–70%[8, 9], suggesting oncologic benefit in comparison with historical controls. However, reported experiences are limited and patient selection criteria, resection extent, and long-term outcomes have not been established. This current study examines the experience and outcome of surgical resection of hepatic metastases from GCT at a single institution. Patients were followed for prolonged periods for oncologic outcomes.

Methods

After approval by the Mayo Clinic Institutional Review Board, the Mayo Clinic Rochester Institutional Tumor Registry was queried for all adult (>16 years old) male patients diagnosed with GCT. Thirty-six patients had metastatic disease involving the liver, and 15 underwent surgical treatment between 1975 and 2002.

Medical records of these patients were retrospectively reviewed for baseline characteristics, operative indications, and response to systemic chemotherapy and/or radiation. Serum tumor markers, including α-fetoprotein (AFP), human chorionic gonadotropin (HCG), and lactate dehydrogenase (LDH) levels were recorded when available. Both extrahepatic and hepatic disease burdens were assessed. Disease stage and risk stratification was according to the joint staging system by the American Joint Committee on Cancer and the International Union Against Cancer.[10] Treatment response was measured both radiographically and by tumor marker levels.

Operative indications included: (1) residual hepatic lesions with normalized tumor markers, (2) residual hepatic lesions with persistent elevation of tumor markers, or progressive radiographic evidence of disease. Details of the operative procedures and pathological findings were reviewed.

All patients were followed for 30 days after the operation for perioperative outcomes. Long-term oncologic outcomes were measured from the time of diagnosis to the date of either the last contact or death. Categories at the time of the last follow-up were: alive with no evidence of disease, alive with disease, died of disease, died of other cause, and died of unknown cause. All survival and disease outcomes obtained from medical record review were cross verified with those recorded in the Institutional Tumor Registry and no discrepancy was noted.

All statistical analyses were performed using the SAS 9.1-Enterprise Guide 3.0 software (Cary, NC, USA). Continuous variables were described by median (range) and categorical variables, by number (percent, %). Overall and disease-free survivals were calculated using the Kaplan–Meier method. A two-sided p value of 0.05 denoted statistical significance.

Results

Patient Characteristics and Presentation

The median age at diagnosis was 30 years (range=16–53). Twelve patients (80%) had nonseminomas and three had seminomas, all with anaplastic features. The histology of the nonseminomas included: mixed histology in eight, choriocarcinoma in three, and embryonal carcinoma in one.

The site of the primary GCT was the testis in 12 patients (80%), the retroperitoneum in two (13%), and the mediastinum in one (6.7%). All patients were classified as stage III b or c, with either poor-risk nonseminoma or intermediate-risk seminoma, based on their disease burden and tumor marker levels at diagnosis (Table 1). Hepatic metastases were present at diagnosis in 11 patients (73%); another four patients developed them at a median of 10 months after diagnosis. The extent of hepatic metastases at diagnosis was single lesion in five (33%) and multiple lesions in the remainder.

Germ cell tumor was discovered in five asymptomatic patients (33%) during routine physical examination or imaging studies for unrelated reasons. In other patients, presenting symptoms included: abdominal/back pain in eight, respiratory symptoms in three, testicular mass in three, and bilateral leg swelling in one.

Prior Therapies and Indications for Hepatic Resection

All patients except one with primary tumor in the mediastinum underwent radical orchiectomy with retroperitoneal lymph node dissection sequentially or concomitantly. Thirteen patients (86.7%) received induction chemotherapy with bleomycin, etoposide, and cisplatin. Second-line or salvage regimens included: vinblastine, ifosfamide, and cisplatin (n=3), etoposide, ifosfamide, and cisplatin (n=2), and others (n=4). One patient underwent peripheral bone marrow transplant for salvage. After the completion of induction therapy, tumor markers normalized in seven patients (46.7%).

The operative indications included: (1) persistent radiographic evidence of disease despite normalization of tumor markers in seven patients (46.7%) and (2) persistent tumor marker elevation with radiographic evidence of disease in the remainder. Within the latter group, six patients (40%) had persistent or new radiographic evidence of disease despite systemic therapy, and two patients (13.3%) treated

Table 1 Patient Characteristics at Diagnosis

Pt. no.	Age (years)	Primary tumor		Metastases at diagnosis				Tumor markers		
		Histology	Origin	Retroperitoneal nodes	Lung	Liver	Other	AFP	HCG	LDH
1	22	Choriocarcinoma	Testis		Y			10.1	10×10^3	172
2	16	Mixed	Testis	Y	Y	Y		1.1×10^3	n.a.	n.a.
3	53	Mixed	RP	Y				37	<3	n.a.
4	30	Choriocarcinoma	RP	Y		Y		n.a.	n.a	n.a
5	49	Mixed	Mediastinum		Y	Y		2.6	5.7×10^3	n.a.
6	31	Mixed	Testis	Y	Y	Y		0.8	1187×10^3	699
7	30	Mixed	Testis	Y		Y	Mediastinum	6.6×10^3	4.9×10^3	n.a.
8	34	Mixed	Testis	Y		Y		n.a.	n.a	n.a.
9	22	Seminoma	Testis	Y		Y		15×10^3	<1	n.a.
10	18	Embryonal carcinoma	Testis	Y	Y	Y		600	637×10^3	n.a.
11	42	Seminoma	Testis	Y	Y	Y		205	552×10^3	n.a.
12	29	Mixed	Testis	Y	Y			0	30×10^3	n.a.
13	25	Choriocarcinoma	Testis	Y	Y	Y		2	554×10^3	n.a.
14	24	Mixed	Testis	Y	Y	Y	Mediastinum	3.5×10^3	10×10^3	n.a.
15	32	Seminoma	Testis	Y	Y			n.a.	n.a.	n.a.

RP retroperitoneal; *Y* yes

prior to 1980 had undergone operative resection without preoperative systemic therapy.

Operative Interventions

Sixteen hepatic procedures were performed in 15 patients, at a median of 7.5 months (range=0.5–27 months) from initial diagnosis. The extent of hepatic disease at resection included single lesion (six patients, 40%), two lesions (two patients, 13.3%), and multiple (seven patients, 46.7%). A variety of hepatic procedures were undertaken, including major hepatectomies (Table 2). Nearly all patients (14, 93.4%) underwent concomitant procedures for disease in the retroperitoneum, abdomen, or chest cavity (Table 2).

The median length of stay after operative intervention was 8.5 days (range=5–35 days). There was no perioperative mortality. While six patients (40%) experienced postoperative complications, none was specific to hepatic resections: transfusion reaction, air leak, diaphragmatic tear, chyle ascites, ileus, and small-bowel obstruction in one patient each. Reoperation was required in two patients (13.3%) to repair the diaphragmatic tear and to resolve the bowel obstruction.

Histology of Hepatic and Extrahepatic Tissue

Hepatic tissue revealed necrosis in five patients (33.3%), mature teratoma in two (13.3%), and benign pathology in four (26.7%, including benign parenchyma in two, focal nodular hyperplasia in one, and cavernous hemangioma in one). Active malignancy was found in four patients (26.7%, Table 2). Pathologic findings of extrahepatic lesions included: necrotic tissue in eight patients (53.3%), mature teratoma in four (26.7%), and viable tumor in two (13.3%, Table 2). Discordance between hepatic and extrahepatic histology was demonstrated in six patients (40%, Table 2).

Outcome

Long-term follow-up was complete and averaged 8.6 years from diagnosis and 7.6 years after hepatic operations. At the last follow-up, 11 patients (73.3%) were alive: five with no evidence of disease, two with tumor marker elevation without radiographic evidence of disease, and four with radiographically evident disease. Four patients (27%) died at an average of 3.5 years from diagnosis and 2.1 years from hepatic operations. The cause of death was progressive disease in two, gastrointestinal hemorrhage in one, and unknown in the other. The calculated 5- and 10-year overall survival was 62% from the time of diagnosis (Fig. 1a). After excluding the subgroup of patients with benign hepatic tissue at resection, the calculated 5- and 10-year overall survival was 65% from diagnosis (Fig. 1b). For the four patients with active malignancy on hepatic pathology, the calculated 5-year survival was 33%, with a median survival of 4.6 years. They appeared to fare worse than other patients found to have necrotic tissue or mature teratoma during resection, although the small numbers of patients preclude a formal statistical comparison (Fig. 2). The calculated 5-year disease-specific survival for 11 patients found to have either necrotic tumor, mature teratoma, or active malignancy at hepatic resection was 50%.

Table 2 Surgical Procedures and Histologic Findings in Patients with Hepatic Metastases and Extrahepatic Disease

Pt. no.	Preoperative tumor markers		Hepatic lesions (largest dimension, cm)	Hepatic procedure	Hepatic pathology	Extrahepatic procedure	Extrahepatic pathology	Outcome	Follow-up (years from diagnosis)
	AFP	HCG							
1	7.4	4.6	1 (2.5)	Wedge (segment IV)	Focal nodular hyperplasia	Wedge, bilateral lung lesions	Necrosis	A, tumor marker	2.3
2	10.1	1.7	2 (10)	Bisegmentectomy (segments VI, VII)	Mature teratoma	Resection RP mass	Mature teratoma	A, tumor marker	9.2
3	48.1	n.a.	1 (2.5)	Wedge (segment V)	Embryonal carcinoma	Resection lymphocele	Necrosis	D, of disease	4.3
4	3.3	3.9	1 (3.5)	Wedge (segment IV)	Necrosis	RPLND, resection portal and mesenteric nodes	Necrosis	A, no disease	18.3
5	3.8	175	2 (n.a.)	Left lateral sectorectomy	Cavernous hemangioma	None	n.a.	D, other cause	3.8
6	3.9	2.1	Multiple	Right hepatectomy, wedge (segment III)	Necrosis	RPLND, resection mass	Necrosis	A, no disease	3.2
7	2	0.5	Multiple	Wedge (segments IV, V)	Benign scar tissue	Resection RP mass	Mature teratoma	A, no disease	16.9
			1 (n.a.)	Wedge (segment V)	Mature teratoma	Resection intracaval, paraspinal mass	Mature teratoma		
8	n.a.	n.a.	1 (1)	Wedge	Embryonal carcinoma	Resection RP mass	Embryonal carcinoma	A, no disease	28.3
9	3.9	1.1	Multiple	Left hepatectomy, wedge (right)	Necrosis	RPLND	Mature teratoma with necrotic tumor	A, no disease	19.3
10	<2	2.6	Multiple	Excisional biopsy	Benign parenchyma	Resection RP mass	Necrosis	A, with disease (liver lesions)	3.2
11	15.5	110	Multiple	Excisional biopsy	Necrosis	Resection RP/IVC mass	Necrosis	D, of disease	1.2
12	13.2	598	1 (3.0)	Wedge resection	Mixed GCT	Resection RP mass	Mixed GCT	A, with disease (RP mass)	1.3
13	n.a.	<1.1	Multiple	Excisional biopsy	Necrosis	Resection RP mass, RPLND	Mature teratoma	A, with disease (RP mass)	11.8
14	3.4	1.4	Multiple	Wedge resection	Mature teratoma	Excision RP nodule	Necrosis	A, with disease (paraaortic nodes)	3.4
15	3.5	0.7	1 (2.9)	Wedge resection	Metastatic seminoma	Resection RP mass, RPLND	Necrosis	D, unknown cause	4.6

RP retroperitoneal, *RPLND* retroperitoneal lymph node dissection, *IVC* inferior vena cava, *A* alive, *D* died

Discussion

Despite the highly effective systemic therapy for GCTs, the presence of hepatic metastases still portends poor overall prognosis. Resection of post-chemotherapy residual tumor masses, including pulmonary metastases, has been advocated not only to assess the response to systemic therapy but also to provide potential oncologic benefit.[6, 10–12] Experiences with resection of metastatic disease in the liver, however, have only been reported in four previous studies.[8, 9, 13, 14] The current study demonstrated that (1) resection of hepatic metastases from GCT can be performed safely, (2) hepatic pathology may be discordant with extrahepatic disease and remain difficult to predict, and (3) long-term overall survival can be achieved. Thus, the experiences reported herein support the integration of hepatic metastasectomy into the multidisciplinary care of patients with metastatic GCT.

Germ cell tumors are unique in that they typically afflict otherwise healthy young men, with peak incidences ranging between 25 and 35 years of age.[1] This has allowed for integration of aggressive surgical resection with systemic chemotherapy. To consider resection of metastatic disease, the mortality and morbidity of such operations must be acceptably low. In our study, a variety of hepatic procedures were undertaken, ranging from wedge resections to major lobectomies. Almost all were undertaken concurrent with other major retroperitoneal resections. Nonetheless, the complication rate was modest at 40% and indeed, none

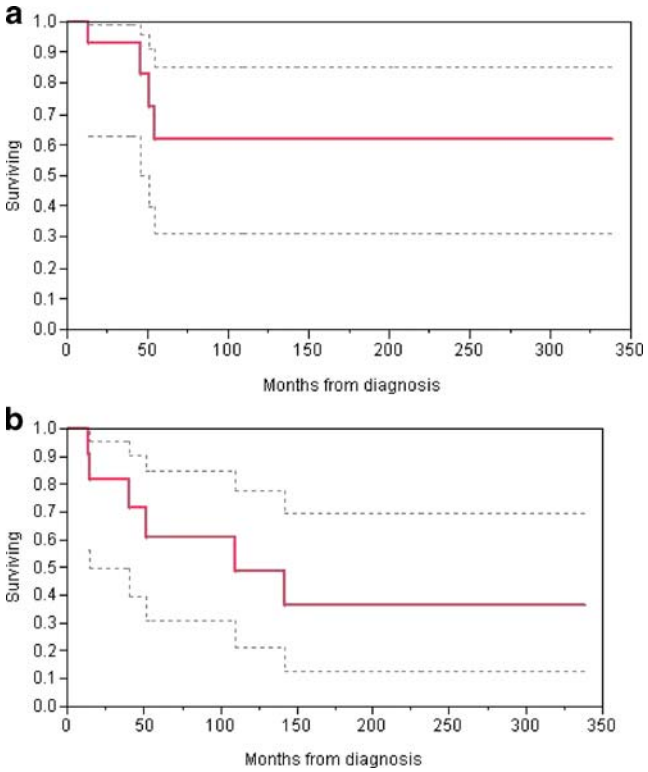

Figure 1 **a** Overall survival of entire study cohort of patients with metastatic germ cell tumor. **b** Overall survival of patients with metastatic germ cell tumor, after excluding patients with benign tissue found at hepatic resection.

was directly attributable to the hepatic resections themselves. These findings were consistent with previous reports. Perioperative mortality has been consistently low at 0–3%.[9, 13, 14] Goulet et al. reported a complication rate of 28% among 28 hepatic operations with or without concomitant resections of extrahepatic disease[13], and an update of the experience showed a consistent 30% morbidity for 60 hepatic resections.[14] Interestingly, chyle ascites occurred in one patient, and it has been recognized as a complication after synchronous hepatic resection and retroperitoneal resection.[6] Nonetheless, the consistently low morbidity associated with hepatic resection for metastatic GCT favors its practice.

One rationale for resection of residual, extrahepatic tumor masses after systemic therapy is its diagnostic value.[2, 4, 5, 15–17] A similar rationale may well apply to the resection of metastatic lesions in the liver. Determining the exact histology of post-chemotherapy lesions is critical in assessing response to prior therapy and for guiding future surveillance and treatment. To date, the histology of residual retroperitoneal masses cannot be reliably predicted based on clinical parameters. While lesion size[9], tumor marker levels[18, 19], and imaging characteristics have all been utilized, studies typically report necrosis in 50% of the resection specimens, teratoma in 35%, and viable tumor in 15%.[5] The extrahepatic histology found in our study showed a remarkably similar distribution: necrosis in 53%, mature teratoma in 27%, and viable tumor in 14% (Table 2). Likewise, hepatic histology cannot be reliably predicted preoperatively at present. Previous studies have found necrosis in 16–67%, teratoma in 12–51%, and viable cancer in 21–55%.[8, 9, 14] In our study, the distribution of these histologies was 33%, 13%, and 27%, respectively, with another 27% being benign hepatic lesions. While no study has specifically examined the role of preoperative hepatic biopsy and the concordance rate between hepatic histology found at preoperative biopsy versus at surgical resection, preoperative hepatic biopsy is only pursued if its findings would alter patient's overall treatment plan. In most patients, hepatic disease co-existed with extrahepatic disease which warranted resection (14 of 15 patients underwent other extrahepatic resections). Furthermore, we report a 40% discordance between hepatic and extrahepatic pathology, similar to the 41% discordance rate reported by Hartmann et al.[8] Indeed, in a recent review, 25–50% discordance has been reported for retroperitoneal and non-retroperitoneal post-chemotherapy residual masses.[6] Thus, it is clear that histology of both extrahepatic and hepatic lesions cannot be safely predicted based on currently available clinical tools. While molecular genetic studies are rapidly emerging[20, 21], surgical excision remains necessary at present for accurate identification of the lesion histology, as a means of accessing response to prior treatment and of guiding the selection of future therapies.

In addition to the diagnostic value, resection of hepatic metastases in GCT may provide oncologic benefit. Improved overall survival and disease progression have been shown with resection of residual retroperitoneal disease in nonseminomas.[16, 22, 23] Secondly, complete resection of

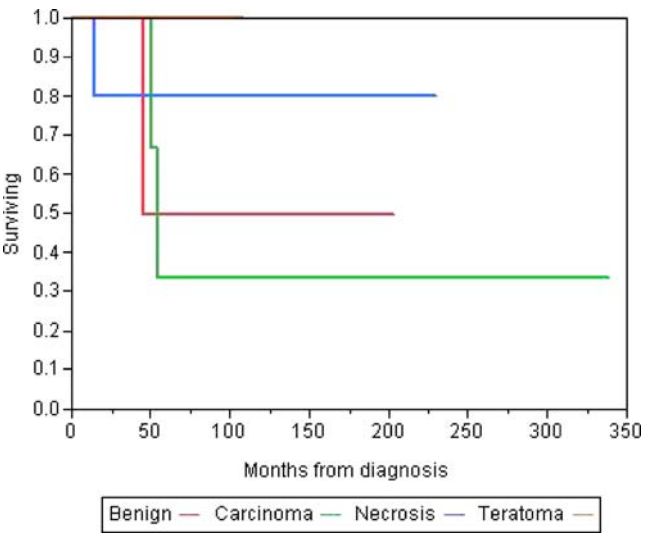

Figure 2 Overall survival of patients according to histology found at hepatic resection.

pulmonary metastases from GCT can lead to a 5-year survival rate of 82%.[11] Thirdly, resection of hepatic metastases has proven survival benefit in select patients with other metastatic malignancies such as colorectal, neuroendocrine, and others.[24–26] In our study, 15 patients underwent hepatic resections. Our calculated 10-year overall survival was 62%, or 65% when patients found to have benign hepatic histology at resection were excluded. These figures suggest oncologic benefit when compared to historical survival figures for poor-risk nonseminomas and intermediate-risk seminomas.[3] They also agree with previous studies; in a series of 57 patients undergoing hepatic metastasectomy, 69% were alive with 63% without disease after 2 years.[14] Similarly, another report of 37 patients revealed that 62% were alive without evidence of disease after 5.5 years of follow-up.[9] Finally, the calculated 5-year survival for the small subset of patients with active tumor at hepatic resection was 33%, with a median survival of 4.6 years. These figures from the subset of patients with worse disease refractory to preoperative treatments compare favorably to the 5-year overall survival rates of 25–40% typically reported after hepatic metastasectomy for patients with colorectal, neuroendocrine, and other malignancies.[24–26] Taken together, these findings suggest that resection of liver metastases from GCT may confer survival benefit in select patients. It should be cautioned, however, that our study is limited by its retrospective design, small patient number, and selection bias for hepatic metastasectomy. As more clinical experience with these patients is accumulated and captured by prospective patient registries, more valid examination of oncologic outcomes and comparisons with histological controls may be made. While a randomized trial with a non-resection arm would be necessary to definitively demonstrate oncologic benefit of hepatic metastasectomy, such a trial would likely not be feasible due to the lack of clinical equipoise.

Prognostic factors associated with poor survival after hepatic resection have not been well defined, largely owing to the rarity of the disease and the limited experiences reported to date. The presence of pure embryonal carcinoma, liver metastases measuring >30 mm, the presence of viable residual disease, and refractoriness to chemotherapy had been suggested by previous investigators.[8, 9] It is thus noteworthy that, of the three patients who died of disease or of unknown cause in our study, one had embryonal carcinoma (patient 5), another had viable tumor at the time of hepatic resection (patient 15), and the last had persistent tumor marker elevation despite systemic therapy (patient 11). Unfortunately, the small and heterogeneous cohort in our study did not allow formal validation of prognostic factors. An additional limitation of our study was that, due to the tertiary referral nature of the practice, long-term patient follow-up often occurred at patient's home institutions, where follow-up practices may have varied and may have led to variable detection of disease recurrence.

Conclusion

Resection of metastatic hepatic disease from GCT after systemic therapy is safe, even when combined with resection of extrahepatic diseases. Hepatic histology is varied and prediction based on currently available clinical factors remains difficult. Prolonged survival can be achieved in select patients. The lack of reliable selection factors, the different hepatic histologies found, and the prolonged survival achieved support a multidisciplinary approach for patients with advanced GCT which includes surgical resection of hepatic metastases.

References

1. McGlynn KA, Devesa SS, Sigurdson AJ, et al. Trends in the incidence of testicular germ cell tumors in the United States. Cancer 2003;97:63–70. doi:10.1002/cncr.11054.
2. Bosl GJ, Motzer RJ. Testicular germ-cell cancer. N Engl J Med 1997;337:242–253. doi:10.1056/NEJM199707243370406.
3. International Germ Cell Consensus Classification. A prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. J Clin Oncol 1997;15:594–603.
4. Schmoll HJ, Souchon R, Krege S, et al. European consensus on diagnosis and treatment of germ cell cancer: a report of the European Germ Cell Cancer Consensus Group (EGCCCG). Ann Oncol 2004;15:1377–1399. doi:10.1093/annonc/mdh301.
5. Sim HG, Lange PH, Lin DW. Role of post-chemotherapy surgery in germ cell tumors. Urol Clin North Am 2007;34:199–217. abstract ix. doi:10.1016/j.ucl.2007.02.010.
6. Katz MH, McKiernan JM. Management of non-retroperitoneal residual germ cell tumor masses. Urol Clin North Am 2007;34:235–243. abstract x. doi:10.1016/j.ucl.2007.02.004.
7. Toner GC. The challenge of poor-prognosis germ cell tumors. Urol Clin North Am 2007;34:187–197. abstract ix. doi:10.1016/j.ucl.2007.02.016.
8. Hartmann JT, Rick O, Oechsle K, et al. Role of postchemotherapy surgery in the management of patients with liver metastases from germ cell tumors. Ann Surg 2005;242:260–266. doi:10.1097/01.sla.0000171303.32006.a2.
9. Rivoire M, Elias D, De Cian F, et al. Multimodality treatment of patients with liver metastases from germ cell tumors: the role of surgery. Cancer 2001;92:578–587. doi:10.1002/1097-0142(20010801)92:3<578::AID-CNCR1357>3.0.CO;2-C.
10. Practice guidelines in oncology: testicular cancer. National Comprehensive Cancer Network. In; 2008. www.nccn.org.
11. Liu D, Abolhoda A, Burt ME, et al. Pulmonary metastasectomy for testicular germ cell tumors: a 28-year experience. Ann Thorac Surg 1998;66:1709–1714. doi:10.1016/S0003-4975(98)00940-0.
12. Rasco DW, Assikis V, Marshall F. Integrating metastasectomy in the management of advanced urological malignancies—where are we in 2005. J Urol 2006;176:1921–1926. doi:10.1016/j.juro.2006.07.003.
13. Goulet RJ Jr, Hardacre JM, Einhorn LH, et al. Hepatic resection for disseminated germ cell carcinoma. Ann Surg 1990;212:290–

293. discussion 293–294. doi:10.1097/00000658-199009000-00007.
14. Hahn TL, Jacobson L, Einhorn LH, Foster R, Goulet RJ Jr. Hepatic resection of metastatic testicular carcinoma: a further update. Ann Surg Oncol 1999;6:640–644. doi:10.1007/s10434-999-0640-0.
15. Bajorin DF, Motzer RJ, Bosl GJ. Germ cell tumors. Curr Ther Endocrinol Metab 1997;6:387–92.
16. Kollmannsberger C, Honecker F, Bokemeyer C. Treatment of germ cell tumors—update 2006. Ann Oncol 2006;17(Suppl 10): x31–x35. doi:10.1093/annonc/mdl232.
17. Sheinfeld J. The role of adjunctive postchemotherapy surgery for nonseminomatous germ-cell tumors: current concepts and controversies. Semin Urol Oncol 2002;20:262–271. doi:10.1053/suro.2002.36977.
18. Beck SD, Patel MI, Sheinfeld J. Tumor marker levels in post-chemotherapy cystic masses: clinical implications for patients with germ cell tumors. J Urol 2004;171:168–171. doi:10.1097/01.ju.0000099714.16082.78.
19. Albers P, Weissbach L, Krege S, et al. Prediction of necrosis after chemotherapy of advanced germ cell tumors: results of a prospective multicenter trial of the German Testicular Cancer Study Group. J Urol 2004;171:1835–1838. doi:10.1097/01.ju.0000119121.36427.09.
20. Cheng L, Zhang S, Wang M, et al. Molecular genetic evidence supporting the neoplastic nature of stromal cells in 'fibrosis' after chemotherapy for testicular germ cell tumours. J Pathol 2007;213:65–71. doi:10.1002/path.2202.
21. Houldsworth J, Korkola JE, Bosl GJ, Chaganti RS. Biology and genetics of adult male germ cell tumors. J Clin Oncol 2006;24:5512–5518. doi:10.1200/JCO.2006.08.4285.
22. Carver BS, Serio AM, Bajorin D, et al. Improved clinical outcome in recent years for men with metastatic nonseminomatous germ cell tumors. J Clin Oncol 2007;25:5603–5608. doi:10.1200/JCO.2007.13.6283.
23. Carver BS, Shayegan B, Serio A, et al. Long-term clinical outcome after postchemotherapy retroperitoneal lymph node dissection in men with residual teratoma. J Clin Oncol 2007;25:1033–1037. doi:10.1200/JCO.2005.05.4791.
24. Antoniou A, Lovegrove RE, Tilney HS, et al. Meta-analysis of clinical outcome after first and second liver resection for colorectal metastases. Surgery 2007;141:9–18. doi:10.1016/j.surg.2006.07.045.
25. O'Rourke TR, Tekkis P, Yeung S, et al. Long-term results of liver resection for non-colorectal, non-neuroendocrine metastases. Ann Surg Oncol 2008;15:207–218. doi:10.1245/s10434-007-9649-4.
26. Rees M, Tekkis PP, Welsh FK, O'Rourke T, John TG. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. Ann Surg 2008;247:125–135.

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ORIGINAL ARTICLE

Hiatal Hernia, Lower Esophageal Sphincter Incompetence, and Effectiveness of Nissen Fundoplication in the Spectrum of Gastroesophageal Reflux Disease

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Abstract
Background and Aims Gastroesophageal reflux disease (GERD) is a spectrum of disease that includes nonerosive reflux disease (NERD), erosive reflux disease (ERD), and Barrett's esophagus (BE). Treatment outcomes for patients with different stages have differed in many studies. In particular, acid suppressant medication therapy is reported to be less effective for treating patients with NERD and Barrett's esophagus. The aims of this study were to investigate (1) the role of mechanical factors including hiatal hernia and lower esophageal sphincter (LES) competence in the spectrum of GERD and (2) outcomes of Nissen fundoplication.
Methods From the records of patients who had undergone laparoscopic Nissen fundoplication after an abnormal pH study, we identified 50 symptomatic consecutive patients with each of the GERD stages: (1) NERD, (2) mild ERD, defined as esophagitis that was healed with acid suppression therapy, (3) severe ERD, defined as esophagitis that persisted despite medical therapy, and (4) BE. Exclusion criteria were normal distal esophageal acid exposure, esophageal pH monitoring performed elsewhere, antireflux surgery less than 1 year previously or previous fundoplication, and a named esophageal motility disorder or distal esophageal low amplitude hypomotility. Patients who could not be contacted for the study were also excluded. All patients completed a detailed preoperative questionnaire; underwent preoperative upper gastrointestinal endoscopy, stationary manometry, and distal esophageal pH monitoring; and were interviewed at least 1 year after operation.
Results One hundred sixty patients meeting the entry criteria were studied. The mean follow-up period was 36.7 months. The only significant preoperative symptom difference was that patients with BE had more moderately severe or severe dysphagia compared to patients with NERD. Patients with severe ERD or BE had a significantly higher prevalence of hiatal hernia, lower LES pressures, and more esophageal acid exposure. Hiatal hernia and hypotensive LES were present in most patients with severe ERD or BE but in only a minority of patients with NERD or mild ERD. Surgical therapy resulted in similarly excellent symptom outcomes for patients in all GERD categories.
Conclusions Compared to mild ERD and NERD, severe ERD and BE are associated with significantly greater loss of the mechanical antireflux barrier as reflected in the presence of hiatal hernia and LES measurements. Restoration of the antireflux barrier and hernia reduction by laparoscopic Nissen fundoplication provides similarly excellent symptom control in all patients.

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Introduction

Gastroesophageal reflux disease (GERD) is a spectrum of disease that extends from nonerosive reflux disease (NERD), in which there are no mucosal breaks on endoscopy, to erosive esophagitis or to Barrett's esophagus (BE).[1] It is currently estimated that between 50% and 70% of patients with GERD have NERD,[2–4] 5% to 10% have BE, and the remainder have

erosive reflux disease (ERD), with either esophageal erosions or ulcerations.[5] As a group, patients with NERD have symptom and quality of life scores similar to patients with erosive reflux disease (ERD).[4,6] Patients can progress from NERD to ERD, even on proton-pump inhibitor (PPI) therapy, but progression from ERD to BE is uncommon and from NERD to BE is very uncommon.[7–9] Labenz et al. reported on the progression of GERD (ProGERD) study of 3,894 patients with GERD who underwent baseline endoscopy and repeat endoscopy at 2 years.[8] As is characteristic of a disease spectrum, many patients had progressed or regressed from one GERD stage to another. Approximately one quarter of patients with NERD had progressed to mild ERD and most patients with ERD had regressed to NERD (treatment was allowed). Patients with severe ERD had the highest rate (5.8%) of progression to BE.[8]

Numerous studies have shown that patients with ERD or BE are effectively treated by antireflux surgery, with safe, long-term control of reflux symptoms, normalization of esophageal acid and nonacid exposure, and a significant improvement in quality of life.[10–14] Few data, in contrast, are available on the results of surgical therapy for all stages of the GERD spectrum including NERD.[13,15] The results of surgical treatment are especially important for patients with NERD as medical treatments are widely reported as being less effective for these patients.[16–18] In this study, we investigated the influence of the endoscopically defined GERD stage on the outcome of laparoscopic Nissen fundoplication. We also compared the demographic, clinical, and physiologic features of patients with different stages of GERD. In particular, we studied the importance of hiatal hernia and lower esophageal sphincter competence, factors which have received less emphasis in other studies.

Patients and Methods

The clinical and esophageal physiology records of patients who had been treated by laparoscopic Nissen fundoplication at the University of Southern California Keck School of Medicine Department of Foregut Surgery (USC) were reviewed. All patients had symptoms suggestive of reflux disease. The mucosal appearance at preoperative endoscopies was used to identify 50 consecutive patients with NERD, 50 consecutive patients with mild ERD, 50 consecutive patients with severe ERD, and 50 consecutive patients with BE. The sample size of 50 patients was selected after a preliminary review of our database indicated that this was likely the maximum number of patients with NERD and persistent esophagitis (severe ERD) available for inclusion in the study period. Since the statistical power of a study is increased by only a relatively small and inefficient amount when the sample sizes are unequal, we did not include all available patients but aimed to limit the sample size to 50 patients in each group.

Patients were classified as having NERD if they had no record of esophagitis, with esophagitis defined by the presence of erosions or ulcerations (modified Savary Miller classification[19]) at any endoscopy. Patients who had received acid suppressant medication therapy prior to their initial endoscopy were excluded from this group. The acid suppressant medication history prior to endoscopy at USC was obtained from the referral letters, USC surgeon's files and reports, and from the patients.

Patients with no erosive esophagitis at preoperative endoscopy but a history of ERD at a previous endoscopy that had been healed by acid suppressant drug therapy were classified as having mild (or healed) ERD. Severe ERD was defined as persistent or nonhealed esophagitis and was diagnosed when esophagitis was found at the preoperative endoscopy in patients who had received at least some acid suppressant therapy. This included PPI therapy in all cases but we did not include the type or dose of medication received as a factor or perform a subanalysis of the medical therapy as many larger studies have addressed the effectiveness of acid suppressive medication using more robust methods including many randomized controlled trials. All patients with ERD thus had at least two endoscopies. BE was diagnosed by the presence of microscopic intestinal metaplasia in a macroscopic columnar-lined esophagus of any length.

All patients underwent preoperative endoscopy performed by the authors at this institution. The results of endoscopies performed elsewhere were obtained from the medical history and the documents and letters of the referring physician. In order to ensure that only patients with definite GERD were studied, only patients with abnormal distal esophageal acid exposure were included.

Patients were excluded if they had undergone Nissen fundoplication less than 1 year previously, if they had had more than one previous antireflux operation, or if they could not be contacted for this study. Patients who had not had a preoperative ambulatory pH study at this institution were also excluded, as were those with a named esophageal motility disorder or distal esophageal low amplitude hypomotility, defined as a mean contraction amplitude less than 20 mmHg. A hiatal hernia was diagnosed when the gastroesophageal junction was located 2 cm or more proximal to the crural impression at endoscopy, with the gastroesophageal junction defined as the proximal extent of the gastric rugal folds.

Symptom Assessment

All patients completed a structured symptom questionnaire at the time of their esophageal pH examination. The symptom of heartburn was graded as 0 (none), 1 (mild; occasional episodes), 2 (moderate; primary reason for

medical visit), or 3 (severe; effects daily life). Regurgitation was graded as 0 (none), 1 (mild; occasional episode after straining or large meal), 2 (moderate, predictable with position change or straining), or 3 (severe, effects daily life, possibly with a history of aspiration). Dysphagia was graded as 0 (none), 1 (mild; occasionally with coarse foods; lasting a few seconds), 2 (moderate; requiring clearing with liquids), or 3 (severe; requiring a semiliquid diet and with a history of meat impaction). These descriptors were also used for postoperative symptom assessment. In order to limit the number of statistical comparisons and the consequent risk of false positive findings, the symptom findings were classified as either "none or mild" or "moderate or severe".

Manometry

All patients underwent preoperative manometry testing. Stationary motility was performed after an overnight fast using a single catheter assembly consisting of five polyethylene tubes bonded together with five lateral openings placed at 5-cm intervals from the distal end and oriented radially around the circumference. Using a pneumohydraulic low compliance pump (Arndorfer Medical Specialties, Greendale, WI, USA), the catheter was perfused with distilled water at a constant rate of 0.6 mL/min. A stationary pull through of the lower esophageal sphincter (LES) and a manual analysis of the polygraph recordings were performed. LES resting pressure was measured at the respiratory inversion point, as described previously.[20] The resting pressure, overall length, and abdominal length of the LES were calculated from the mean of the five recordings. A structurally defective LES was defined either by a resting pressure <6 mmHg, overall length <2 cm, abdominal length <1 cm, or any combination of these. Assessment of the esophageal body motility was performed as described previously.[20]

pH and Bilirubin Monitoring

All the patients underwent 24-h distal esophageal pH monitoring. Proton-pump inhibitor medications were discontinued at least 2 weeks before testing and other reflux medications were discontinued at least 72 h before testing. The pH monitoring was performed as previously described, by positioning a glass pH electrode (Mui Scientific, Toronto, Ontario, Canada) or an antimony crystal ph electrode (Synectics Medical, Irving, TX, USA) 5 cm above the manometrically measured upper border of the LES.[21] The electrode was connected to a digital recording device (Microdigitrapper, Synectics Medical, Irving, TX, USA) and pH continually monitored for 24 h. The patients' diets were limited to foods having a pH in the range 5–7. The stored data were transferred to a personal computer and analyzed using a standard software package (Multigram, Gastrosoft, Irving, TX, USA). All patients had abnormal esophageal acid exposure, with an esophageal pH less than 4 for more than 4.4% of the total study period.[21]

Esophageal exposure to duodenal juice was measured using a fiberoptic probe designed to detect bilirubin by spectrophotometry at 453 nm, the specific wavelength for absorption of bilirubin (Bilitec 2000, Medtronic Synectics, Shoreview, MN, USA).[22] The probe was passed transnasally and positioned at the same level as the pH electrode. Twenty-four-hour absorbance data were recorded on a portable optoelectric data logger and analyzed with a software program (Multigram, Gastrosoft, Irving, TX, USA). Bilirubin exposure was quantified as the percentage of time above an absorbance threshold of 0.2. The upper limit of the normal range for bilirubin exposure was 1.7% of the total time above an absorbance threshold of 0.2.[22] Patient diets were restricted to three meals per day with no foods with an absorbance similar to that of bilirubin.

Operative Technique

Laparoscopic Nissen fundoplication was performed as previously described.[23] Important technical elements included crural and hiatal dissection, crural closure, and complete fundic mobilization by division of the short gastric vessels. A 2-cm loose fundoplication was constructed over a 60-Fr bougie by enveloping the distal esophagus with the anterior and posterior walls of the gastric fundus so that the anterior and posterior fundic lips met at the right lateral position on the esophagus.

Statistical Analysis

Fisher's exact test was used to compare proportions between two groups and the linear-by-linear chi-square test was used to compare proportions between more than two groups. Continuous data were compared using the Mann–Whitney *U* test for two groups and the Kruskal–Wallis test for more than two groups. All *P* values are two-sided. SPSS version 10.0.5 software (SPSS Inc., Chicago IL, USA) was used for all statistical analyses. All values are shown as median with (interquartile range) or as number of patients with (percentage).

Results

After excluding patients according to the criteria listed above, the study population consisted of 160 patients. The number of patients in each GERD category and demographic data are

shown in Table 1. There were no significant differences between the patients in the four GERD categories for either age (*P* value for all groups 0.86, chi-square test) or sex (*P* value for all groups 0.19, chi-square test). There were also no significant differences between any two individual groups for these factors. The mean follow-up period was 36.7 months for all 160 patients (median 30 months, range 12–92 months). The duration of follow-up was significantly longer for BE patients compared to patients in any of the other groups but was not significantly different between any of the other three patient groups (Table 1 legend).

Preoperative Evaluation

Symptoms

Preoperative symptom results are shown in Table 2. The only significant differences were that a higher proportion of patients with severe ERD had moderately severe or severe regurgitation compared to patients with mild ERD ($P=0.05$), and moderately severe or severe dysphagia was significantly more prevalent among patients with BE compared to patients with NERD ($P=0.013$, both Fisher's exact test).

Hiatal Hernia

Hiatal hernia was present in 107 (66.9%) of the 160 patients. As shown in Table 3, hernia was significantly more prevalent in patients with either severe ERD or BE compared to those with either mild ERD or NERD.

Stationary Manometry

Patients with either BE or severe ERD had significantly lower LES resting pressures than patients with NERD or mild ERD (Table 3). Similarly, a hypotensive LES was more frequently found in patients with BE (30/44 patients (68.2%)) compared to patients with either NERD (14/39 (35.9%), $P=0.005$) or mild ERD (16/42 (38.1%), $P=0.009$, both Mann–Whitney *U* test). As for BE, most (19/35 (54.3%)) patients with severe ERD also had a hypotensive LES.

Regardless of group, most patients had a mechanically defective LES with one or more of the factors hypotensive LES, short total LES length, or short intra-abdominal LES length being present. A mechanically defective LES was present in a higher proportion of patients with severe ERD or BE patients (80.0% and 77.3%, respectively) compared to patients with NERD or mild ERD (56.4% and 59.5%, respectively, $P=0.046$ for NERD versus severe ERD, Mann–Whitney *U* test).

Distal Esophageal pH and Bilirubin Exposure

As required for study entry, all patients had GERD, defined by abnormally high distal esophageal acid exposure on ambulatory pH monitoring. Distal esophageal acid exposure, measured as the total percent time the pH was less than 4 during the study period, was significantly higher in patients with either severe ERD or BE compared to patients with either NERD or mild ERD (see Table 3). Furthermore, all other measures of acid reflux (upright % time, supine % time, number of reflux episodes, number of reflux episodes longer than 5 min, duration of longest reflux episode, and composite (DeMeester) score) were significantly more abnormal in patients with BE compared to patients with either NERD or mild ERD (data not shown). Five acid reflux measures were also more severe in the BE group compared to the severe ERD group, with only the number of reflux episodes and duration of longest episode not significantly different (data not shown). Four of the seven acid reflux measures were also significantly more abnormal in patients with severe ERD compared to NERD patients (data not shown). Only the supine percent time was significantly different in the NERD and mild ERD groups, being higher in the mild ERD group (data not shown).

As shown in Table 3, there was a progressive increase in median DeMeester score with increasing mucosal injury, from NERD to mild ERD, severe ERD, and BE. The score was significantly different between all groups except the NERD and mild ERD groups and in five of the six comparisons shown in Table 3. The total percent time was significantly different in four of the six comparisons (Table 3). These results, although prespecified, have not

Table 1 Demographic Factors

GERD stage	NERD	Mild ERD	Severe ERD	Barrett's esophagus	Total
Number of patients	39	42	35	44	160
Male (%)	25 (64)	28 (67)	23 (66)	35 (79)	111 (69)
Age[a]	49 (22)	48.5 (19.5)	48 (13)	47.5 (12.5)	48 (15.75)
Duration of follow-up in months[a]	25 (21)	25.5 (18.2)	24 (45)	55 (34.7)[b]	30 (37)

[a] Values for age and duration of follow-up are median and (interquartile range)

[b] Duration of follow-up was significantly longer for patients with Barrett's esophagus compared to other groups (Barrett's versus NERD patients $P=0.001$, Barrett's versus mild ERD $P<0.001$, Barrett's versus severe ERD $P=0.029$, all Mann–Whitney test). There were no other significant demographic differences between the patient groups

Table 2 Preoperative Symptoms

GERD stage	NERD	Mild ERD	Severe ERD	Barrett's esophagus	Total
Heartburn					
None or mild	3 (7.7%)	4 (9.5%)	4 (11.4%)	2 (4.5%)	13 (8.1%)
Moderate or severe	36 (92.3%)	38 (90.5%)	31 (88.6%)	42 (95.5%)	147 (91.9%)
Regurgitation					
None or mild	14 (35.9%)	18 (42.9%)	7 (20.0%)	11 (25.0%)	50 (31.3%)
Moderate or severe	25 (64.1%)	24 (57.1%)	28 (80.0%)	33 (75.0%)	110 (68.8%)
Dysphagia					
None or mild	36 (92.3)	36 (85.7%)	26 (74.3%)	31 (70.5%)	129 (80.6%)
Moderate or severe	3 (7.7%)	6 (14.3)	9 (25.7%)	13 (29.5%)	31 (19.4%)

Data shown are numbers of patients with (percentage)

been adjusted to take into account multiple comparisons and therefore need to be validated in further studies.

Bilirubin exposure was measured in 92 (56.8%) patients. Bile reflux, as measured by the percentage of time that absorbance at the wavelength of bilirubin was above the 0.2 threshold, was significantly higher in patients with BE (median 13.1, interquartile range 20.3) than in patients with either mild ERD (median 0.3 (14.3)) or severe ERD (2.8 (18.7), P=0.013 and 0.021, respectively, Mann–Whitney test). Abnormally high esophageal bile exposure was present in a considerably higher proportion of BE patients (23/29 patients (79.3%)) compared to the other groups of patients (NERD 10/19 patients (52.6%), mild ERD 10/22 patients (45.5%), severe ERD 10/20 patients (50%)), but this difference was significant only for the comparison of BE versus mild ERD patients (P=0.018, Fisher's exact test).

Postoperative Evaluation

The postoperative results are shown in Table 4. There were no significant differences in the prevalence of any of the symptoms heartburn, regurgitation, or dysphagia among any groups.

Discussion

This study documents the clinical presentation, pathophysiologic features, and response to surgical therapy in patients at different stages of the spectrum of gastroesophageal reflux disease. We included only patients with abnormal distal esophageal acid exposure shown on ambulatory pH monitoring, thus reducing the risk of studying patients whose symptoms were not reflux-related. The patients were classified using their index endoscopy report and antireflux medication history. Patients who received acid suppressant medication therapy prior to index endoscopy showing NERD were excluded because of the effect of these medications in healing erosive disease and the consequent inability to distinguish whether these patients had NERD or healed ERD.

We believe that this study includes patients with true NERD who had not received antireflux medications prior to

Table 3 Preoperative Hiatal Hernia, LES Pressure, and Esophageal Acid Exposure

GERD stage	NERD	Mild ERD	Severe ERD	Barrett's esophagus	Total	NERD versus Mild ERD	NERD versus Severe ERD	NERD versus BE	Mild versus Severe ERD	Mild ERD versus BE	Severe ERD versus BE
Factor						P values					
Hernia[a]	21 (53.8%)	19 (45.2%)	30 (85.7%)	37 (84.1%)	107 (66.9%)	0.508	0.005	0.004	<0.001	<0.001	1.0
LES resting pressure (mmHg)[b]	8.4 (8.8)	7 (7.1)	5.5 (4.2)	5.2 (5.3)	6.2 (6.15)	0.667	0.004	0.005	0.02	0.025	0.78
Total % time pH<4[b]	7.4 (3.33)	7.1 (5.2)	9.0 (5.6)	13.0 (12.4)	8.7 (6.6)	0.698	0.026	<0.001	0.12	<0.001	0.005
DeMeester score[b]	24.8 (13.83)	27.9 (21.5)	36.3 (26.4)	50.6 (52.1)	33 (27.73)	0.395	0.002	<0.001	0.031	<0.001	0.035

[a] Data shown as number of patients with (percentage). P values calculated using Fisher's exact test
[b] Data shown as median with (interquartile range). P values calculated using Mann–Whitney U test

Table 4 Postoperative Symptoms

GERD Stage	NERD	Mild ERD	Severe ERD	Barrett's esophagus	Total
Heartburn					
None or mild	36 (92.3%)	40 (95.2%)	35 (100%)	42 (95.5%)	153 (95.6%)
Moderate or severe	3 (7.7%)	2 (4.8%)	0 (0%)	2 (4.5%)	7 (4.4%)
Regurgitation					
None or mild	39 (100%)	41 (97.6%)	34 (97.1%)	42 (95.5%)	156 (97.5%)
Moderate or severe	0 (0%)	1 (2.4%)	1 (2.9%)	2 (4.5%)	4 (2.5%)
Dysphagia					
None or mild	38 (97.4%)	41 (97.6%)	35 (100%)	42 (95.5%)	156 (97.5%)
Moderate or severe	1 (2.6%)	1 (2.4%)	0 (0%)	2 (4.5%)	4 (2.5%)

Data shown are numbers of patients with (percentage)

endoscopy at USC. The availability of these patients in a surgery study reflects the probably unusual referral basis of the USC Foregut Surgery Division in that our patient base includes some patients with reflux symptoms who are referred by their family physician directly to this unit rather than through a gastroenterologist. All patients were contacted, increasing our confidence in their classification, but we acknowledge it is not possible to be certain about the pre-endoscopy medication use of all patients because patients have an imperfect recall of their medication history and the referral correspondence can be incomplete. Similarly, we acknowledge in this retrospective study that the patients with persistent esophagitis despite medical therapy may have received an inadequate dosage or not been fully compliant, although the significant anatomical and physiological differences between the "healed esophagitis" and "persistent esophagitis" patient groups (Fig. 1) indicate that these groups differ in the mechanical properties of their antireflux barrier rather than merely in the dose of antireflux medication received.

An important finding of our study was that the preoperative mechanical factors hiatus hernia, LES resting pressure, and LES lengths were significantly more impaired in patients with severe ERD and BE compared to those with mild ERD and NERD. Esophageal acid and bile reflux also tended to be worse in the more severe GERD categories. It is well recognized that hiatal hernia is present in most patients with BE, and a lower frequency of hernia in patients with NERD has been reported.[4,24,25] In a large case control study, the presence and size of hernia was strongly associated with risk of developing high grade dysplasia or adenocarcinoma in patients with BE.[26] Hiatal hernia has also be identified as an important factor for the development of ERD in patients with NERD. In a longitudinal study of 47 patients with NERD who underwent annual endoscopy for 5 years, hiatal hernia was a highly significant risk factor for the development of ERD.[27]

Our study provides further support for the importance of the length as well as the resting pressure of the LES in the etiology of GERD.[28] Most of the patients, all of whom had abnormal esophageal acid exposure, had a mechanically defective LES because of either a low resting pressure or a short total or intra-abdominal LES length. The LES tended to be more frequently and more severely defective, with significantly lower LES pressures in particular, in patients with severe ERD or BE compared to those with mild ERD or NERD. As with hiatal hernia, similarly good outcomes are provided by fundoplication regardless of GERD category because the operation recreates a mechanically competent high pressure zone.

Our findings suggest that the endoscopic extent of mucosal injury reflects, and is likely to result from, the extent of mechanical abnormality at the gastroesophageal barrier and the consequent severity of gastroesophageal

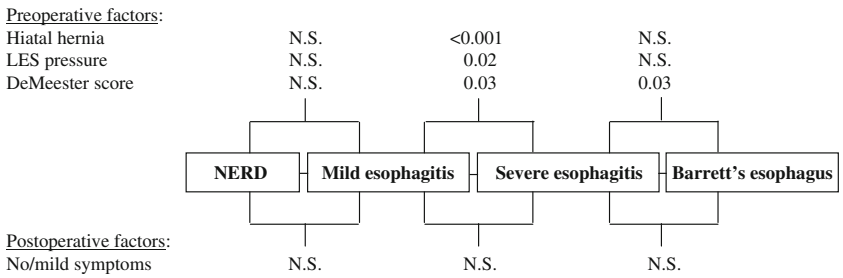

Figure 1 The numbers shown are *P* values for selected preoperative factors and postoperative outcome comparing NERD versus mild ERD, mild versus severe ERD, and severe ERD versus BE. *N.S.* not significant.

reflux. Furthermore, they suggest that progression to severe GERD usually requires the development of a hiatal hernia and a defective LES. This hypothesis is supported by a study from Northwestern University in which regression analysis was used to model the major risk factors for ERD in patients with symptomatic GERD. Similar to our findings, the authors reported that hiatal hernia size and LES pressure are the dominant determinants of esophagitis presence and severity.[29]

Several studies have found similar quality of life and symptom severity scores for patients with ERD and NERD.[4,24,30,31] Consistent with this, the symptom presentation for patients with NERD was not significantly different to that for patients with ERD in this study. The severity of reflux symptoms in patients with NERD indicates that these patients have significant illness and the same need for effective treatment as patients with ERD or BE. Patients with severe ERD or BE tended to have more severe regurgitation and dysphagia, which corresponds with the worse reflux and higher prevalence of hernia in these groups. A high prevalence of dysphagia among patients with BE has been noted previously.[32]

As expected, patients with BE had the most severe gastroesophageal reflux. All measures of acid reflux were significantly more abnormal in patients with BE compared to either NERD or mild ERD patients. Patients with NERD tended to have less severe reflux than patients with ERD, especially those with severe ERD. This correlates with the observation that the severity of esophagitis correlates with amount of acid exposure[33] and similar findings have been reported by others.[25] The composite (DeMeester) score, which includes all the acid reflux measures in a weighted calculation of reflux severity, discriminated most clearly between the different GERD stages in this and a similar study.[34]

We have presented the findings without applying a correction for multiple comparisons; thus, one explanation is that they are false positive results due to chance alone. However, we observed consistent positive findings for different variables that are known to share an association (e.g., hernia and pH exposure), reducing the likelihood of this explanation. Furthermore, the findings are consistent with those expected from the large number of previous studies that have examined the influence of mechanical factors in the etiology of GERD. Even if the most conservative (Bonferroni) correction is applied to take into account the multiple (20 comparisons, corrected $P<0.0025$) analyses performed in the analysis with the largest number of comparisons (Table 3), although fewer findings would be classified as statistically significant, the same principal conclusions apply.

All patients underwent a circumferential (Nissen) laparoscopic fundoplication and they were all contacted for this study at least 1 year after operation. We found similarly excellent symptom control in all patient groups, with no significant differences in outcome according to the stage of GERD. In contrast, consistently and significantly worse outcomes are reported for medical treatment for NERD compared to erosive disease.[16–18] Lind et al., for example, documented complete symptom resolution in only 46% of NERD patients using 20 mg omeprazole daily for 4 weeks, and satisfaction with therapy was reported by only two thirds of patients.[35] In a pooled data study of 2,458 patients who received differing but standard PPI doses, complete heartburn resolution was achieved in only 63% of patients at the end of 4 weeks' treatment.[36]

The results for surgery for patients with NERD in this and other surgery studies[15,34,37] are far superior to those for medical PPI therapy. In a study of 89 patients with NERD who underwent laparoscopic Nissen fundoplication, the improvement in quality of life, as measured using the Gastrointestinal Quality of Life Index tool, was significantly greater in those with NERD compared to patients with erosive esophagitis because quality of life was more impaired preoperatively in the NERD group.[37] At 5 years after surgery, quality of life in both NERD and ERD patient groups was comparable to healthy controls.[37]

The favorable results for surgical therapy in these and the current study may be partly explained by the fact that the patients without erosive esophagitis all had pH study proven reflux disease.[15,34,37] We and others have previously reported better postfundoplication outcomes in patients with abnormal distal esophageal acid exposure compared to patients with normal pH study results,[38,39] and the surgeon should be wary of operating on patients with no mucosal injury and acid reflux within the normal range. These patients are diagnosed with GERD by correlating symptoms with reflux events (positive symptom index)[40] or by demonstrating relief of symptoms with a test course of antacid or acid suppressant therapy. There is evidence that esophageal visceral hypersensitivity, sustained esophageal contractions, and abnormal tissue resistance[41] may be involved in causing symptoms in patients with minimal acid reflux, but stress,[42] psychological,[43,44] and psychiatric[45] illness may also be factors in the these patients with "functional heartburn" or the "hypersensitive esophagus".[40,46,47]

Several studies have shown that NERD, ERD, and BE are not separate diseases but part of a spectrum of GERD.[1,8] As is typical of a spectrum disease, patients can progress and regress to and from different endoscopic stages. Our results suggest that, as well as being a spectrum disease, GERD can also be usefully regarded as a categorical disease that includes the two categories mild (NERD and mild ERD) and severe (severe ERD and BE) GERD. In support of categorizing GERD as mild and severe disease, the ProGERD study reported that mild erosive esophagitis

(Los Angeles classification grade A or B) behaved in a similar way to NERD.

Conclusions

The spectrum of GERD includes NERD, mild and severe ERD, and BE. The clinical presentation is similar at different stages of this spectrum, although patients with severe ERD or BE may have more severe regurgitation or dysphagia. The stage of disease correlates well with the mechanical and anatomic features of the gastroesophageal reflux barrier, with hiatal hernia and a hypotensive lower esophageal sphincter significantly more prevalent in patients with severe ERD or BE. Nissen fundoplication, which reduces the hernia and augments the lower esophageal high pressure zone, provides similarly good or excellent results, regardless of the endoscopic appearance, in patients with all stages of GERD.

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References

1. Pace F, Pallotta S, Vakil N. Gastroesophageal reflux disease is a progressive disease. Dig Liver Dis 2007;39(5):409–414. doi:10.1016/j.dld.2006.11.015.
2. Trimble KC, Douglas S, Pryde A, Heading RC. Clinical characteristics and natural history of symptomatic but not excess gastroesophageal reflux. Dig Dis Sci 1995;40(5):1098–1104. doi:10.1007/BF02064206.
3. Jones RH, Hungin APS, Phillips J, Mills JG. Gastro-oesophageal reflux disease in primary care in Europe: clinical presentation and endoscopic findings. Eur J Gen Pract 1995;1:149–154.
4. Carlsson R, Dent J, Watts R, et al. Gastro-oesophageal reflux disease in primary care: an international study of different treatment strategies with omeprazole. International GORD Study Group. Eur J Gastroenterol Hepatol 1998;10(2):119–124. doi:10.1097/00042737-199802000-00004.
5. 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(2): 172–180.
6. Kulig M, Leodolter A, Vieth M, et al. Quality of life in relation to symptoms in patients with gastro-oesophageal reflux disease—an analysis based on the ProGERD initiative. Aliment Pharmacol Ther 2003;18(8):767–776. doi:10.1046/j.1365-2036.2003.01770.x.
7. Labenz J, Jaspersen D, Kulig M, et al. Risk factors for erosive esophagitis: a multivariate analysis based on the ProGERD study initiative. Am J Gastroenterol 2004;99(9):1652–1656. doi:10.1111/j.1572-0241.2004.30390.x.
8. Labenz J, Nocon M, Lind T, et al. Prospective follow-up data from the ProGERD study suggest that GERD is not a categorial disease. Am J Gastroenterol 2006;101(11):2457–2462.
9. Bajbouj M, Reichenberger J, Neu B, et al. A prospective multicenter clinical and endoscopic follow-up study of patients with gastroesophageal reflux disease. Z Gastroenterol 2005;43 (12):1303–1307. doi:10.1055/s-2005-858874.
10. Peters JH, DeMeester TR, Crookes P, et al. The treatment of gastroesophageal reflux disease with laparoscopic Nissen fundoplication: prospective evaluation of 100 patients with "typical" symptoms. Ann Surg 1998;228(1):40–50. doi:10.1097/00000658-199807000-00007.
11. Trus TL, Laycock WS, Waring JP, et al. Improvement in quality of life measures after laparoscopic antireflux surgery. Ann Surg. 1999;229(3):331–336. doi:10.1097/00000658-199903000-00005.
12. Lord RV. Antireflux surgery for Barrett's oesophagus. ANZ J Surg 2003;73(4):234–246. doi:10.1046/j.1445-1433.2003.02569.x.
13. Zaninotto G, Portale G, Costantini M, et al. Long-term results (6–10 years) of laparoscopic fundoplication. J Gastrointest Surg 2007;11(9):1138–1145. doi:10.1007/s11605-007-0195-y.
14. Morgenthal CB, Shane MD, Stival A, et al. The durability of laparoscopic Nissen fundoplication: 11-year outcomes. J Gastrointest Surg 2007;11(6):693–700. doi:10.1007/s11605-007-0161-8.
15. Watson DI, Foreman D, Devitt PG, Jamieson GG. Preoperative endoscopic grading of esophagitis versus outcome after laparoscopic Nissen fundoplication. Am J Gastroenterol 1997;92 (2):222–225.
16. Fass R. Erosive esophagitis and nonerosive reflux disease (NERD): comparison of epidemiologic, physiologic, and therapeutic characteristics. J Clin Gastroenterol 2007;41(2):131–137. doi:10.1097/01.mcg.0000225631.07039.6d.
17. Dean BB, Gano AD Jr, Knight K, et al. Effectiveness of proton pump inhibitors in nonerosive reflux disease. Clin Gastroenterol Hepatol 2004;2(8):656–664. doi:10.1016/S1542-3565(04)00288-5.
18. van Pinxteren B, Numans ME, Bonis PA, Lau J. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane Database Syst Rev 2006;3:CD002095.
19. Ollyo JB, Lang F, Fontolle CH, Monnier PH. Savary's new endoscopic grading of reflux oesophagitis: a simple, reproducible, logical, complete and useful classification. Gastroenterology 1990;89:A100.
20. Zaninotto G, DeMeester TR, Schwizer W, et al. The lower esophageal sphincter in health and disease. Am J Surg 1988;155 (1):104–111. doi:10.1016/S0002-9610(88)80266-6.
21. 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(9):1102–1111.
22. Kauer WK, Burdiles P, Ireland AP, et al. Does duodenal juice reflux into the esophagus of patients with complicated GERD? Evaluation of a fiberoptic sensor for bilirubin. Am J Surg 1995;169(1):98–103. doi:10.1016/S0002-9610(99)80116-0.
23. Lord RVN, DeMeester TR. Reflux disease and hiatal hernia. Oxford Textbook of Surgery. vol. 2. Oxford: Oxford University Press, 2000, pp 1239–1262.
24. Venables TL, Newland RD, Patel AC, et al. Omeprazole 10 milligrams once daily, omeprazole 20 milligrams once daily, or ranitidine 150 milligrams twice daily, evaluated as initial therapy for the relief of symptoms of gastro-oesophageal reflux disease in general practice. Scand J Gastroenterol 1997;32(10):965–73. doi:10.3109/00365529709011211.
25. Frazzoni M, De Micheli E, Savarino V. Different patterns of oesophageal acid exposure distinguish complicated reflux disease

from either erosive reflux oesophagitis or non-erosive reflux disease. Aliment Pharmacol Ther 2003;18(11–12):1091–1098. doi:10.1046/j.1365-2036.2003.01768.x.
26. Avidan B, Sonnenberg A, Schnell TG, et al. Hiatal hernia size, Barrett's length, and severity of acid reflux are all risk factors for esophageal adenocarcinoma. Am J Gastroenterol 2002;97 (8):1930–1936. doi:10.1111/j.1572-0241.2002.05902.x.
27. Kawanishi M. Will symptomatic gastroesophageal reflux disease develop into reflux esophagitis? J Gastroenterol 2006;41(5):440–443. doi:10.1007/s00535-006-1791-4.
28. DeMeester TR, Peters JH, Bremner CG, Chandrasoma P. Biology of gastroesophageal reflux disease: pathophysiology relating to medical and surgical treatment. Annu Rev Med 1999;50:469–506. doi:10.1146/annurev.med.50.1.469.
29. Jones MP, Sloan SS, Rabine JC, et al. Hiatal hernia size is the dominant determinant of esophagitis presence and severity in gastroesophageal reflux disease. Am J Gastroenterol 2001;96 (6):1711–1717. doi:10.1111/j.1572-0241.2001.03926.x.
30. Havelund T, Lind T, Wiklund I, et al. Quality of life in patients with heartburn but without esophagitis: effects of treatment with omeprazole. Am J Gastroenterol 1999;94(7):1782–1789. doi:10.1111/j.1572-0241.1999.01206.x.
31. Tew S, Jamieson GG, Pilowsky I, Myers J. The illness behavior of patients with gastroesophageal reflux disease with and without endoscopic esophagitis. Dis Esophagus 1997;10(1):9–15.
32. DeMeester SR, DeMeester TR. Columnar mucosa and intestinal metaplasia of the esophagus: fifty years of controversy. Ann Surg 2000;231(3):303–321. doi:10.1097/00000658-200003000-00003.
33. Masclee AA, de Best AC, de Graaf R, et al. Ambulatory 24-hour pH-metry in the diagnosis of gastroesophageal reflux disease. Determination of criteria and relation to endoscopy. Scand J Gastroenterol 1990;25(3):225–230.
34. Bammer T, Freeman M, Shahriari A, et al. Outcome of laparoscopic antireflux surgery in patients with nonerosive reflux disease. J Gastrointest Surg 2002;6(5):730–737. doi:10.1016/S1091-255X(02)00042-2.
35. Lind T, Havelund T, Carlsson R, et al. Heartburn without oesophagitis: efficacy of omeprazole therapy and features determining therapeutic response. Scand J Gastroenterol 1997;32 (10):974–979. doi:10.3109/00365529709011212.
36. Talley NJ, Armstrong D, Junghard O, et al. Predictors of treatment response in patients with non-erosive reflux disease. Aliment Pharmacol Ther 2006;24(2):371–376. doi:10.1111/j.1365-2036.2006.02983.x.
37. 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(4):494–500. doi:10.1007/s00464-003-9267-6.
38. Campos GM, Peters JH, DeMeester TR, et al. Multivariate analysis of factors predicting outcome after laparoscopic Nissen fundoplication. J Gastrointest Surg 1999;3:292–300. doi:10.1016/S1091-255X(99)80071-7.
39. Khajanchee YS, Hong D, Hansen PD, Swanstrom LL. Outcomes of antireflux surgery in patients with normal preoperative 24-hour pH test results. Am J Surg 2004;187(5):599–603. doi:10.1016/j.amjsurg.2004.01.010.
40. Shi G, Bruley dV, Scarpignato C, et al. Reflux related symptoms in patients with normal oesophageal exposure to acid. Gut 1995;37(4):457–464. doi:10.1136/gut.37.4.457.
41. Barlow WJ, Orlando RC. The pathogenesis of heartburn in nonerosive reflux disease: a unifying hypothesis. Gastroenterology. 2005;128(3):771–778. doi:10.1053/j.gastro.2004.08.014.
42. Bradley LA, Richter JE, Pulliam TJ, et al. The relationship between stress and symptoms of gastroesophageal reflux: the influence of psychological factors. Am J Gastroenterol 1993;88 (1):11–19.
43. Johnston BT, Lewis SA, Collins JS, et al. Acid perception in gastro-oesophageal reflux disease is dependent on psychosocial factors. Scand J Gastroenterol 1995;30(1):1–5. doi:10.3109/00365529509093228.
44. Norton GR, Norton PJ, Asmundson GJ, et al. Neurotic butterflies in my stomach: the role of anxiety, anxiety sensitivity and depression in functional gastrointestinal disorders. J Psychosom Res 1999;47(3):233–240. doi:10.1016/S0022-3999(99)00032-X.
45. Avidan B, Sonnenberg A, Giblovich H, Sontag SJ. Reflux symptoms are associated with psychiatric disease. Aliment Pharmacol Ther 2001;15(12):1907–1912. doi:10.1046/j.1365-2036.2001.01131.x.
46. Trimble KC, Pryde A, Heading RC. Lowered oesophageal sensory thresholds in patients with symptomatic but not excess gastro-oesophageal reflux: evidence for a spectrum of visceral sensitivity in GORD. Gut 1995;37(1):7–12. doi:10.1136/gut.37.1.7.
47. Achem SR. Endoscopy-negative gastroesophageal reflux disease. The hypersensitive esophagus. Gastro Clin Nth Am 1999;28 (4):893–904. doi:10.1016/S0889-8553(05)70096-0.

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ORIGINAL ARTICLE

Risk Prediction Scores for Postoperative Mortality After Esophagectomy: Validation of Different Models

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Abstract
Background Different prediction models for operative mortality after esophagectomy have been developed. The aim of this study is to independently validate prediction models from Philadelphia, Rotterdam, Munich, and the ASA.
Methods The scores were validated using logistic regression models in two cohorts of patients undergoing esophagectomy for cancer from Switzerland (n=170) and Australia (n=176).
Results All scores except ASA were significantly higher in the Australian cohort. There was no significant difference in 30-day mortality or in-hospital death between groups. The Philadelphia and Rotterdam scores had a significant predictive value for 30-day mortality (p=0.001) and in-hospital death (p=0.003) in the pooled cohort, but only the Philadelphia score had a significant prediction value for 30-day mortality in both cohorts. Neither score showed any predictive value for in-hospital death in Australians but were highly significant in the Swiss cohort. ASA showed only a significant predictive value for 30-day mortality in the Swiss. For in-hospital death, ASA was a significant predictor in the pooled and Swiss cohorts. The Munich score did not have any significant predictive value whatsoever.
Conclusion None of the scores can be applied generally. A better overall predictive score or specific prediction scores for each country should be developed.

No score generally applicable

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Keywords Risk prediction models · Esophagectomy · In-hospital death · 30-day mortality

Introduction

Surgical resection is the cornerstone of curative treatment for esophageal cancer. Despite advances in surgical, anesthetic, and intensive care techniques, hospital mortality is still substantial, with rates reported to be up to 14%.[1] Different approaches to decrease the perioperative morbidity and mortality have been used, such as the introduction of minimally invasive surgical techniques, thoracic epidural analgesia, standardized perioperative pathways, and preoperative selection of patients.[2,3] As esophageal cancer usually occurs in the elderly population and many of these individuals have significant comorbidities, careful preoperative assessment of fitness and subsequent selection of appropriate surgical candidates are important steps which can improve short-term outcomes for individuals undergoing this surgery.

A number of studies have investigated risk factors for in-hospital mortality following esophagectomy. Age, comorbidity, and pulmonary status have been identified as independent risk factors.[4,5] Hospital volume has also been shown to significantly influence mortality rates, with 50% lower rates in high-volume centers.[6] Several risk prediction models have been developed, but only a minority of them have been validated in independent cohorts.

The Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (POSSUM) has been adjusted to accurately predict death from gastric and esophageal surgery (O-POSSUM).[7] Three subsequent studies evaluated the O-POSSUM and showed a poor goodness of fit of the model and substantial overprediction of postoperative death using independent patient cohorts worldwide.[8–10]

Other more simplified and practical prediction models have been proposed. Steyerberg et al.[11] from Rotterdam, the Netherlands, developed a simple score which included age, comorbidity, hospital volume, and whether the patient received neoadjuvant treatment. Very similar, but without using neoadjuvant treatment a as variable, is the recently described prediction model of Ra et al.[12] from Philadelphia. Siewert's group[13] in Munich proposed a score based on pulmonary, hepatic, and cardiac function as well as on general status. The American Society of Anesthesiologists (ASA) score has also been shown to be a reliable predictor of mortality.[14] All of these models accurately predicted postoperative hospital death in the initial validation studies. However, to our knowledge, these models have not been validated in independent cohorts of esophageal cancer patients. Hence, the aim of our study was to investigate the prognostic value of these four prediction models (Rotterdam, Philadelphia, Munich, ASA; Table 1) in two geographically different cohorts, as well as in a pooled cohort of patients undergoing esophagectomy for cancer.

Patients and Methods

Two cohorts of patients undergoing esophagectomy for cancer from Switzerland and Australia were used to assess the validity of four different prediction models. The Swiss cohort of patients consisted of a consecutive series of 170 patients who underwent esophagectomy at one large teaching hospital in Zurich from 1990 to 2007. The Australian cohort consisted of a consecutive series of 176 patients operated in Adelaide, South Australia between 1999 and 2007 at two university hospitals and two private hospitals. All patients underwent surgery using a transthoracic approach, and in all patients the stomach was used as conduit for reconstruction. The anastomosis was either performed with a stapled technique or hand-sewn, according to the individual surgeon's preference. In both countries, patients with advanced tumors (T3 or N+) usually received neoadjuvant treatment. This usually entailed two cycles of 5-fluorouracil and cisplatin in combination with 45 to 50 Gy of radiotherapy. Surgery was performed 4 to 8 weeks after the completion of any pretreatment.

For both cohorts, data (demographics, comorbidity, tumor stage, morbidity, mortality) were retrospectively retrieved from the case notes for patients undergoing surgery between 1990 and 1998. From 1999 onwards, data were prospectively retrieved and stored in databases in both sites. Both 30-day mortality and in-hospital mortality outcomes were determined.

For all individual patients, the Rotterdam, Philadelphia, and ASA scores were calculated, and no data were missing. The Munich score includes an aminopyrine breath test to classify hepatic function as either normal, compromised, or severely compromised. As this test was not performed in either the Swiss or the Australian cohort, hepatic status was assessed using routine clinical data such as liver function tests (alanine aminotransferase, ALT, aspartate aminotransferase, AST, gamma-glutamyl transferase, GGT) in preoperative blood samples as well as radiological findings. ALT was considered to be pathologic if serum levels exceeded 50 iU/l, AST if more than 40 iU/l, and GGT if more than 60 iU/l. Routine imaging with computed tomography was performed for all patients. Evidence of liver cirrhosis or portal hypertension was also noted. Patients were classified as having normal hepatic function when neither blood tests nor imaging showed any evidence of liver disease. If liver function tests were elevated or imaging showed evidence of mild cirrhosis without portal hypertension, hepatic function was considered to be compromised. No patients with severe cirrhosis or portal hypertension underwent esophagectomy in either of these cohorts.

Additionally, the Munich score uses the Karnofsky index to assess the general status of the patient. This index was not initially part of the prospective databases, and hence for this aspect the general physical status was assessed retrospectively using the clinical notes. Theses results were then adapted to the Karnofsky score. Obesity was defined as a body mass index (BMI) above 30 kg/m^2.

The study was approved by the responsible clinical research ethics committees in the two countries.

Statistical Analysis

Comparison of demographic and clinical data between the two patient cohorts (Swiss and Australia) was undertaken using Chi-squared tests for categorical data and Student's *t*

Table 1 The Four Validated Prediction Scores

Variable	Definition of variable	Points
Rotterdam score [11]		
Age (years)	50	−1
	65	0
	80	1
Comorbidity	Pulmonary	1
	Cardiovascular	1
	Diabetes	1
	Hepatic	1
	Renal	1
Neoadjuvant therapy	Radiotherapy	1.5
	Chemoradiotherapy	1
Hospital volume	Low (≤1)	0
	Intermediate (1.1-2.5)	−0.5
	High (≥2.6)	−1.5
	Very high (≥50)	−2
Philadelphia score [12]		
Age	65−69	0
	70−79	1
	80+	2
Hospital volume	High	0
	Medium	2
	Low	2
Charlson score	0	0
	1	0
	≥2	2
Munich score [13]		
Pulmonary function (weighting factor 2)	Normal (vital capacity >90% and PaO2 >70 mmHg)	1
	Compromised (vital capacity <90% or PaO_2 <70 mmHg)	2
	Severely compromised (vital capacity <90% and PaO_2 <70 mmHg)	3
Hepatic function (weighting factor 2)	Normal (aminopyrine breath test >0.4)	1
	Compromised (aminopyrine breath test <0.4, no cirrhosis)	2
	Severely compromised (cirrhosis)	3
Cardiac function based on cardiologists impression (weighting factor 3)	Normal (normal risk for major surgery)	1
	Compromised (increased risk for major surgery)	2
	Severely compromised (high risk for major surgery)	3
General status (weighting factor 4)	Normal (Karnofsky index >80% and good cooperation)	1
	Compromised (Karnofsky index ≤80% or poor cooperation)	2
	Severely impaired (Karnofsky index ≤80% and poor cooperation)	3
American Society of Anesthesiologists (ASA) score [14]		
	Normal healthy patient	1
	Patient with mild systemic disease	2
	Patient with severe systemic disease	3
	Patient with severe systemic disease that is a constant threat to life	4
	Moribund patient who is not expected to survive without the operation	5
	Declared brain-dead patient whose organs are removed for donor purposes	6

tests or Mann–Whitney *U* tests for continuous data. Since all four prediction scores were skewed, correlation between them was assessed by Spearman rank correlation. Logistic regression was used to calculate whether each score could predict 30-day mortality, in-hospital mortality, or prolonged ventilation. The latter was used as a marker of severe morbidity. Prolonged ventilation was defined as ventilation required for more than 72 h.

Models were developed for each of the three-outcome and four-risk-score combinations, i.e., 12 models in total. For each combination, the initial model included the score, country, and score–country interaction term. If the latter was statistically significant, separate models were developed for each country collection with no attempt to pool the data across the two countries. The Hosmer and Lemeshow test was performed to evaluate

Table 2 Basic Descriptives Between the Swiss and Australian Cohorts

		Australians $N=176$	Swiss $N=170$	p value
Age (SEM)		62.2 (0.7)	62.5 (0.8)	0.814[a]
Sex	Male	137 (77.8%)	147 (86.5%)	0.036[b]
	Female	39 (22.2%)	23 (13.5%)	
Comorbidity	Yes	110 (62.5%)	76 (44.7%)	0.001[b]
	No	65 (37.5%)	94 (55.3%)	
Obesity	Yes	30 (17.0%)	20 (11.8%)	0.163[b]
	No	146 (83.0%)	150 (88.2%)	
Neoadjuvant treatment	Yes	96 (54.5%)	44 (25.9%)	<0.001[b]
	No	80 (45.5%)	126 (74.1%)	
Type	Adeno	134 (76.1%)	125 (73.5%)	0.010[b]
	SCC	29 (16.5%)	42 (24.7%)	
	Other	13 (7.4%)	3 (1.8%)	

SEM standard error of mean
[a] Students t test
[b] Chi-squared test

the goodness of fit of each logistic regression model. Nagelkerke's R-squared test was used to determine the percentage of variability in outcome explained by the model.

Statistical significance for each model was set at $p<0.05$. Statistical analyses were performed with SPSS® version 16 for Windows. For all outcomes, a logistic regression of a binary response variable (Y) on a continuous normally distributed variable (X) with a sample size of 289 observations for in-hospital death, 425 observations for 30-day mortality, and 154 observations for prolonged ventilation achieved 80% power at a 0.05 significance level. This detected a change in probability ($Y=1$) from the value of 0.060 (6% mortality) at the mean of X to 0.113 when X is increased to one standard deviation above the mean. This change corresponds to an odds ratio of 2.000.

Results

The pooled cohort included 346 patients. The two cohorts from Switzerland ($n=170$) and Australia ($n=176$) did not differ in age or the percentage of obese patients. There were, however, significant differences in some other patient or tumor characteristics, as shown in Table 2. All scores were significantly different between the cohorts, with the Australian cohort having higher scores except for ASA (Table 3). There were no significant differences in 30-day mortality, in-hospital death, or the frequency of prolonged ventilation between groups (Table 4). There was a good correlation between the Philadelphia and Rotterdam scores, whereas no correlation to or in between the other scores was detected (Table 5).

Pooling was allowed in all scores and outcomes (Table 6). The Philadelphia and Rotterdam scores had a significant predictive value for 30-day mortality and in-hospital death in the pooled cohort. After stratifying into the two countries, only the Philadelphia score had a significant prediction value for 30-day mortality in both cohorts. The Rotterdam score had no significant predictive value for 30-day mortality in Australians and neither score showed any predictive value for in-hospital death in Australians. Both scores were highly significant in the Swiss cohort.

The Munich score did not have any significant predictive value for operative mortality in the pooled data or in any of the cohorts. ASA showed only a significant predictive value for 30-day mortality in the Swiss but not in the pooled or Australian cohorts. For in-hospital death, ASA was a significant predictor in the pooled and Swiss cohorts.

Concerning prediction of prolonged ventilation as an indicator for severe morbidity, the Munich score had a significant predictive value in the Australians but neither in the pooled or Swiss cohorts. ASA predicted prolonged hospitalization only in the pooled cohort but not in the country subgroups.

Table 3 Results of the Four Scores in the Two Different Cohorts

		Philadelphia score	Rotterdam score	Munich score	ASA score
Australians ($n=176$)	Median	1.00	−0.205	11.0	2.0
	Mean rank	184.3	187.3	187.7	162.0
	Minimum	0	−2.5	4	1
	Maximum	5	3.0	16	3
Swiss ($n=170$)	Median	1.00	−0.500	11.0	2.0
	Mean rank	162.4	158.8	158.8	185.4
	Minimum	0	−2.5	6	1
	Maximum	4	2.5	16	3
p value[a]		0.030	0.008	0.003	0.012

ASA American Society of Anesthesiologists
[a] Monte Carlo Exact Mann–Whitney U test

Table 4 30-day Mortality, In-Hospital Death, and Incidence of Prolonged Ventilation in the Two Cohorts

		Australians (n=176)	Swiss (n=170)	p value[a]
30-day mortality	Yes	8 (4.5%)	7 (4.1%)	1.000
	No	168 (95.5%)	163 (95.9%)	
In-hospital mortality	Yes	14 (8.0%)	8 (4.7%)	0.272
	No	162 (92.0%)	162 (95.3%)	
Prolonged ventilation	Yes	20 (11.4%)	26 (15.3%)	0.344
	No	156 (88.6%)	144 (84.7%)	

[a] Chi-squared test

Discussion

Analysis of the pooled data in this study demonstrated that two of the risk prediction scores, Philadelphia and Rotterdam, correlated with operative mortality following esophagectomy in this group of esophageal cancer patients. The predictive value was highly significant for the Swiss population, whereas the scores were only marginally or not significant in the Australian cohort. The ASA score only predicted operative mortality for the Swiss cohort but not for the Australian cohort. The Munich score had no significant predictive value in either patient cohort.

The Rotterdam score and the Munich score were developed using logistic regression analysis in a primary cohort and then validation in other cohorts. Both scores showed good agreement between the predicted risks and the observed risks.[11,13] The Philadelphia and ASA scores were developed again with logistic regression, but these scores were not validated with other cohorts. Both models accurately predicted postoperative mortality in initial reports.[12,14] The time period over which the patients were collected was long for three of the scores (22 years in the Rotterdam score, 14 years in the Munich score, and 15 years in the ASA score), whereas the data for the validation of the Philadelphia score were collected over a 6-year period.

There were some significant differences between the two cohorts of patients we analyzed in our study and this might explain some of our findings. The Australian cohort had higher Philadelphia, Rotterdam, and Munich scores but a lower ASA score. The Rotterdam score includes comorbidity and neoadjuvant treatment, both of which were more prevalent in the Australian cohort, thus explaining the higher scores. The higher Munich score can be again explained by the more frequent comorbidity seen in the Australian cohort. The significant difference in ASA scores is related to the number of patients with ASA score of 1 (Australia 38 vs. Switzerland 11). The reason for this difference is unclear. A possible explanation is that the ASA score is defined by the individual anesthetist, and this might be influenced by differences in clinical assessment.

The Munich score in this study was not done with an aminopyrine breath test. However, we did assess the hepatic function by other means, and it was not difficult to classify patients as having either a normal or compromised liver function. Furthermore, no patients with significant liver disease underwent surgery in either country. It is therefore likely that all patients were adequately assessed for this criterion.

Concerning prolonged ventilation as a marker of severe morbidity, the ASA score was a significant predictor in the pooled cohort, and the Munich score was also predictive in the Australian cohort. However, cautious interpretation of these results is necessary as all scores were primarily developed to predict hospital mortality. The prediction of morbidity with the ASA score as demonstrated by Sauvanet et al.[14] is only reproduced in our pooled cohort not in the subcohorts. This might indicate that a large number of patients are necessary to reach statistical significance, and for this reason the true prediction value was not established in the individual cohorts. Sauvanet et al. evaluated the ASA score in a group of over 1,000 patients. There were sufficient patients in our pooled cohort of patients to ensure sufficient statistical power of the study for valid assessment of all other risk assessment tools.

Table 5 Spearman Rank Correlation Between Scores Stratified According to Country

		Philadelphia score	Rotterdam score	Munich score	ASA score
Australians (n=176)	Philadelphia score	1.000	0.822	0.581	0.345
	Rotterdam score	0.822	1.000	0.643	0.399
	Munich score	0.581	0.643	1.000	0.483
	ASA score	0.345	0.399	0.483	1.000
Swiss (n=170)	Philadelphia score	1.000	0.815	0.609	0.264
	Rotterdam score	0.815	1.000	0.561	0.277
	Munich score	0.609	0.561	1.000	0.379
	ASA score	0.264	0.277	0.379	1.000

ASA American Society of Anesthesiologists

Table 6 Results of the Logistic Regression Analyses

		Australians (n=176)	Swiss (n=170)	Pooled (n=346)
30-day mortality				
Philadelphia score	p value	0.045	0.012	0.001
	Hosmer and Lemeshow test	0.825	0.248	0.735
	Nagelkerke R-squared	0.068	0.125	0.092
Rotterdam score	p value	0.269	0.003	0.003
	Hosmer and Lemeshow test	0.608	0.465	0.266
	Nagelkerke R-squared	0.022	0.207	0.085
Munich score	p value	0.959	0.188	0.431
	Hosmer and Lemeshow test	0.345	0.989	0.634
	Nagelkerke R-squared	<0.001	0.033	0.006
ASA score	p value	0.661	0.019	0.065
	Hosmer and Lemeshow test	0.601	0.867	0.747
	Nagelkerke R-squared	0.004	0.135	0.034
In-hospital death				
Philadelphia score	p value	0.068	0.004	0.001
	Hosmer and Lemeshow test	0.924	0.232	0.784
	Nagelkerke R-squared	0.042	0.158	0.082
Rotterdam score	p value	0.088	0.002	<0.001
	Hosmer and Lemeshow test	0.681	0.688	0.064
	Nagelkerke R-squared	0.039	0.224	0.098
Munich score	p value	0.611	0.090	0.490
	Hosmer and Lemeshow test	0.415	0.958	0.035
	Nagelkerke R-squared	0.003	0.050	0.004
ASA score	p value	0.271	0.008	0.021
	Hosmer and Lemeshow test	0.869	0.880	0.270
	Nagelkerke R-squared	0.016	0.163	0.043
Prolonged ventilation				
Philadelphia score	p value	0.500	0.070	0.095
	Hosmer and Lemeshow test	0.304	0.771	0.286
	Nagelkerke R-squared	0.005	0.032	0.014
Rotterdam score	p value	0.535	0.067	0.105
	Hosmer and Lemeshow test	0.965	0.016	0.174
	Nagelkerke R-squared	0.004	0.034	0.014
Munich score	p value	0.029	0.476	0.060
	Hosmer and Lemeshow test	0.083	<0.001	<0.001
	Nagelkerke R-squared	0.055	0.005	0.019
ASA score	p value	0.060	0.060	0.006
	Hosmer and Lemeshow test	0.530	0.323	0.024
	Nagelkerke R-squared	0.042	0.037	0.041

p value, goodness-of-fit measure, and percentage of variability in outcome explained by the model for 30-day mortality, in-hospital death, and prolonged ventilation in the two collections and in the pooled data (where pooling was allowed after testing for country interaction). The first column shows the score used for prediction. The p value refers to the statistical significance of the regression coefficient. A Hosmer and Lemeshow statistic of $p>0.05$ demonstrates a good fit

The female-to-male ratio was different in our two cohorts. To our knowledge, only one study has identified sex as an independent predictor of death, with women having an odds ratio of 1.5 for inpatient death.[15] The majority of studies have not shown any influence of sex on hospital mortality.[1,4,12,16–18] However, a difference in outcome between histological subtypes has been suggested. The percentage of adenocarcinomas was very similar in both of our groups. One previous study has shown a higher operative mortality for patients with squamous cell cancer, but this has not been supported by other studies.[18,19] Many studies, however, do report long-term survival differences for different histological subtypes.[18–22]

Operative mortality and the frequency of prolonged ventilation were similar in both cohorts and comparable to other published series.[17,18,23,24] A trend towards higher in-hospital mortality in the Australian cohort was seen, whereas 30-day mortality rates were similar. In-hospital mortality may better reflect general comorbidities, as

patients with surgical complications may die earlier, whereas pulmonary, cardiac, and renal impairment may lead to a prolonged postoperative course with slow deterioration and ultimately death after more than 30 days of hospitalization.

There was a good correlation between the Philadelphia and Rotterdam risk scores with a correlation coefficient of over 0.8. This is not surprising as these models used similar variables. Interestingly, the Philadelphia score does not include neoadjuvant treatment, yet this variable was not even evaluated in the primary regression analysis. Whether neoadjuvant treatment has an influence on perioperative mortality and morbidity is unclear. A number of studies did not detect higher operative mortality.[25–27] A meta-analysis of randomized controlled trials showed a trend toward higher operative mortality in pretreated patients (odds ratio of 1.72; 0.96, 3.07 95% confidence interval, $p=0.07$).[28] The Rotterdam study demonstrated a significant influence for neoadjuvant treatment, chemotherapy alone, or radiochemotherapy. The Munich score includes only comorbidity and performance status of the patient. As this score was developed 1998, before the era of wide application of neoadjuvant treatment, it may be outdated by now. This is reflected by the poor predictive value in all cohorts, including the pooled data. ASA score, the simplest and oldest of the four validated scores, had no correlation to the other scores at all.

The most surprising finding of this validation study is that the two most recently developed scores, Philadelphia and Rotterdam, had different predictive values for operative mortality in the two country cohorts. Both scores were excellent outcome predictors for the Swiss cohort but not for the Australian cohort. This suggests that these scores cannot be reliably applied to all centers undertaking esophageal cancer surgery.

The difference in predictive value might be explained by differences in perioperative management, differences in the medical systems, and the fact that all Swiss patients were operated in a single institution whereas the Australian patients were operated in two university hospitals and two private hospitals, albeit by members of the same surgical group. The basic surgical approaches and postoperative management guidelines in these two cohorts were similar. In contrast to the Australian medical system, where a number of consultant surgeons work in different public and private institutions, the Swiss system has full-time consultant surgeons in one institution only. This might result in more tightly supervised postoperative management. Hospital and surgeon volume has been shown to influence outcome.[15,29–31] In our study, all hospitals met previous definitions of high-volume centers.

The patients in the Swiss cohort were collected over a time period of 17 years compared to 8 years in the Australian cohort. This might have influenced the results. However, the number of surgeons performing esophagectomies in the Swiss cohort was stable during that period and all procedures were supervised by the same head of department.

The Munich score had no significant predictive value and poor goodness of fit for operative mortality in both cohorts as well as in the pooled data. The main difference between the Philadelphia and Rotterdam scores and the one from Munich is the variety of variables used. The Munich score concentrates on comorbidity and general performance status whereas the two other scores include variables such as age, neoadjuvant treatment, and hospital volume. The range of variables having an impact on hospital mortality discussed in the literature is very wide and to some extent controversial. Age, sex, race, hospital volume, neoadjuvant treatment, comorbidity, cancer stage, smoking, pulmonary function (FEV 1, FVC), blood loss, and localization of the tumor have all been shown to significantly influence hospital death.[1,4,11–15,17,18] This diversity of possible factors might render it difficult to develop a uniformly applicable score.

The development of risk prediction models in esophageal surgery is important for two reasons: it allows improvement of outcome by appropriate selection of patients for surgery and it enables auditing results in comparison to other institutions, countries, and published series. The ideal prediction score should be simple to apply, and it should reproducible across different institutions and patient cohorts. This generalization has not yet been achieved with these four scores

Conclusion

The results of this study show that none of the scores can be applied generally to all institutions undertaking esophagectomy and that a better overall predictive score or specific prediction scores for each country might need to be developed.

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References

1. McCulloch P, Ward J, Tekkis PP for the ASCOT group of surgeons. Mortality and morbidity in gastro-oesophageal cancer surgery: initial results of ASCOT multicentre prospective cohort study. BJM 2003;327:1192–7. doi:10.1136/bmj.327.7425.1192.
2. Low DE, Kunz S, Schembre D, Otero H, Malpass T, His A et al. Esophagectomy—it's not just about mortality anymore:

standardized perioperative clinical pathways improve outcomes in patients with esophageal cancer. J Gastrointest Surg 2007;11:1395–402. doi:10.1007/s11605-007-0265-1.
3. Luketich JD, Alvelo-Rivera M, Buenaventura PO, Christie NA, McCaughan JS, Litle VR et al. Minimally invasive esophagectomy. Outcomes in 222 patients. Ann Surg 2003;238:486–95.
4. Liu JF, Watson DI, Devitt PG, Mathew G, Myburgh J, Jamieson GG. Risk factor analysis of postoperative mortality in oesophagectomy. Dis Esophagus 2000;13:130–135. doi:10.1046/j.1442-2050.2000.00099.x.
5. Schroeder W, Bollschweiler E, Kossow C, Hoelscher AH. Preoperative risk analysis—a reliable predictor of postoperative outcome after transthoracic esophagectomy. Langenbecks Arch Surg 2006;391:455–460. doi:10.1007/s00423-006-0067-z.
6. Dimick JB, Wainess RM, Upchurch GR Jr, Iannettoni MD, Orringer MB. National trends in outcomes for esophageal resection. Ann Thorac Surg 2005;79:212–216. doi:10.1016/j.athoracsur.2004.06.044.
7. Tekkis PP, McCulloch P, Poloniecki JD, Prytherch DR, Kessaris N, Steger AC. Risk-adjusted prediction of operative mortality in oesophagogastric surgery with O-POSSUM. Br J Surg 2004;91:288–295. doi:10.1002/bjs.4414.
8. Lai F, Kwan TL, Yuen WC, Wai A, Siu YC, Shung E. Evaluation of various POSSUM models for predicting mortality in patients undergoing elective oesophagectomy for carcinoma. Br J Surg 2007;94:1171–1178. doi:10.1002/bjs.5793.
9. Lagarde SM, Maris AK, de Castro SM, Busch OR, Obertop H, van Lanschot JJ. Evaluation of O-POSSUM in predicting in-hospital mortality after resection for oesophageal cancer. Br J Surg 2007;94:1521–1526. doi:10.1002/bjs.5850.
10. Nagabhushan JS, Srinath S, Weir F, Angerson WJ, Sugden BA, Morran CG. Comparison of P-POSSUM and O-POSSUM in predicting mortality after oesophagogastric resections. Postgrad Med J 2007;83:355–358. doi:10.1136/pgmj.2006.053223.
11. Steyerberg EW, Neville BA, Koppert LB, Lemmens VE, Tilanus HW, Coeberg JW et al. Surgical mortality in patients with esophageal cancer: development and validation of a simple risk score. J Clin Oncol 2006;24:4277–4284. doi:10.1200/JCO.2005.05.0658.
12. Ra J, Paulson EC, Kucharczuk J, Armstrong K, Wirtalla C, Rapaport-Kelz R et al. Postoperative mortality after esophagectomy for cancer: development of a preoperative risk prediction model. Ann Surg Oncol 2008;15:1577–1584. doi:10.1245/s10434-008-9867-4.
13. Bartels H, Stein HJ, Siewert JR. Preoperative risk analysis and postoperative mortality of oesophagectomy for resectable oesophageal cancer. Br J Surg 1998;85:840–844. doi:10.1046/j.1365-2168.1998.00663.x.
14. Sauvanet A, Mariette C, Thomas P, Lozac'h P, Segol P, Tiret E et al. Mortality and morbidity after resection for adenocarcinoma of the gastrointestinal junction: predictive factors. J Am Coll Surg 2005;201:253–262. doi:10.1016/j.jamcollsurg.2005.02.002.
15. Rodgers M, Jobe BA, O'Rourke RW, Sheppard B, Diggs B, Hunter JG. Case volume as a predictor of inpatient mortality after esophagectomy. Arch Surg 2007;142:829–837. doi:10.1001/archsurg.142.9.829.
16. Karl RC, Schreiber R, Boulware D, Baker S, Coppola D. Factors affecting morbidity, mortality and survival in patients undergoing Ivor Lewis esophagogastrectomy. Ann Surg 2000;231:635–643. doi:10.1097/00000658-200005000-00003.
17. Law S, Wong KH, Kwok KF, Chu KM, Wong J. Predictive factors for postoperative pulmonary complications and mortality after esophagectomy for cancer. Ann Surg 2004;240:791–800. doi:10.1097/01.sla.0000143123.24556.1c.
18. Abunasra H, Lewis S, Beggs L, Duffy J, Beggs D, Morgan E. Predictors of operative death after oesophagectomy for carcinoma. Br J Surg 2005;92:1029–1033. doi:10.1002/bjs.5049.
19. Alexiou C, Khan OA, Black E, Field ML, Onyeaka P, Beggs L et al. Survival after esophageal resection for carcinoma: the importance of the histologic cell type. Ann Thorac Surg 2006;82:1073–1077. doi:10.1016/j.athoracsur.2006.03.012.
20. Siewert RJ, Stein HJ, Feith M, Bruecher BLDM, Bartels H, Fink U. Histologic tumor type is an independent prognostic parameter in esophageal cancer: lessons from more than 1000 consecutive resections at a single center in the western world. Ann Surg 2001;234:360–369. doi:10.1097/00000658-200109000-00010.
21. Orringer MB, Marshall B, Iannettoni MD. Transhiatal esophagectomy: clinical experience and refinements. Ann Surg 1999;230:392–403. doi:10.1097/00000658-199909000-00012.
22. Khan OA, Alexiou C, Soomro I, Duffy JP, Morgan WE, Beggs FD. Pathological determinants of survival in node-negative oesophageal cancer. Br J Surg 2004;91:1586–1591. doi:10.1002/bjs.4778.
23. Hulscher JB, van Sandick JW, de Boer AG, Wijnhoven BP, Tijssen JG, Fockens P et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med 2002;347:1662–1669. doi:10.1056/NEJMoa022343.
24. Wijnhoven BP, Tran KT, Esterman A, Watson DI, Tilanus HW. An evaluation of prognostic factors and tumor staging of resected carcinoma of the esophagus. Ann Surg 2007;245:717–725. doi:10.1097/01.sla.0000251703.35919.02.
25. Urba SG, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol 2001;19:305–13.
26. Mariette C, Piessen G, Lamblin A, Mirabel X, Adenis A, Triboulet JP. Impact of preoperative radiochemotherapy on postoperative course and survival in patients with locally advanced squamous cell oesophageal carcinoma. Br J Surg 2006;93:1077–1083. doi:10.1002/bjs.5358.
27. Rice DC, Correa AM, Vaporciyan AA, Sodhi N, Smythe WR, Swisher SG et al. Preoperative chemoradiotherapy prior to esophagectomy in elderly patients is not associated with increased morbidity. Ann Thorac Surg 2005;79:391–397. doi:10.1016/j.athoracsur.2004.08.045.
28. Urschel JD, Vasan H. A meta-analysis of randomized controlled trials that compared neoadjuvant chemoradiation and surgery to surgery alone for resectable esophageal cancer. Am J Surg 2003;185:538–543. doi:10.1016/S0002-9610(03)00066-7.
29. Kuo EY, Chang Y, Wright CD. Impact of hospital volume on clinical and economic outcomes for esophagectomy. Ann Thorac Surg 2001;72:1118–1124. doi:10.1016/S0003-4975(01)02962-9.
30. Swisher SG, Deford L, Merriman KW, Walsh GL, Smythe R, Vaporicyan A et al. Effect of operative volume on morbidity, mortality and hospital use after esophagectomy for cancer. J Thorac Cardiovasc Surg 2000;119:1126–1132. doi:10.1067/mtc.2000.105644.
31. Santin B, Kulwicki A, Price P. Mortality rate associated with 56 consecutive esophagectomies performed at a low-volume hospital: is procedure volume as important as we are trying to make it. J Gastrointest Surg 2008;12:1346–1350. doi:10.1007/s11605-008-0550-7.

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ORIGINAL ARTICLE

Mode of Lymphadenectomy and Surgical Outcome of Upper Thoracic Esophageal Squamous Cell Carcinoma

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Abstract
Introduction Only a few studies have evaluated the impact of clinicopathological variables and cervical lymphadenectomy on survival in patients with upper thoracic esophageal squamous cell carcinoma (SCC).
Material and Methods From 1960 to 2005, a total of 167 consecutive patients with upper thoracic esophageal SCC underwent esophagectomy. Of these patients, 108 underwent surgery between 1960 and 1989 and 59 between 1990 and 2005. A total of 65 patients were treated with cervical lymphadenectomy. Univariate and multivariate analyses were performed to evaluate the impact of clinicopathological variables on surgical outcome and possible predictors for cervical lymph node metastasis.
Results and Discussion The overall 5-year survival of the later period was significantly better than the former period (43% vs 13%, $p<0.01$). Based on Cox's proportional hazards model, T3/T4 tumors, thoracic or abdominal node metastasis, venous invasion, residual cancer, absence of cervical lymphadenectomy, and hospital morbidity were independent risk factors for reduced survival in patients with upper thoracic esophageal SCC. A total of 31 (48%) of 65 patients who underwent cervical lymphadenectomy showed positive nodes in cervical field.
Conclusion Based on logistic regression analysis, T3/T4 tumors and recurrent nerve node metastasis were possible risk factors for cervical node metastasis.

Keywords Esophageal cancer · Squamous cell carcinoma · Upper thoracic esophageal carcinoma · Lymph node · Prognosis

This manuscript retrospectively analyzed prognostic factors for surgical outcome in patients with upper thoracic esophageal squamous cell carcinoma. Impact of the mode of lymphadenectomy and clinicopathological factors on survival are discussed.

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Abbreviations

SCC	squamous cell carcinoma
2FLD	two-field lymph node dissection
3FLD	three-field lymph node dissection

Introduction

Although upper thoracic tumors frequently spread to cervical lymph nodes, cervical lymph node metastasis is regarded as a distant metastasis and classified as stage IV.[1] In Japan, three-field lymph node dissection (3FLD),[2,3] i.e., neck, mediastinal, and abdominal lymphadenectomy, has been introduced to improve the long-term survival of such patients through 1980s. Nevertheless, despite improved surgical techniques[4] and adjuvant therapy,[5–7] early recurrence is still frequently observed in patients with upper thoracic tumors.[8] Because only a few reports have analyzed the distribution of positive lymph nodes and prognostic

factors for patients with upper thoracic esophageal carcinoma,[8–10] it is still unclear which patients should be treated with cervical lymph node dissection. Therefore, we retrospectively analyzed a consecutive series of 167 patients with primary upper thoracic esophageal SCC in order to analyze surgical outcome. Then, we focused on 65 patients treated with 3FLD in order to analyze the risk factors for cervical lymph node metastasis and survival.

Material and Methods

Patients and Surgical Procedure

Between January 1960 and the end of 2005, 167 patients were surgically treated for primary upper thoracic esophageal squamous cell carcinoma (SCC) at the Department of Surgery, Chiba University Hospital (Chiba, Japan). Patients were classified pathologically according to the pTNM/UICC classification.[1]

Before 1980, only paraesophageal lymph node dissection was performed. After 1980, thoracic lymph node dissection was performed according to standard procedures that have been described previously.[2,3] This procedure, called a "D2 lymphadenectomy" according to the Japanese classification of esophageal carcinoma,[11] involves dissecting the non-paraesophageal nodes. The patients who showed positive finding by neck ultrasonography received cervical lymphadenectomy. After 1990, cervical lymph nodes were routinely dissected in patients under 70 years of age.

A total of 96 patients underwent curative resection (R0), and a total of 65 patients were treated with 3FLD. Of these 65 patients, 31 (48%) were diagnosed pathologically with cervical lymph node metastases. After surgery, all patients underwent clinical examinations and imaging studies on a regular basis either until death or until the end of 2007. All clinicopathological data, including disease recurrence and treatment, were collected and maintained monthly at the Department of Surgery, Chiba University Hospital (Chiba, Japan).

Preoperative Staging Techniques

Standard staging techniques before 1980 were limited to esophagography and an esophagoscope. After 1980, standard staging techniques included endoscopic ultrasonography, computed tomography, and neck ultrasonography. After 1990, positron emission tomography was introduced for patients with advanced tumors to screen for distant metastases or to predict malignant potential. We have not performed thoracoscopy or laparoscopy.[4]

Perioperative Adjuvant Therapy

Over the years, both postoperative management and postoperative adjuvant therapy for esophageal cancer have gradually improved. Before 1980, preoperative radiation therapy was usually undertaken for clinical T2–T4 tumors.[12] Postoperative adjuvant chemotherapy was administered to all eligible patients according to the protocols of the Japan Esophageal Oncology Group, which conducted three consecutive randomized controlled trials after 1980.[5–7] Preoperative adjuvant therapy was administered as follows: one patient received chemotherapy, 95 patients received radiation therapy, and 27 patients received chemoradiation therapy. Postoperative adjuvant therapy was administered as follows: 19 patients received radiation therapy and 21 patients received chemotherapy. Thus, a total of 49 patients received perioperative chemotherapy.

Statistical Analysis

Because postoperative care and treatment modalities for recurrent disease have gradually improved during the time period of our 40-year retrospective study, the consecutive series of 167 patients was divided into two groups according to the time period of surgery: 1960 to 1989 (n=108) and 1990 to 2005 (n=59). The results of surgical treatment and several other variables regarding prognosis were compared between these two time periods to make the results of this retrospective study as meaningful as possible. Fisher's exact probability test was used to determine the significance of any group differences.

Outcome was evaluated at the end of 2007. Survival probabilities were calculated using the Kaplan–Meier product limit method and survival differences between the two groups were tested using the log-rank test. The influence of clinicopathological variables on survival was individually assessed by Cox's proportional hazards model. The influence of each clinicopathological variable on the risk of cervical lymph node metastases was assessed by logistic regression analysis. All statistical analyses were carried out using the Stat View 5.0 for Windows (SAS Institute Inc., Cary, NC, USA); P values were considered to be statistically significant at the 5% level.

Results

Clinicopathological Features of Patients with Upper Thoracic Esophageal Squamous Cell Carcinoma According to the Mode of Lymphadenectomy

Of the 167 patients with upper thoracic esophageal SCC, 150 were men (90%) and 17 women (10%), with a mean

age of 60 years (range, 35 to 82 years). The mean size of the tumors was 38 mm (range, 4 to 130 mm). The mean number of totally dissected lymph nodes and metastatic lymph nodes per patient was 42 (range, 5 to 118). Overall hospital morbidity and hospital mortality rates were 57% and 7.8%, respectively.

Patients treated with 3FLD included those treated more recently and those with less invasive tumors, more metastatic lymph nodes, less residual cancer, and more dissected lymph nodes than seen in patients treated with 2FLD (Table 1).

Survival of 167 Patients According to Clinicopathological Factors

The overall 5-year survival rate of the entire group of 167 patients was 38%. A total of 97 patients (58%) developed recurrent disease by the end of 2007. The overall survival curves (according to time period of surgery) gradually increased. The 5-year overall survival rates in each decade were 7% (1960s), 15% (1970s), 14% (1980s), 36% (1990s), and 57% (2000s), respectively. The patients treated after 1990 showed significantly better survival than did the other groups. Cervical lymphadenectomy (Fig. 1a), no lymph node metastases (Fig. 1c), and no residual cancer (Fig. 1d) were significant good prognostic factors for survival. Although the 5-year survival rate of T1 tumors was more than 60%, the survival rates of T2–T4 tumors were below 30% (Fig. 1b). A total of 12 patients of 108 patients, who received 2FLD, survived more than 5 years without recurrent disease, and a total of 17 of 59 patients, who received 3FLD, survived more than 5 years without recurrent disease.

Using univariate analysis, ten of the 14 variables provided a significant estimate of the prognosis for overall survival in patients (Table 2). The following factors were identified as significant predictors of poor survival: former time period of surgery, large tumor, T3/T4 tumor, presence of lymph node metastasis, presence of venous invasion, fewer dissected lymph nodes, 2FLD, and presence of hospital morbidity.

A multivariate analysis using Cox's proportional hazard model was performed to re-evaluate the impact of clinicopathological variables (Table 2). T3/T4 tumor, abdominal positive nodes, presence of residual cancer, 2FLD, and presence of venous invasion were identified as independent risk factors for reduced survival.

Distribution of Positive Lymph Nodes and the Risk Factors for Cervical Lymph Node Metastasis

In 65 patients who underwent 3FLD, the overall positive rates of each lymph node field were 48% in the cervical field, 38% in the thoracic field, and 11% in the abdominal field. The most frequent metastasis was observed in the supraclavicular node (45%) followed by the cervical paraesophageal node (34%) (Fig. 2).

Because the cervical field was the most frequent metastatic site, clinicopathological features were compared according to the status of cervical node metastasis (Table 3). T3/T4 tumor was significantly associated with cervical node metastasis (29% of T1/T2 tumors vs 65% of T3/T4

Table 1 Comparison of Clinicopathological Features in 167 Patients with Upper Thoracic Esophageal Squamous Cell Carcinoma According to the Mode of Lymphadenectomy

Variables (total number of patients)	Two-field lymphadenectomy (n=102)	Three-field lymphadenectomy (n=65)	P value[a]
Time period of surgery, before/after 1990 (108/59)	89/13	19/46	<0.01
Gender, male/female (150/17)	90/12	60/5	0.44
Age (years), <60/≥60 (75/92)	47/55	28/37	0.75
Tumor size, <50/≥50 mm (119/48)	69/33	50/15	0.22
Tumor depth, T1T2/T3T4 (62/105)	31/71	31/34	0.03
Lymph node status, N0/N1 (69/98)	45/57	24/41	0.42
Thoracic node metastasis, (−)/(+) (122/45)	82/20	40/25	0.01
Abdominal node metastasis, (−)/(+) (139/28)	83/19	56/9	0.53
Venous invasion, (−)/(+) (75/92)	46/56	29/36	>0.99
Residual cancer, (−)/(+) (96/71)	44/58	52/13	<0.01
Perioperative chemotherapy, (−)/(+) (118/49)	76/32	42/17	0.58
Number of dissected lymph nodes, <30/≥30 (101/66)	97/5	4/61	<0.01
Hospital morbidity, (+) (95)	53	42	0.11
Hospital mortality, (+) (13)	10	3	0.25

[a] Two-tailed Fisher's exact probability

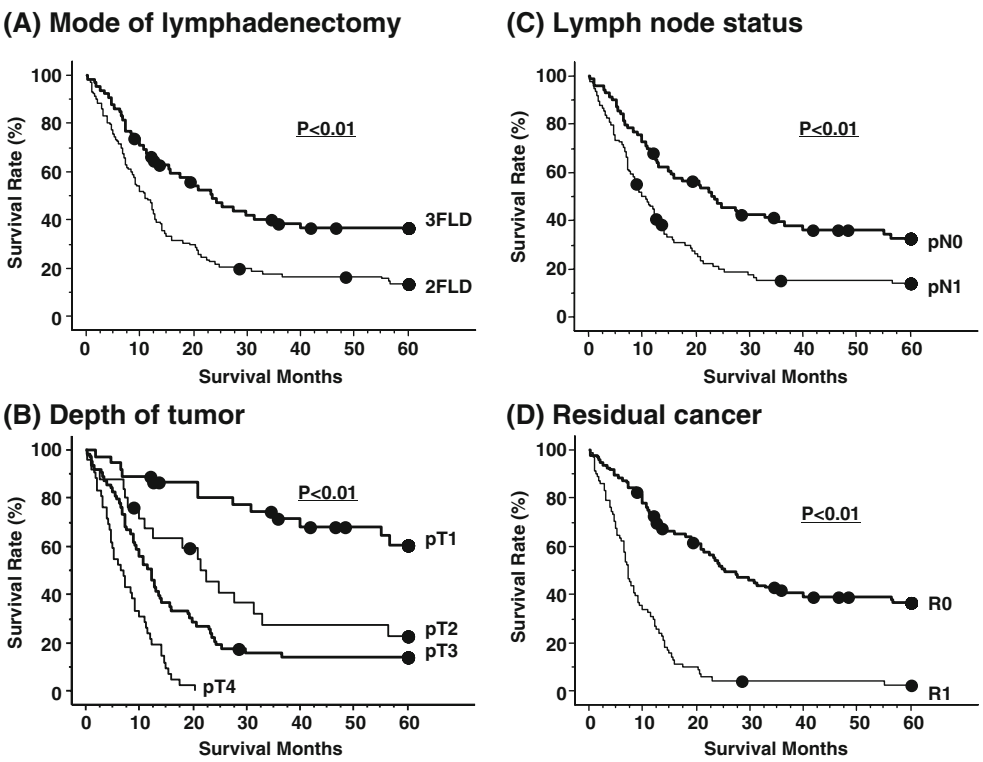

Figure 1 Kaplan–Meier over all survival curves according to mode of lymphadenectomy (**a**), depth of tumor (**b**), lymph node status (**c**), and status of residual cancer (**d**). *Circles* depict survivors. *P* values were determined using the log-rank test.

tumors). Recurrent nerve node metastasis was also significantly associated with cervical node metastasis (40% of recurrent nerve node negative tumors vs 71% of recurrent nerve node positive tumors). Venous invasion was also significantly associated with cervical node metastasis (31% of non-venous invasion tumors vs 61% of venous invasion tumors). In a multivariate analysis, T3/T4 tumor was an independent risk factor for cervical node metastasis. Although the differences were not statistically significant, recurrent nerve node metastasis and venous invasion were also associated with a high risk of cervical node metastasis.

Table 2 Univariate and Multivariate Analysis for Survival in 167 Patients with Upper Thoracic Esophageal Squamous Cell Carcinoma

Variables (total number patients)	Overall 5-year survival rate (%)	*P* value[c]	Overall survival adjusted hazard ratio (adjusted 95% CI)	*P* value[a]
Time period of surgery, before/after 1990	13/43	<0.01	NA	
Gender male/female	22/23	0.69	1.05 (0.51–1.76)	0.87
Age (years), ≥60/<60	22/22	0.97	1.10 (0.76–1.60)	0.61
Tumor size, ≥50/<50 mm	18/27	<0.01	1.37 (0.92–2.04)	0.12
Tumor depth, T3T4/T1T2	8/44	<0.01	2.80 (1.78–4.37)	<0.01
Lymph node status, N1/N0	14/32	<0.01	NA	
Thoracic node metastasis, (+)/(−)	18/22	0.40	1.02 (0.66–1.59)	0.91
Abdominal node metastasis, (+)/(−)	6/23	<0.01	1.65 (1.02–2.67)	0.04
Venous invasion, (+)/(−)	12/32	0.02	1.52 (1.02–2.27)	0.04
Residual cancer, (+)/(−)	2/36	<0.01	2.53 (1.63–3.92)	<0.01
Perioperative chemotherapy, (−)/(+)	21/21	0.70	1.02 (0.69–1.63)	0.80
2FLD/3FLD	12/35	<0.01	1.60 (1.04–2.44)	0.03
Number of dissected lymph nodes, <30/≥30	12/38	<0.01	NA	
Hospital morbidity, (+)/(−)	18/26	0.02	1.55 (1.03–2.32)	0.03

FLD field of lymphadenectomy, *NA* not applicable
[a] Log-rank test

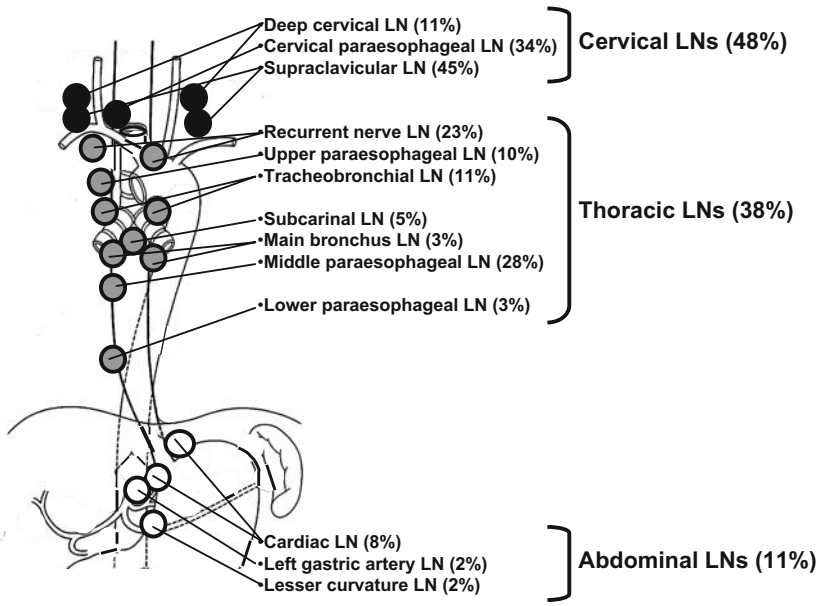

Figure 2 Positive rates of each lymph node in 65 patients underwent three-field lymph node dissection.

Overall Survival in 65 Patients who Underwent 3FLD

Univariate analysis in 65 patients who underwent 3FLD, using clinicopathological variables, are shown in Table 4. A multivariate analysis showed that T3/T4 tumor, thoracic node metastasis, and residual cancer were independent risk factors for poor survival. However, former time period of surgery, cervical node metastasis, and abdominal node metastasis were not selected as independent risk factors for poor survival.

Discussion

We retrospectively analyzed clinicopathological factors and mode of lymphadenectomy of a consecutive series of 167 patients with primary upper thoracic esophageal SCC. Because preoperative staging guided the type of lymphadenectomy through 1980s, only 19 of 108 patients underwent cervical lymphadenectomy. After 1990, cervical lymph nodes were routinely dissected in patients under 70 years of age.

Examination of our series showed that the long-term overall survival of patients after surgery significantly depended on the depth of tumor invasion, status of lymph node metastasis, status of venous invasion, residual cancer, mode of lymphadenectomy, and hospital morbidity. Survival curves according to each clinicopathological variable were similar to those in previous reports.[8] The overall 5-year survival rate of the subgroup with T3/T4 tumors and venous invasion was only 7%.

Table 3 Clinicopathological Features and Risk of Cervical Lymph Node Metastases in 65 Patients with Upper Thoracic Esophageal Squamous Cell Carcinoma Treated with Three-Field Lymph Node Dissection

Variables (total number of patients)	Cervical LD (+) (n=31)	P value[a]	Adjusted hazard ratio (adjusted 95% CI)	P value[b]
Gender, female/male (5/60)	3/28	>0.99	5.82 (0.61–55.26)	0.13
Age (years), <60/≥60 (28/37)	14/17	0.81	0.94 (0.30–3.01)	0.92
Tumor size, <50 mm/≥50 mm (50/15)	24/7	>0.99	0.38 (0.10–1.55)	0.18
Tumor depth, T1T2/T3T4 (31/34)	9/22	<0.01	7.75 (2.03–29.58)	<0.01
Thoracic node metastasis, (+)/(−) (25/40)	15/16	0.13	NA	
Recurrent nerve node metastasis, (+)/(−) (17/48)	12/19	0.04	3.31 (0.80–13.61)	0.09
Abdominal node metastasis, (+)/(−) (9/56)	5/26	0.73	1.04 (0.21–5.14)	0.97
Venous invasion, (+)/(−) (36/29)	22/9	0.02	2.70 (0.81–8.96)	0.11

NA not applicable
[a] Two-tailed Fisher's exact probability
[b] Logistic regression analysis

Table 4 Univariate and Multivariate Analysis for Survival in 65 Patients with Upper Thoracic Esophageal Squamous Cell Carcinoma After Three-Field Lymph Node Dissection

Variables (total number patients)	Overall 5-year survival rate (%)	*P* value[a]	Overall survival adjusted hazard ratio (adjusted 95% CI)	*P* value[a]
Time period of surgery, before/after 1990	13/49	<0.01	2.14 (0.85–5.34)	0.10
Gender male/female	35/65	0.16	3.49 (0.34–36.11)	0.23
Age (years) ≥60/<60	33/41	0.54	1.37 (0.65–2.89)	0.42
Tumor size, ≥50/<50 mm	11/42	0.02	1.02 (0.38–2.76)	0.96
Tumor depth, T3T4/T1T2	8/70	<0.01	4.65 (1.72–12.82)	<0.01
Lymph node status, N1/N0	28/51	<0.01	NA	
Cervical node metastasis, (+)/(−)	25/45	0.04	1.56 (0.58–4.21)	0.38
Thoracic node metastasis, (+)/(−)	21/44	0.01	2.82 (1.19–6.67)	0.02
Abdominal node metastasis, (+)/(−)	22/40	0.31	1.11 (0.41–3.02)	0.83
Venous invasion, (+)/(−)	23/52	0.06	1.12 (0.43–2.90)	0.79
Residual cancer, (+)/(−)	0/46	<0.01	3.80 (1.35–10.75)	<0.01
Perioperative chemotherapy, (−)/(+)	32/54	0.02	0.99 (0.42–2.30)	0.98
Number of dissected lymph nodes, <30/≥30	0/37	0.51	1.19 (0.31–5.62)	0.82
Hospital morbidity, (+)/(−)	39/53	0.06	1.08 (0.41–2.87)	0.88

[a] Log-rank test

Although cervical lymphadenectomy seemed to improve overall survival in multivariate analysis, mode of lymphadenectomy itself was not selected as a significant prognostic factor after co-analysis with "time period of surgery" (data not shown). This was explained partly because all 102 patients who underwent 2FLD were in "former period."

In terms of adjuvant therapy, neither preoperative radiation therapy nor chemotherapy demonstrated a survival benefit in this series (data not shown). However, the latest randomized trials of the Japan Esophageal Oncology Group, which included part of our series, surgery plus postoperative chemotherapy (cisplatinum+5-fluoruracil) improved disease-free survival in node-positive patients.[7] Although multivariate analysis did not suppose survival benefit of perioperative chemotherapy, patients in later time period more frequently received postoperative chemotherapy consisting of cisplatinum+5-fluoruracil than patients in former time period. These differences might partly contribute to improve survival of patients who received cervical lymphadenectomy.

The precise extent of positive lymph nodes associated with upper thoracic esophageal SCC was only seen in patients who received a 3FLD. A total of 31 patients (48%) of 65 patients had cervical node metastases. Among them, 30 patients had supraclavicular node metastases and seven patients had deep cervical node metastases. Although some part of the cervical paraesophageal node could be dissected through a thoracic approach by using thoracoscopy, the supraclavicular and deep cervical nodes were not possible targets through the thoracic approach. Therefore, cervical lymphadenectomy through cervical incision might be essential in these patients. Although hospital morbidity rates in both groups, 2FLD and 3FLD, were relatively high, hospital mortality rate in 3FLD group was less than 5%. However, some of the patients with poor general condition may be a candidate to omit prophylactic deep cervical node dissection.

Paratracheal node and/or recurrent nerve node metastasis were reported to be associated with cervical node metastasis.[14,15] The same tendency was confirmed in the present series of 65 patients who underwent cervical lymphadenectomy. Cervical lymphadenectomy through cervical incision was essential in upper thoracic esophageal carcinoma with T3/T4 tumors and/or recurrent nerve node metastasis. Among ten patients with T3/T4 tumors with recurrent nerve node metastases, nine patients had cervical node metastases. Although T1/T2 tumors and/or thoracic node-negative tumors were less likely to have cervical node metastasis than the other advanced tumors, six (30%) of 20 patients with T1 tumors without thoracic node metastases still had cervical node metastases. Therefore, so far, it has been difficult to define exactly a subgroup of patients among those with upper thoracic esophageal SCC who should be treated with cervical lymphadenectomy.

In conclusion, the outcome for upper thoracic esophageal cancer has significantly improved after 1990, partly dependent on the introduction of cervical lymphadenectomy. T3/T4 tumors, large tumor size, and venous invasion are still unfavorable factors for survival even after 3FLD. Because the supraclavicular and/or cervical paraesophageal nodes were the ones most frequently affected by metastases, cervical lymphadenectomy might be important in upper thoracic esophageal SCC. However, further study is still required to confirm this in a prospective randomized fashion.

References

1. Sobin LH, Wittekind CH, editors. UICC International Union Against Cancer TNM Classification of Malignant Tumours, 6th ed. New York: Wiley, 2002, pp 60–64.
2. Isono K, Sato H, Nakayama K. Results of a nationwide study on the three-field lymph node dissection of esophageal cancer. Oncology 1991;48:411–420.
3. Akiyama H, Tsurumaru M, Udagawa H et al. Radical lymph node dissection for cancer of the thoracic esophagus. Ann Surg 1994;220:364–373. doi:10.1097/00000658-199409000-00012.
4. Shimada H, Matsubara H, Okazumi S et al. Improved surgical results in thoracic esophageal squamous cell carcinoma: a 40-year analysis of 792 patients. J Gastrointest Surg 2008;12:518–526. doi:10.1007/s11605-007-0280-2.
5. Japanese Esophageal Oncology Group. A comparison of chemotherapy and radiotherapy as adjuvant treatment to surgery for esophageal carcinoma. Chest 1993;104:203–207. doi:10.1378/chest.104.1.203.
6. Ando N, Iizuka T, Kakegawa T et al. A randomized trial of surgery with and without chemotherapy for localized squamous cell carcinoma of the thoracic esophagus: the Japan Clinical Oncology Group Study. J Thorac Cardiovasc Surg 1997;114:205–209. doi:10.1016/S0022-5223(97)70146-6.
7. Ando N, Iizuka T, Ide H et al. Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus: A Japan Clinical Oncology Group Study-JCOG9204. J Clin Oncol 2003;24:4592–4596. doi:10.1200/JCO.2003.12.095.
8. Igaki H, Kato H, Tachimori Y et al. Surgery for clinical T3 carcinomas of the upper thoracic oesophagus and the need for new strategies. Br J Surg 2005;92:1235–1240. doi:10.1002/bjs.5081.
9. Fang WT, Chen WH, Chen Y et al. Selective three-field lymphadenectomy for thoracic esophageal squamous carcinoma. Dis Esophagus 2007;20:206–211. doi:10.1111/j.1442-2050.2007.00671.x.
10. Li H, Zhang Y, Cai H et al. Pattern of lymph node metastases in patients with squamous cell carcinoma of the thoracic esophagus who underwent three-field lymphadenectomy. Eur Surg Res 2007;39:1–6. doi:10.1159/000096925.
11. Japanese Society for Esophageal Diseases. Guidelines for clinical and pathologic studies on carcinoma of the esophagus, ninth edition: Preface, general principales, part I. Esophagus 2004;1:61–88.
12. Nakayama K, Orihata H, Yamaguchi K. Surgical treatment combined with preoperative concentrated irradiation for esophageal cancer. Cancer 1967;20:778–788. doi:10.1002/1097-0142(1967)20:5<778::AID-CNCR2820200532>3.0.CO;2-B.
13. Nabeya Y, Ochiai T, Matsubara H et al. Neoadjuvant chemoradiotherapy followed by esophagectomy for initially resectable squamous cell carcinoma of the esophagus with multiple lymph node metastasis. Dis Esophagus 2005;18:388–397. doi:10.1111/j.1442-2050.2005.00521.x.
14. Sato F, Shimada Y, Li Z et al. Paratracheal lymph node metastasis is associated with cervical lymph node metastasis in patients with thoracic esophageal squamous cell carcinoma. Ann Surg Oncol 2002;9:65–70. doi:10.1245/aso.2002.9.1.65.
15. Shiozaki H, Yano M, Tsujinaka T et al. Lymph node metastasis along the recurrent nerve chain is an indication for cervical lymph node dissection in thoracic esophageal cancer. Dis Esophagus 2001;14:191–196. doi:10.1046/j.1442-2050.2001.00206.x.

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ORIGINAL ARTICLE

Increased Fat Content and Body Shape Have Little Effect on the Accuracy of Lymph Node Retrieval and Blood Loss in Laparoscopic Distal Gastrectomy for Gastric Cancer

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Abstract
Background Fat volume and large abdominal shape are known to disrupt the procedures of lymph node retrieval used in gastric cancer surgery. The present study examined the effect of increasing fat content on surgical outcomes, including estimated blood loss and the number of lymph nodes retrieved during gastrectomy.
Methods Of 154 patients, 50 underwent the conventional open procedure (OPEN) and 104 underwent laparoscopy-assisted distal gastrectomy (LADG). The BMI-related factors of total fat, subcutaneous fat, and visceral fat area, as well as the peritoneum–celiac axis distance were calculated by computed tomography. Regression analysis was used to determine the effects of BMI-related factors that obstruct the surgical procedures on the specific outcomes of estimated blood loss and the number of lymph nodes retrieved.
Results In the OPEN, but not in the LADG, increases in all BMI-related factors were related to increases in estimated blood loss. The increases in BMI, subcutaneous fat, and the peritoneum-celiac axis distances were related to decreased numbers of retrieved lymph nodes only in the OPEN. Only the factor of visceral fat at the celiac level was modestly associated with a decreased number of dissected lymph node in both groups.
Conclusions The present study demonstrated that increased fat content and large body shape have little effect on the number of lymph nodes retrieved and blood loss in LADG. However, for patients undergoing conventional open distal gastrectomy, increased fat content and large body shape do impact on the amount of blood lost and the number of lymph nodes retrieved.

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Introduction

The technical difficulties associated with conventional open distal gastrectomy with D2 lymph node dissection of gastric cancer are increased in patients with high body mass index (BMI) values, since the N2 regional lymph nodes lie deep within the fatty tissues around the major abdominal vessels, which may be associated with hemorrhage.[1] Multivariate logistic regression analysis of a large number of patients who underwent gastrectomy with D2 and D3 lymph node dissection has revealed that obesity is one of major predictors of serious surgical complications,[2,3] and several studies have

demonstrated increased postoperative morbidity and mortality after gastrectomy in obese patients.[4–7,2]

A person who is twice the ideal weight or who has a BMI value >40 kg/m^2 is considered to be obese.[4] The excess intraperitoneal fat tissue in obese patients often results in a reduced field of view and difficulty in controlling intraoperative blood loss during surgery. In addition, both the fat volume and abdominal shape of gastric cancer patients influence their short-term surgical outcomes after distal gastrectomy with D2 lymph node dissection.[8] However, little is known about the individual factors (e.g., intra-abdominal fat, subcutaneous fat, and abdominal shape) that make lymph node dissection difficult.

Laparoscopy-assisted distal gastrectomy (LADG), which is increasingly used for gastric cancer surgery,[9,10] is a safe and useful technique when performed by a skilled surgeon.[11] Several studies have reported lower intraoperative blood loss[9,12–14] and similar accuracy of lymph node dissection[15,14] for LADG compared with conventional open distal gastrectomy. Accurate lymph node dissection requires a clear operative field without massive bleeding. Laparoscopy provides a good field of vision even in the depths of the abdominal cavity, which facilitates lymph node dissection. However, few studies have examined the feasibility of LADG in obese patients.[16,17]

In the present study, we evaluate the influence of fat volume such as subcutaneous fat, and visceral fat as the respective fatty areas, and body size assessed by the distance between the peritoneum and root of celiac axis measured by multidetector row computed tomography (MDCT) when performing a distal gastrectomy for gastric cancer. Additionally, we examine these factors when the operation is laparoscopy assisted (LADG).

Materials and Methods

Patient Characteristics

Between March 2005 and June 2006, 154 patients with early gastric cancer underwent distal gastrectomy with modified D2 lymph node dissection at the Department of Gastrointestinal Surgery of the Cancer Institute, Tokyo, Japan. The indication for LADG is limited to clinically diagnosed early gastric cancer, which is an extra-indication for endoscopic submucosal dissection (ESD). Of these patients, 50 underwent distal gastrectomy with the conventional open procedure (OPEN) and 104 underwent LADG (LADG). Although the number of LADG procedures performed in Japan is increasing gradually, LADG is not standard therapy for early gastric cancer. Further, the Japanese Research Society for Gastric Cancer (JRSGC) has defined LADG as a therapeutic approach for use in clinical trials.[19] Therefore, we ask patients preoperatively whether they are willing to undergo LADG or would prefer the conventional open method. In the present study, the greater number of LADG procedures was due to patient requests. In addition, the two gastric cancer specialists recruited to the study have extensive experience with LADG, having performed more than 300 such procedures. All data were collected retrospectively and the collection of patients' individual data was approved by an institutional review board. The patients' backgrounds and clinicopathologic characteristics were analyzed retrospectively.

Histologically, all of the tumors were classified as adenocarcinomas that had invaded the mucosa or submucosa of the stomach without lymph node metastasis (cT1, cN0). Clinical classification of tumor depth (cT) and nodal involvement (cN) was evaluated preoperatively and intraoperatively by barium radiography, upper gastrointestinal tract endoscopy, abdominal ultrasonography, computed tomography (CT), and endoscopic ultrasonography. The indication for these surgical procedures was intramucosal or submucosal carcinoma without lymph node metastasis (cT1, cN0). Gender, age, BMI, preoperative complications, and clinical staging were documented for all the patients.

Exclusion Criteria

Patients were excluded if they had cardiac (higher than grade II in the New York Heart Association scale), pulmonary (higher than grade II in the Hugh–Jones scale), hepatic (Child classes B and C) or renal insufficiency.

Lymphadenectomy for Gastric Cancer

For patients in the OPEN and the LADG groups, the scope of lymph node dissection was as described previously.[18] The lymph node stations correspond to the specific lymph node tiers designated by the Japanese Research Society for Gastric Cancer (JRSGC).[19] Lymphadenectomy of the modified D2 dissection (D1+beta) was performed for all patients who were diagnosed preoperatively as having mucosal or submucosal gastric cancer. We used the recently revised definition of second-tier nodes by the JRSGC,[19] which includes the hepatoduodenal ligament (station 12a) and the root of the superior mesenteric vein (station 14 v), in addition to the criteria of the American Joint Committee on Cancer (AJCC; 1987).[20] Complete D2 dissection is defined by the JRSGC as including all of the above stations. The dissection of first-tier nodes as well as preferential lymph nodes along the left gastric (station 7), common hepatic (station 8a) and celiac (station 9) arteries is defined as a modified D2 dissection, and these four stations are defined as selective second-tier stations.

Reconstruction

Pylorus-preserving gastrectomy (PPG) was indicated if the cancer was located in the distal stomach, at least 5 cm proximal to the pyloric ring. The application of PPG was restricted to patients with cancer in the gastric body, so as to maintain a safe distal margin (2 cm) from the lesion. The distal part of the stomach was resected while retaining a 3-cm pyloric cuff. LADG with Billroth I (B-I) anastomosis was indicated if the cancer was located in the distal stomach less than 5 cm proximal to the pyloric ring. In this instance, B-I reconstruction was performed using end-to-end anastomosis (EEA) with a mechanical stapling device (Tyco Healthcare, Japan). All anastomotic procedures were established extracorporealy; therefore, this operation is not purely laparoscopic distal gastrectomy but laparoscopic-assisted distal gastrectomy.

Clinical Data

The following parameters were recorded: operation time, estimated blood loss, degree of lymph node dissection, and intraoperative complications. All resected stomachs were opened immediately after surgery, and the dissected lymph nodes were categorized and counted by pathologist according to the anatomic distribution and numbering of the regional lymph nodes, based on the JRSGC classification system.[19] Lymph nodes were retained for comparison of the procedures with respect to the quality of the lymph node dissection. Sections cut from formalin-fixed specimens were stained with hematoxylin–eosin. Histologic determinations were made of the depth of wall invasion, number of harvested lymph nodes, and presence or absence of lymph node metastasis.

The following postoperative data were recorded: gastric fullness (for cases of upper abdominal distention, remnant stomach fullness on X-ray, and starvation longer than 24 h), anastomotic problems (leakage, stenosis, bleeding ulcer), ileus, early-dumping syndrome, pancreatitis and pancreatic juice leakage, total amount of analgesic drugs up to and including postoperative Day 3, time to first flatus, time to first oral intake, and postoperative hospital stay.

Evaluation of Factors Related to High BMI

To estimate the BMI-related factors, subcutaneous fat, and visceral fat were calculated from the respective fat area at the celiac axis using MDCT with a fat area evaluation program (Slim Vision; KGT Inc., Japan). In addition, the distance between the peritoneum and root of the celiac axis were measured using the Slim Vision software.

All the CT scans were performed in the 4-week period before surgery. CT scans were performed using a four-channel MDCT (LightSpeed QX/i; GEYMS, Japan) using the following parameters: 120 kVp, 200 mAs, 10.0-mm beam collimation, 0.75 beam pitch, 2.5-mm slice thickness, prone position for 60 s after contrast medium (Iopamiron-370 syringe or iopamidol; Nihon Schering, Japan) injection.

Influences of Fat Volume and Body Shape on Operation Time, Estimated Blood Loss, and Numbers of Excised Lymph Nodes

To evaluate the influences of fat volume and abdominal shape on operation time, estimated blood loss, and numbers of excised lymph nodes, we fitted separate regression models with different slopes and different intercepts corresponding to OPEN and LADG. The individual influences of OPEN and LADG were tested by the *t* test for the regression coefficients of the slopes. The differences between the influences of OPEN and LADG were tested by the *F* test for the comparison of the two regression coefficients of the slopes.

Statistical Analysis

All data are presented as means±SE. The results were compared for patients undergoing OPEN and LADG. Statistical analysis was performed using Welch's *t* test to examine the differences between the means of variables, and the Fisher's exact test was used to test the level of independence between the two groups. The hypotheses were tested with a significance level (*P* value) of 0.05.

Results

Clinicopathologic Characteristics of the Patients

The clinical histories were similar for all the patients (Table 1), as were their concurrent illnesses. There were no significant differences between the groups in terms of age, BMI or clinical staging, although the number of females was significantly higher in the LADG group.

The mean operation time for the OPEN procedure was more than 45 min shorter than that for the LADG procedure (176±6 min vs. 227±5 min; $P<0.001$).The mean estimated blood loss volume for the OPEN procedure was more than four times greater than that for the LADG procedure (167± 15 mL vs. 38±3 mL; $P<0.001$). The mean number of dissected lymph nodes in the LADG group was higher than that in the OPEN group (34±1 vs. 29±1; $P<0.002$).

Comparison of BMI Values, Fat Volumes, and Abdominal Shapes between LADG and OPEN

The BMI values and BMI-related factors are summarized in Table 2. There were no significant differences between the

Table 1 Characteristics of Patients Undergoing Conventional Open Distal Gastrectomy (OPEN) or Laparoscopy-assisted Distal Gastrectomy (LADG)

		OPEN	LADG	*P* value
N		50	104	
Sex	Male/female	34/16	49/55	0.024*
Age	Average (year)	60±1	60±1	0.600
	Range (year)	35–79	34–86	
Preoperative complication				
Diabetes		2 (4%)	3 (3%)	0.828
Ischemic heart disease		1 (2%)	1 (1%)	0.588
Hypertension		5 (10%)	8 (8%)	0.911
Clinical staging				
IA		44 (88%)	94 (90%)	0.863
IB		4 (8%)	8 (8%)	0.799
II		2 (4%)	1 (1%)	0.513
IIIA		0 (0%)	1 (1%)	0.707
Mean operation time (min)		176±6	227±5	<0.001*
Mean estimated blood loss (mL)		167±15	38±3	<0.001*
Mean number of retrieved lymph nodes		29±1	34±1	<0.002*

Data are presented as means±SE. An unpaired *t* test was used to test the equality between the two means of the variables. The Fisher exact test or χ^2 test was used to test the independence between the two groups. *P=0.050 was considered statistically significant

groups in terms of BMI and subcutaneous fat area. The visceral fat areas at the celiac axis (P=0.020) were significantly larger in the OPEN group, and the peritoneum to root of the celiac axis distance was significantly longer in the OPEN group (P=0.015).

Influences of Fat Volume and Abdominal Shape on Operation Times of LADG and OPEN

The influences of fat volume and abdominal shape on operation time were evaluated as regression coefficients. No significant positive regression coefficients for operation time were found for either the OPEN or LADG procedure with respect to BMI, subcutaneous fat at the celiac level, visceral fat at celiac level, and distance between the peritoneum and celiac axis. A comparison of the two regression coefficients of operation time between the LADG and OPEN procedures did not show any significant differences for any of the factors.

Influences of Fat Volume and Abdominal Shape on Estimated Blood Losses during LADG and OPEN

For the OPEN procedure, significant increased regression coefficients were found for all factors related to fat volume and abdominal shape, including BMI (P<0.001; Fig. 1A), subcutaneous fat at the celiac level (P=0.029; Fig. 1B), visceral fat at the celiac level (P<0.001; Fig. 1C) and distance between the peritoneum and celiac axis (P<0.001; Fig. 1D). The increases in all these factors were significantly related to increases in estimated blood loss in the OPEN procedure. On the other hand, no significant increases in the regression coefficients for factors related to fat volume and abdominal shape, including BMI (P=0.167; Fig. 1A), subcutaneous fat at the celiac level (P=0.573; Fig. 1B), visceral fat at the celiac level (P=0.068; Fig. 1C), and distance between the peritoneum and celiac axis (P=0.122; Fig. 1D), were found for estimated blood

Table 2 Fat Volumes and Body Shapes of Patients Undergoing Conventional Open Distal Gastrectomy (OPEN) and Laparoscopy-assisted Distal Gastrectomy (LADG)

		OPEN (N=50)	LADG (N=104)	*P* value
BMI	(kg/m^2)	22.7±3.8	22.4±0.4	0.657
Subcutaneous fat (celiac level)	(m^2)	55±31	59±3	0.448
Visceral fat (celiac level)	(m^2)	87±10	63±5	0.020*
Peritoneum–celiac axis distance	(mm)	107±3	99±2	0.015*

Data are presented as means±SE. *BMI* body weight/height^2 (kg/m^2). An unpaired *t* test was used to test the equality between the two means of the variables. *P<0.05 was considered statistically significant

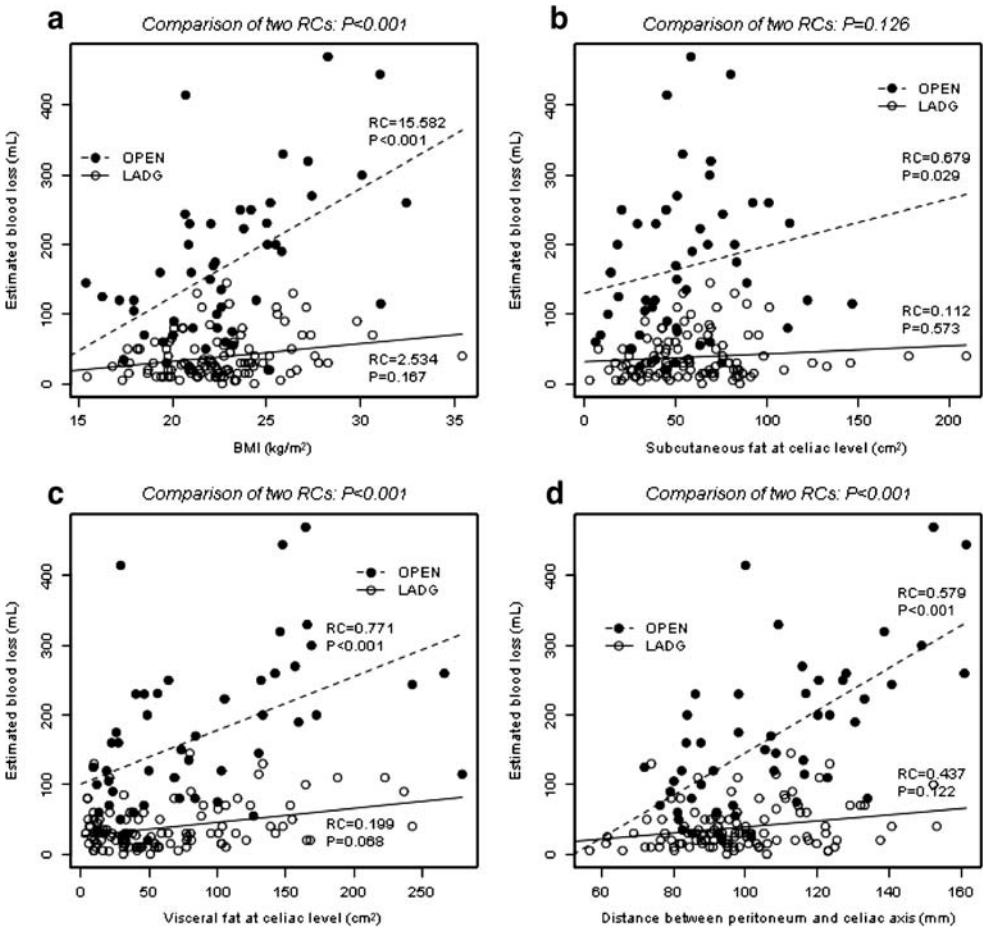

Figure 1 Influence of fat volume and abdominal shape on estimated blood loss. To evaluate the influences of fat volume and abdominal shape on estimated blood loss, separate regression models were fitted with different slopes and different intercepts corresponding to OPEN and LADG. Data are presented as the regression coefficients and corresponding *P* values. The individual influences of OPEN and LADG are tested by the *t* test for their regression coefficients of the slopes. The differences in the influences of OPEN and LADG are tested by the *F* test for the comparison of two regression coefficients of the slopes. *BMI* Body weight/height^2. *P* values<0.05 are considered to indicate statistical significance. Effects on estimated blood loss of: **a** BMI, **b** subcutaneous fat volume at the celiac level, **c** visceral fat volume at the celiac level; and **d** distance between the peritoneum and celiac axis on estimated blood loss.

loss in the LADG procedure. Comparison of the regression coefficients for estimated blood loss between the LADG and OPEN procedures showed significant differences, albeit not for the factor of subcutaneous fat (P=0.125).

Influences of Fat Volume and Abdominal Shape on Numbers of Dissected Lymph Nodes of LADG and OPEN

For the OPEN procedure, negative regression coefficients for the numbers of dissected lymph nodes were found for BMI (P=0.010; Fig. 2A), subcutaneous fat at the celiac level (P=0.018; Fig. 2B), and distance between the peritoneum and celiac axis (P<0.001; Fig. 2D). The factor of visceral fat at the celiac level (P=0.133; Fig. 2C) showed only modest influence on the numbers of dissected lymph nodes for the OPEN procedure. In contrast to the data obtained for the OPEN procedure, no negative regression coefficients were found for any of the factors in the LADG group. However, the factor of visceral fat at the celiac level (P=0.142; Fig. 2C) showed modest influence on the numbers of dissected lymph nodes. Comparison of the regression coefficients for numbers of dissected lymph nodes between the LADG and OPEN procedures showed significant differences for BMI (P=0.050), subcutaneous fat at the celiac level (P=0.049), and distance between the peritoneum and celiac axis (P<0.001).

Discussion

Since 1996, the use of LADG has increased rapidly in Japan,[21] and many retrospective[22–24,13] and prospective[9,25] studies have shown the safety, efficacy, and feasibility of laparoscopy-assisted gastrectomy. However, LADG with extended lymph node dissection for gastric cancer is generally considered to be more complicated than the conventional open procedure, owing to the complexity of lymph node dissection.[26,25] Additional technical difficulties, including high conversion or extension of incisions and prolonged operation time, have been noted for LADG in heavier patients.[16] Open gastric surgery also shows higher rates of postoperative complications, longer operation times, greater estimated blood loss volumes, and lower numbers of

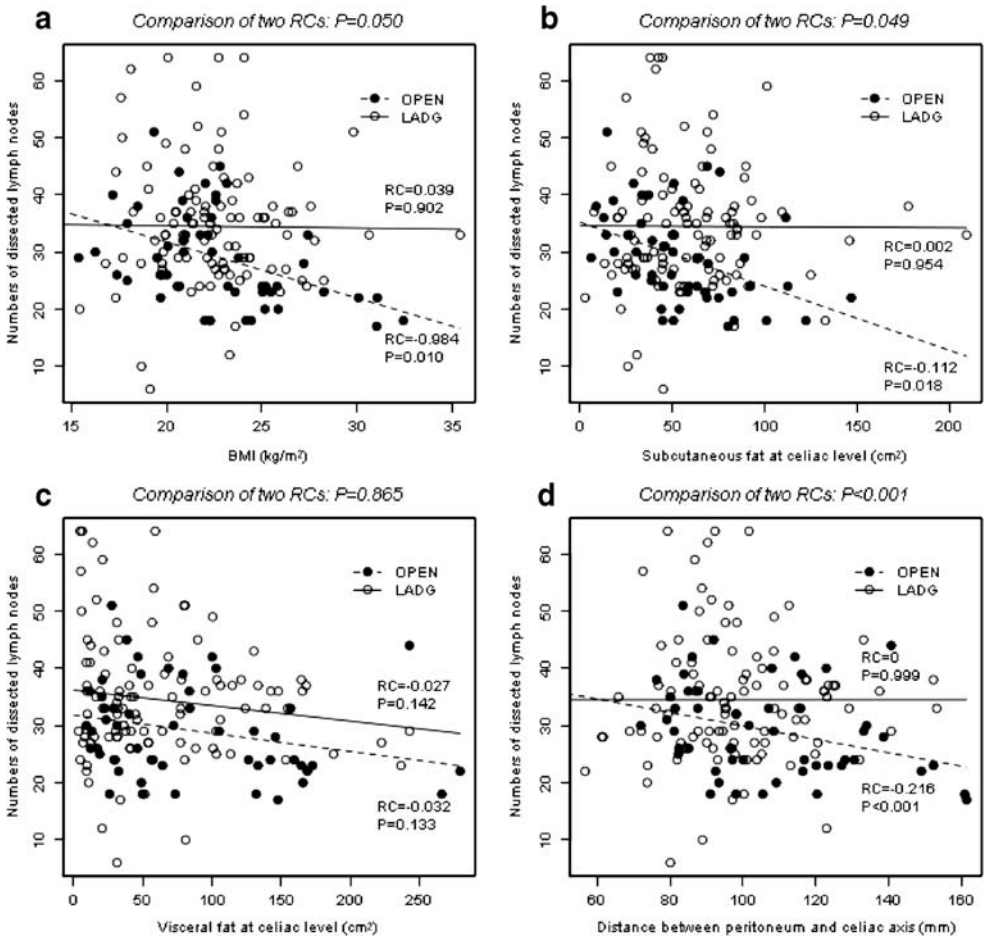

Figure 2 Influence of fat volume and abdominal shape on numbers of excised lymph nodes. To evaluate the influences of fat volume and abdominal shapes on the numbers of excised lymph nodes, separate regression models were fitted with the different slopes and different intercepts corresponding to OPEN and LADG. Data are presented as the regression coefficients and corresponding *P* values. The individual influences of OPEN and LADG are tested by the *t* test for their regression coefficients of the slopes. The differences in the influences of OPEN and LADG are tested by the *F* test for the comparison of two regression coefficients of the slopes. *BMI* weight/height^2. *P* values<0.05 are considered to indicate statistical significance. Effects on numbers of excised lymph nodes of: **a** BMI, **b** subcutaneous fat volume at the celiac level, **c** visceral fat volume at the celiac level, and **d** distance between the peritoneum and celiac axis.

dissected lymph nodes in obese patients than in non-obese patients.[5–7] However, in several studies of laparoscopic cholecystectomy[27,28] and LADG,[17] no significant differences have been found between obese and non-obese patients in terms of operating time, conversion rate to open surgery, postoperative complication rate or length of hospital stay. Therefore, we propose that LADG can be used to treat obese patients if the surgeon is skilled.

Early operative outcomes are assessed using the parameters of operation time, estimated blood loss volume, and number of dissected lymph nodes.[15,12] Although some studies have demonstrated significantly higher numbers of dissected lymph node in OPEN procedures compared to LADG procedures,[14,12,29] we have previously demonstrated that the quality of lymph node dissection in LADG is comparable to that in OPEN procedures[15] if the surgeon is skilled and experienced. In the present study, there was less blood loss and more lymph nodes dissected in the LADG group compared with the OPEN group. Both of these outcomes can be explained by the better accessibility of the laparoscopic view in deep lesions in the abdominal cavity afforded by LADG and better control of bleeding because of the improved view, even in abundant adipose tissues. The proportion of males was higher in the OPEN group than in the LADG group. Visceral fat and larger abdominal shape are recognized more often in male patients than in female patients with same BMI. The analysis of BMI-related factors revealed different body compositions, such as significantly more visceral fat and longer peritoneum to celiac axis distance, in the OPEN group. These factors might disrupt the operative procedures, resulting in poor surgical outcomes in the OPEN group, such as greater blood loss and fewer dissected lymph nodes.

To reveal the BMI-related factors that disrupt the operative procedure and give poorer operative outcomes in the OPEN group, regression analysis was performed to evaluate the influences of these BMI-related factors on the operative outcomes as continuous variables. The operative time in both groups was not extended without affecting the degree of obesity and large abdominal shape. The effect on estimated blood loss was significantly different between the two procedures. Although BMI-related factors affected blood loss in the OPEN group, none of the BMI-related factors were associated with blood loss in the LADG group. Further multivariate analysis identified a strong association between peritoneum to celiac distance and increased

estimated blood loss during the OPEN procedure (data not shown). Among all the BMI-related factors, factors related to abdominal shape were the most disruptive for the OPEN procedure. The advantages of LADG for obese and large-bodied patients, i.e., ensuring accessibility and reducing bleeding, may account for the reduced blood loss during LADG, as compared to the OPEN procedure.

For the OPEN procedure, BMI, subcutaneous fat, and distance between the peritoneum and celiac axis were associated with a decreased number of dissected lymph nodes. On the other hand, there were no influences of these BMI-related factors on lymph node dissection in the LADG procedure. Only the factor of visceral fat at the celiac level was modestly associated with a decreased number of dissected lymph node in both groups. These data suggest that lymph node dissection in obese and large-bodied patients is more disrupted by the OPEN procedure than by the LADG procedure. However, it should be noted that intra-abdominal obesity may disturb lymph node dissection even in the LADG.

Several studies have pointed out that for patients who are undergoing OPEN gastrectomy, being overweight increases the risk of surgical complications.[2,3,5,6,8] In the present study, no influence of BMI-related factors on complication rate was detected for either group (data not shown). As this was a single institutional trial with a limited number of patients, the overall complication rate was not as high as that seen in other studies with high numbers of patients.

In conclusion, the present study clearly demonstrates that increasing fat content and body size have little effect on bleeding and lymph nodes retrieved in LADG, whereas increasing fat content and body size disturbs the precise lymph nodes dissection and increase the blood loss in purely conventional open distal gastrectomy probably due to the high level of accessibility and clear view of the operative field conferred by the laparoscope and laparoscopic grasper forceps.

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References

1. Barry JD, Blackshaw GR, Edwards P, Lewis WG, Murphy P, Hodzovic I, Thompson IW, Allison MC. Western body mass indices need not compromise outcomes after modified D2 gastrectomy for carcinoma. Gastric Cancer 2003;6:80–85.
2. Kodera Y, Sasako M, Yamamoto S, Sano T, Nashimoto A, Kurita A. Identification of risk factors for the development of complications following extended and superextended lymphadenectomies for gastric cancer. Br J Surg 2005;92:1103–1109.
3. Tsujinaka T, Sasako M, Yamamoto S, Sano T, Kurokawa Y, Nashimoto A, Kurita A, Katai H, Shimizu T, Furukawa H, Inoue S, Hiratsuka M, Kinoshita T, Arai K, Yamamura Y. Influence of overweight on surgical complications for gastric cancer: results from a randomized control trial comparing D2 and extended para-aortic D3 lymphadenectomy (JCOG9501). Ann Surg Oncol 2007; 14:355–361.
4. Moriwaki Y, Kunisaki C, Kobayashi S, Harada H, Imai S, Kasaoka C. Does body mass index (BMI) influence morbidity and long-term survival in gastric cancer patients after gastrectomy? Hepatogastroenterology 2003;50:284–288.
5. Dhar DK, Kubota H, Tachibana M, Kotoh T, Tabara H, Masunaga R, Kohno H, Nagasue N. Body mass index determines the success of lymph node dissection and predicts the outcome of gastric carcinoma patients. Oncology 2000;59:18–23.
6. Kodera Y, Ito S, Yamamura Y, Mochizuki Y, Fujiwara M, Hibi K, Ito K, Akiyama S, Nakao A. Obesity and outcome of distal gastrectomy with D2 lymphadenectomy for carcinoma. Hepatogastroenterology 2004;51:1225–1228.
7. Inagawa S, Adachi S, Oda T, Kawamoto T, Koike N, Fukao K. Effect of fat volume on postoperative complications and survival rate after D2 dissection for gastric cancer. Gastric Cancer 2000;3:141–144.
8. Lee JH, Paik YH, Lee JS, Ryu KW, Kim CG, Park SR, Kim YW, Kook MC, Nam BH, Bae JM. Abdominal shape of gastric cancer patients influences short-term surgical outcomes. Ann Surg Oncol 2007;14:1288–1294.
9. Kitano S, Shiraishi N, Fujii K, Yasuda K, Inomata M, Adachi Y. A randomized controlled trial comparing open vs laparoscopy-assisted distal gastrectomy for the treatment of early gastric cancer: an interim report. Surgery 2002;131:S306–S311. doi:10.1067/msy.2002.120115.
10. Adachi Y, Suematsu T, Shiraishi N, Katsuta T, Morimoto A, Kitano S, Akazawa K. Quality of life after laparoscopy-assisted Billroth I gastrectomy. Ann Surg 1999;229:49–54.
11. Adachi Y, Shiraishi N, Shiromizu A, Bandoh T, Aramaki M, Kitano S. Laparoscopy-assisted Billroth I gastrectomy compared with conventional open gastrectomy. Arch Surg 2000;135:806–810.
12. Lee SI, Choi YS, Park do J, Kim HH, Yang HK, Kim MC. Comparative study of laparoscopy-assisted distal gastrectomy and open distal gastrectomy. J Am Coll Surg 2006;202:874–880.
13. Noshiro H, Nagai E, Shimizu S, Uchiyama A, Tanaka M. Laparoscopically assisted distal gastrectomy with standard radical lymph node dissection for gastric cancer. Surg Endosc 2005; 19:1592–1596.
14. Mochiki E, Kamiyama Y, Aihara R, Nakabayashi T, Asao T, Kuwano H. Laparoscopic assisted distal gastrectomy for early gastric cancer: five years' experience. Surgery 2005;137:317–322.
15. Kim MC, Jung GJ, Kim HH. Learning curve of laparoscopy-assisted distal gastrectomy with systemic lymphadenectomy for early gastric cancer. World J Gastroenterol 2005;11:7508–7511.
16. Noshiro H, Shimizu S, Nagai E, Ohuchida K, Tanaka M. Laparoscopy-assisted distal gastrectomy for early gastric cancer: is it beneficial for patients of heavier weight? Ann Surg 2003; 238:680–685.
17. Yasuda K, Inomata M, Shiraishi N, Izumi K, Ishikawa K, Kitano S. Laparoscopy-assisted distal gastrectomy for early gastric cancer in obese and nonobese patients. Surg Endosc 2004;18:1253–1256.
18. Shimoyama S, Kaminishi M, Joujima Y, Oohara T, Hamada C, Teshigawara W. Lymph node involvement correlation with survival in advanced gastric carcinoma: univariate and multivariate analyses. J Surg Oncol 1994;57:164–170.
19. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma—2nd English edition. Gastric Cancer 1998; 1:10–24.
20. Beahrs OH, Henson DE, Hutter RVP, Myers MH. American Joint Committee on Cancer, eds. Manual for Staging of Cancer 3rd ed Philadelphia, Pa: J B Lippincott 1988;1988.

21. Kitano S, Shiraishi N. Current status of laparoscopic gastrectomy for cancer in. Japan Surg Endosc 2004;18:182–185.
22. Mochiki E, Nakabayashi T, Kamimura H, Haga N, Asao T, Kuwano H. Gastrointestinal recovery and outcome after laparoscopy-assisted versus conventional open distal gastrectomy for early gastric cancer. World J Surg 2002;26:1145–1149.
23. Asao T, Kuwano H, Mochiki E. Laparoscopic surgery update for gastrointestinal malignancy. J Gastroenterol 2004;39:309–318.
24. Yano H, Monden T, Kinuta M, Nakano Y, Tono T, Matsui S, Iwazawa T, Kanoh T, Katsushima S. The usefulness of laparoscopy-assisted distal gastrectomy in comparison with that of open distal gastrectomy for early gastric cancer. Gastric Cancer 2001;4:93–97.
25. Hayashi H, Ochiai T, Shimada H, Gunji Y. Prospective randomized study of open versus laparoscopy-assisted distal gastrectomy with extraperigastric lymph node dissection for early gastric cancer. Surg Endosc 2005;19:1172–1176.
26. Rosin D, Brasesco O, Rosenthal RJ. Laparoscopy for gastric tumors. Surg Oncol Clin N Am 2001;10:511–529.
27. Angrisani L, Lorenzo M, De Palma G, Sivero L, Catanzano C, Tesauro B, Persico G. Laparoscopic cholecystectomy in obese patients compared with nonobese patients. Surg Laparosc Endosc 1995;5:197–201.
28. Collet D, Edye M, Magne E, Perissat J. Laparoscopic cholecystectomy in the obese patient. Surg Endosc 1992;6:186–188.
29. Fujiwara M, Kodera Y, Kasai Y, Kanyama Y, Hibi K, Ito K, Akiyama S, Nakao A. Laparoscopy-assisted distal gastrectomy with systemic lymph node dissection for early gastric carcinoma: a review of 43 cases. J Am Coll Surg 2003;196:75–81.

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ORIGINAL ARTICLE

Hexose Transporter Expression and Function in Mouse Small Intestine: Role of Diurnal Rhythm

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Abstract
Background Expression and function of hexose transporters vary diurnally in rat small intestine; however, this subject remains unexplored in mice.
Aim The aim of the study was to investigate the diurnal expression and function of hexose transporters SGLT1, GLUT2, and GLUT5 in mouse small bowel.
Methods Twenty-four c57bl6 mice maintained in a 12-h light/dark room (6 AM–6 PM) were sacrificed at 9 AM, 3 PM, 9 PM, and 3 AM (n=6 each). In duodenal, jejunal, and ileal mucosa, total cellular mRNA and protein levels were quantitated by real-time PCR and semiquantitative Western blotting, respectively. The everted sleeve technique measured transporter-mediated glucose uptake at 9 AM and 9 PM.
Results mRNA expression of SGLT1, GLUT2, and GLUT5 varied diurnally in all three intestinal segments ($p \leq 0.03$). SGLT1, GLUT2, and GLUT5 protein levels varied diurnally in duodenum and jejunum ($p < 0.05$) but not in ileum. Transporter-mediated glucose uptake was greater at 9 PM than 9 AM ($p \leq 0.04$) in all three segments. V_{max} was greater in duodenum (10 vs 6 nmol/cm/s) and jejunum (8 vs 5 nmol/cm/s) at 9 PM compared to 9 AM (p=0.01); K_m remained unchanged.
Summary mRNA levels of intestinal hexose transporters varied diurnally. Protein levels peaked 6–12 h later during dark cycle when >70% of food intake occurred; glucose transport followed a similar pattern with increased uptake at 9 PM.
Conclusion Hexose transporter expression and function vary diurnally with nocturnal feeding patterns of mice.

Keywords Hexose transporters · Diurnal rhythm · Mice · Small intestine · Sugar absorption

Introduction

Sodium glucose co-transporter 1 (SGLT1), glucose transporter 2 (GLUT2), and glucose transporter 5 (GLUT5) are the primary hexose transporters present in rodent small intestine.[1,2] Expression of these transporters is regulated by luminal substrates, hormonal regulation, neural regulation, ontogenic programmed expression, and by diurnal rhythm possibly via clock genes.[1,3–8] Expression of mRNA and protein of these transporters vary diurnally and in a temporally coordinated, segmental manner throughout rat small intestine.[1,7–10] Elucidating the interaction between regulatory mechanisms of these transporters may help develop novel treatments for patients with malabsorptive disorders and diabetes.

Virtually all the previous work on diurnal variation in glucose transporters has been limited to the rat mod-

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el.[1,7,8,10,11] Uncovering the molecular mechanisms regulating this periodicity would be more feasible in the mouse model where the genome is more readily exploited;[11] however, this diurnal variation has not been characterized in mice.

It is important to understand both the mechanisms regulating the expression of nutrient absorptive proteins as well as the presence or absence of a diurnal variation in their expression and activities at a segmental level to better understand neural and/or hormonal control of this regulation. We hypothesized that the expression and function of the hexose transport proteins SGLT1, GLUT2, and GLUT5 follow a coordinated diurnal rhythm throughout the mouse small intestine.

Methods

Animal handling and care was conducted in conformity with the NIH guidelines on the humane use and care of laboratory animals after approval from our Institutional Animal Care and Use Committee.

Design

To determine the presence or absence of diurnal rhythmicity, relative levels of total cellular hexose transporter mRNA and protein levels for mucosal hexose transporters from six mice at each of four time points (9 AM, 3 PM, 9 PM, and 3 AM) were determined from mucosal scrapings of duodenum, jejunum, and ileum. In addition, transporter-mediated glucose uptake was determined using the everted sleeve technique at 9 PM and 9 AM (n=6 at each time point, corresponding with presumed peak and trough levels of protein expression, respectively).[12]

Procedure

Adult male, c57bl6 mice (Harlan, Indianapolis, IN, USA) weighing 20–25 g were maintained in an alternating 12-h, light–dark cycle (6 AM–6 PM, respectively) with free access to chow (Lab Diet 5001, Brentwood, MO, USA) and water. Mice were acclimated to this facility at least 1 week prior to study. Food consumption was monitored every 12 h (6 AM–6 PM) for 1 week separately in six mice.

Mice were anesthetized using inhaled 2% isoflurane (Abbott Laboratories, North Chicago, IL, USA) for induction and intraperitoneal pentobarbital (40 mg/kg; Ampro-Pharmacy, Arcadia, CA, USA) for maintenance of anesthesia. After a midline celiotomy, the proximal duodenum was cannulated, and the entire small intestine was flushed with cold (4°C), iso-osmotic phosphate-buffered solution (PBS) to remove intraluminal content. Care was taken to prevent disruption of blood supply to the bowel during this procedure. Duodenal, jejunal, and ileal segments were placed immediately in PBS at 4°C. Harvested duodenal segments were 4 cm in length, extending from the pylorus to the ligament of Treitz, jejunal specimens were 8 cm in length with the proximal limit as ligament of Treitz, and ileal samples were 10–12 cm in length extending proximally from the cecum. Mucosa was obtained from each of these segments by scraping the opened segment with a glass slide. Part of the mucosal sample was placed in RNA stabilization buffer (RNALater, Qiagen, Valenica, CA, USA), and the remainder in cold PBS with protease inhibitor (Complete tablets, Roche Diagnostics, Indianapolis, IN, USA) for protein studies. All samples were snap-frozen in liquid nitrogen immediately after sample acquisition and kept at −80°C until analysis.

RNA

Total RNA was isolated using the RNeasy Midi Kit (Qiagen) according to the manufacturer's recommendations. RNA concentrations in each sample were then determined using a spectrophotometer (DU 650, Beckman, Fullerton, CA, USA). Then, 2 μg of RNA from each sample was incubated for 15 min with 2 μl of DNase enzyme (amplification grade) in DNAse buffer (Invitrogen, Carlsbad, CA, USA) to digest any residual DNA. Next, each sample was reverse-transcribed using the SuperScriptIII kit (Invitrogen) with random hexamer priming. To eliminate variability, *all* samples from each segment were reverse-transcribed simultaneously. cDNA was kept at −20°C until further analysis.

Real-time PCR analysis was performed using Taqman assays (Applied Biosystems, Foster City, CA, USA). Each reaction consisted of 2 μl of standard, control, or unknown sample combined with 23 μl of a standard master mix (Applied Biosystems). Plasmids containing the cDNA transcripts for SGLT1, GLUT2, and GLUT5 were purchased from Open Biosystems (Huntsville, AL, USA). Serial dilutions of plasmids with known copy numbers were used to generate a standard curve during each real-time PCR run. The cycle threshold for unknown samples was then compared to the standard curve to determine the copy numbers present for each transcript in each sample. DNase-free water was used as negative control. Each sample was run in duplicate, and all samples to be compared were run together on the same analysis to avoid variability between runs of real-time PCR analysis. Expression levels of each transporter were expressed as a ratio to glyceraldehyde 6-phosphate dehydrogenase (GAPDH), a housekeeping gene whose mRNA and protein levels are expressed in stable amounts in intestinal mucosal cells.

Protein

The intestinal mucosal samples in PBS buffer containing protease inhibitors were thawed on ice and homogenized in RIPA lysis buffer also containing the protease inhibitors using a Kontes Pellet Pestle (Fischer Scientific, Pittsburg, PA, USA).[6] Cellular debris was removed by centrifugation at 10,000 rpm for 15 min at 4°C, and total protein was collected in the supernatant. Protein concentrations were then determined using the bichinchonink acid method (Pierce, Rockford, IL, USA) and protein plate reader (Microplate Manager III, BioRad, Hercules, CA, USA) at a wavelength of 570 nm. Next, 200 μg of protein from each sample was resolved on a 10% polyacrylamide gel (BioRad). Precision Plus protein standards (BioRad) were used for identification of molecular weights. Proteins were then transferred onto a PVDF membrane (Millipore, Bedford, MA, USA) using a semidry technique and blocked with 5%, nonfat milk (BioRad) in Tris-buffered saline in Tween (TBS-T). Membranes were then incubated overnight in primary antibody against SGLT1 (1:3,000 dilution, Chemicon International, Tenecula, CA, USA), GLUT2 (1:500 dilution, Chemicon International), GLUT5 (1:25 dilution, CoCalico Biologicals, Reamstown, PA, USA), or GAPDH (1:500 dilution, US Biological, Swampscott, MA, USA). Subsequently, membranes were washed three times in TBS-T and blocked in 5% milk for 10 min prior to incubation in the secondary antibodies (1:10,000 dilution, antirabbit IgG for SGLT1, GLUT2, and GLUT5; and 1:10,000 dilution of antimouse IgG for GAPDH; Sigma-Aldrich, St. Louis, MO, USA) at room temperature for 1 h. Membranes were washed three times in TBS-T and once in TBS alone. Colorimetric reaction was then performed using Opti-4CN (BioRad) substrate for 10 min. Amplified Opti-4CN substrate kit (BioRad) was used to enhance the SGLT1 band. Immunoreactive bands produced by this method were identified at about 70 kDa for SGLT1, 65 kDa for GLUT2, 55 kDa for GLUT5, and 35 kDa for GAPDH. Membranes were scanned, and densitometric analysis of the bands was performed using Scion Image (Scion Corporation, Frederick, MD, USA). All samples were run in duplicate; values were expressed as a ratio of the transporter to GAPDH levels in each sample.

GLUT5 Primary Antibody Production

Due to the unavailability of commercially prepared GLUT5 primary antibody, we developed an antibody using a GLUT5 epitope (the last 15 amino acids at the C-terminal of GLUT5 protein according to the NCBI sequence—EEKELNDLPPATREQ). The epitope was used by CoCalico Biologicals to induce production of antibody to the GLUT5 epitope in rabbits. After several boosts, serum from the production bleed was obtained. Western blot was performed using this unpurified antibody, and a band was identified as expected at 55 kDa. To validate that the antibody was indeed against GLUT5, we repeated our experiment by incubating GLUT5 primary antibody with the epitope peptide for 1 h; the band at 55 kDa disappeared, supporting the specificity of this antibody.

Transporter-Mediated Glucose Uptake

Transporter-mediated glucose uptake was measured using the everted sleeve technique,[12] whereby the harvested intestine was everted to expose the mucosal surface externally. One-centimeter, everted segments of duodenum, jejunum, and ileum were then mounted on steel rods and secured with 5-0 silk ties in preformed grooves, leaving the mucosal surface exposed to the bath solutions. These everted sleeves were kept in chilled (4°C) mammalian Ringers solution (in millimolar: 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) bubbled with 95% O_2/5% CO_2 until studied. Prior to transport studies, the everted sleeves were then preincubated in 8 ml of 38°C mammalian Ringers solution bubbled with 95% O_2/5% CO_2 for 5 min. After preincubation, the segments were immersed in an 8-ml incubation bath maintained at 38°C containing Ringers solution with iso-osmotic replacement of NaCl with either 1, 20, or 50 mM D-glucose and stirred at 1,200 rpm. ^{14}C-D-Glucose was used as the marker of transporter-mediated uptake, while ^{3}H-L-glucose (which is not absorbed via carrier-mediated facilitated transport) was used to correct for passive diffusion and adherent fluid. After a 1-min incubation, tissues were rinsed in 30 ml of chilled Ringers solution stirred at 1,200 rpm for 20 s and placed in glass scintillation vials. One half milliliters of tissue solubilizer (Solvable™, PerkinElmer, Boston, MA, USA) was used to solubilize the segments over a 3-h period in a 50°C water bath. After complete solubilization, 10 ml of scintillation counting cocktail (Opti-Fluor®, PerkinElmer) was added, and disintegrations per minute (DPM) were obtained using liquid scintillation counting. Radioactivity was measured using dual-isotope counting on a Beckman liquid scintillation counter. A standard quench curve was constructed, and corrections were performed to account for spillover. All counts were then expressed as DPM. Uptake was calculated using the following equation:[11]

$$J = (P - R \times M)/H \times t \times m$$

where P is the DPM of $^{14}C_{tiss}$, M is the DPM of $^{3}H_{inc}$, R is the DPM $^{14}C_{inc}$/DPM $^{3}H_{inc}$, H is the DPM $14C_{inc}$/nmol $glucose_{inc}$, t is time, m is length, tiss is the tissue, and inc is the incubation fluid.

Lineweaver Burke plots were constructed to calculate V_{max} and K_m values.

Statistical Analysis

Ratio of total cellular mRNA and protein expression for each transporter is expressed as a ratio of the transporter to the housekeeping gene GAPDH and is reported as the median value with interquartile ranges. Kruskal–Wallace and Wilcoxon rank sum tests were used to analyze the variation between the four time points and within each group at different anatomic regions (duodenum, jejunum, ileum). Fold changes in mRNA and protein were calculated as the maximal levels divided by minimum levels. Glucose uptake values are reported as the mean and standard error of the mean ($\bar{x} \pm$ SEM). ANOVA and Student's *t* tests were used to compare transport data across segments and within each segment, respectively. *p* value of <0.05 after Bonferroni corrections was considered significant; *n* values are number of mice.

Results

Feeding Pattern

Mice followed a nocturnal-based feeding pattern. Greater than 70% of chow intake occurred between 6 PM and 6 AM (data not shown).

Segmental Diurnal Variation in Expression of mRNA and Protein

All three intestinal segments showed a diurnal variation in expression of hexose transporter mRNA; total cellular protein levels showed a similar diurnal variation in duodenum and jejunum but with a delay of 12–18 h in time.

Duodenum mRNA levels of the three hexose transporters SGLT1, GLUT2, and GLUT5 peaked at 3 PM in duodenum ($p<0.05$ in all; Fig. 1). The relative fold changes (peak over minimum level) were twofold for SGLT1, threefold for GLUT2, and ninefold for GLUT5. Protein levels peaked at 9 AM, 18 h after mRNA levels for all three transporters ($p<0.02$ each for all three transporters; Fig. 1a). The relative fold change was twofold for all the three transporters.

In about half of the duodenal samples, we were unable to measure any protein for the hexose transporters or for GAPDH. This inability to identify and thus quantify protein tended to occur at 9 PM and 3 AM, requiring us to harvest tissues from additional mice at these time points to obtain an *n* of at least six mice at each time point.

Jejunum SGLT1 mRNA levels peaked at 9 PM ($p\leq0.04$; Fig. 1b). GLUT2 and GLUT5 mRNA levels peaked at 3 PM ($p\leq0.03$ each). Relative fold changes were threefold for SGLT1 and GLUT2 and 24-fold for GLUT5. Peaks in protein expression followed with a delay of 6–12 h for all three transporters; protein levels of SGLT1, GLUT2, and GLUT5 were greatest at 3 AM ($p<0.05$ each; Fig. 1b). GLUT2 levels remained high at 9 AM, while the other two transporter levels declined. Relative fold changes were twofold for SGLT1 and 1.5-fold for GLUT2 and GLUT5. Representative Western blots for jejunal protein levels are shown in Fig. 2.

Ileum mRNA levels of all three hexose transporters peaked at 9 PM ($p<0.03$ for all; Fig. 1c). Relative fold changes were threefold for SGLT1, tenfold for GLUT2, and eightfold for GLUT5. In contrast to duodenum and jejunum, protein levels of all three hexose transporters did not vary diurnally in ileum ($p\geq0.5$ each).

Transporter-Mediated Glucose Uptake

Uptake in all three segments demonstrated saturation kinetics consistent with transporter-mediated uptake. Glucose uptake in duodenum was greater at 9 PM compared to 9 AM for all three glucose concentrations (Fig. 3a). A similar pattern of increased uptake at 9 PM compared to 9 AM was also seen in jejunum and ileum, but only at 1 and 20 mM glucose concentrations (Fig. 3b and c). Uptake in ileum was much less than in duodenum and jejunum. Calculated V_{max} increased at 9 PM compared to 9 AM in duodenum and jejunum, but remained unchanged in ileum (Fig. 4a). K_m did not differ amongst the segments at 9 AM vs the 9 PM group (Fig. 4b).

Discussion

Many groups have studied the regulatory mechanisms of expression of hexose transporter mRNA and protein in the rat small intestine, all demonstrating a diurnal rhythm in the expression of SGLT1, GLUT2, and GLUT5.[1,2,7,9] Peak levels of mRNA occur in an anticipatory fashion just before or just after the onset of the dark cycle before the majority of feeding takes place, while total cellular protein levels peak 6–12 h later, coinciding with maximal chow intake.[10,13] All these investigations have been conducted in rats, and because of the relative inability to genetically alter the rat genome, the ability to further define the molecular-based mechanisms of underlying signaling pathways and other cellular mechanisms that might contribute to these regulatory changes is complicated. We believed

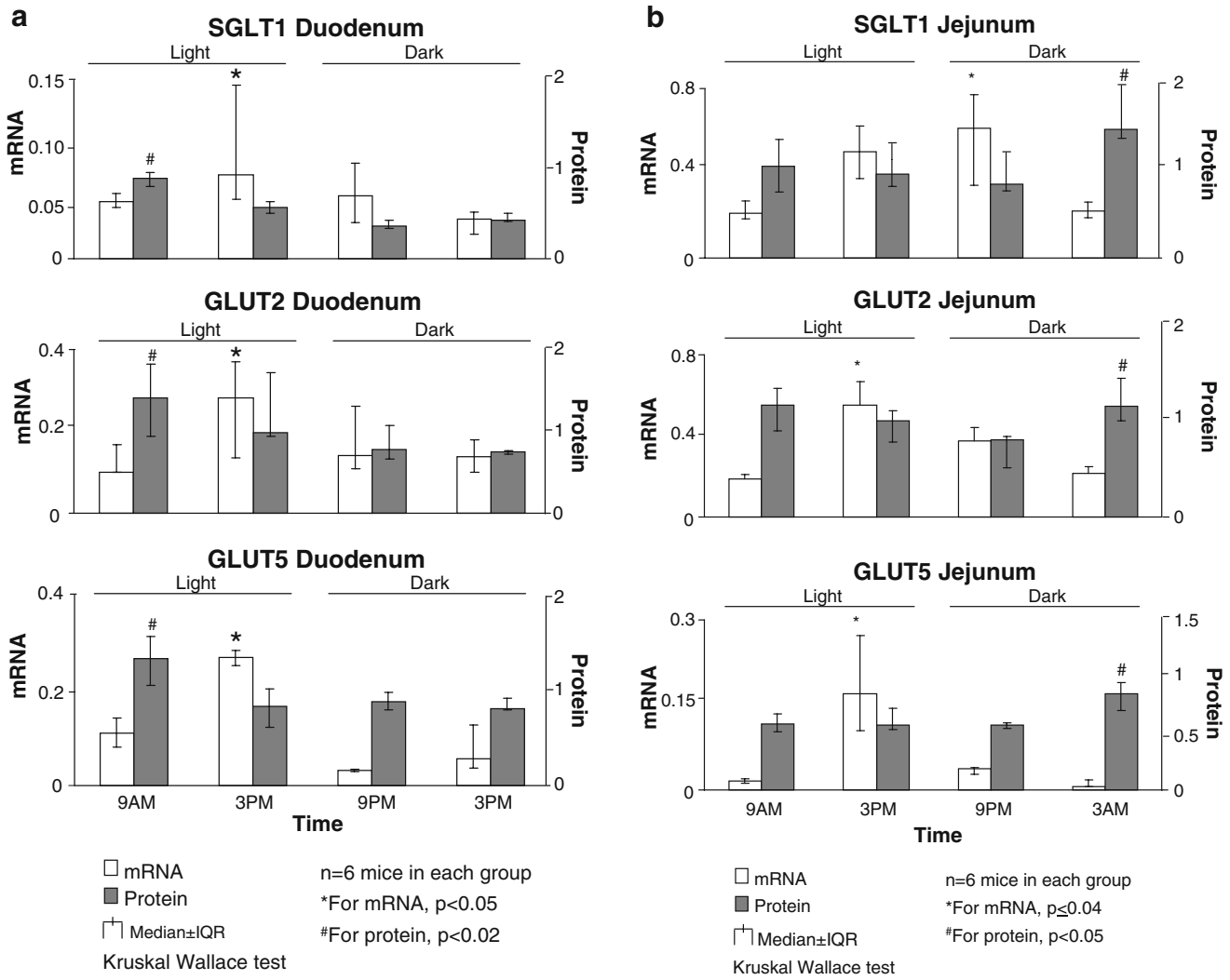

Figure 1 Variations in mRNA and protein expression levels of SGLT1, GLUT2, and GLUT5 transporters at four time points during the day in **a** duodenum, **b** jejunum, and **c** ileum; mRNA expression relative to expression of the housekeeper GAPDH demonstrated diurnal variation in all three segments of the small intestine. Total cellular protein levels varied diurnally in duodenum and jejunum only.

that it would be important to establish the existence of a similar, diurnal rhythm in the mouse to broaden genetic investigation into the regulation of hexose transport. To the best of our knowledge, there have been no such comprehensive reports of a diurnal expression of hexose transporters in mouse small intestine nor a correlation of the expression of these transporters with their actual absorptive function.

We demonstrated that when mice had free access to food and water, like rats, most of their food intake (>70%) occurred during the dark cycle between 6 PM and 6 AM. This diurnal feeding cycle correlated with the total cellular expression of mRNA and protein of the hexose transporters SGLT1, GLUT2, and GLUT5, as well as the timing of maximal transporter function, as measured by the everted sleeve technique. The levels of mRNA of the transporters in the duodenum and jejunum peaked in an anticipatory fashion during the late hours of the light cycle and just before the onset of the dark cycle when feedings occurred; this increased transcription appeared to occur in preparation for translation into the transport proteins to coincide with maximal feeding during the dark cycle. Indeed, the protein levels for SGLT1, GLUT2, and GLUT5 displayed a diurnally varying pattern of expression in the jejunum with greatest expression at 3 AM. This finding was supported by the demonstration of maximal transporter-mediated uptake by the small intestine during the dark cycle when food intake was greatest. Also, associated with this increased uptake was a 1.6-fold increase in V_{max} (a function of the number of transporters) from 9 AM to 9 PM, while K_m, a function of the receptor's transporter affinity for its

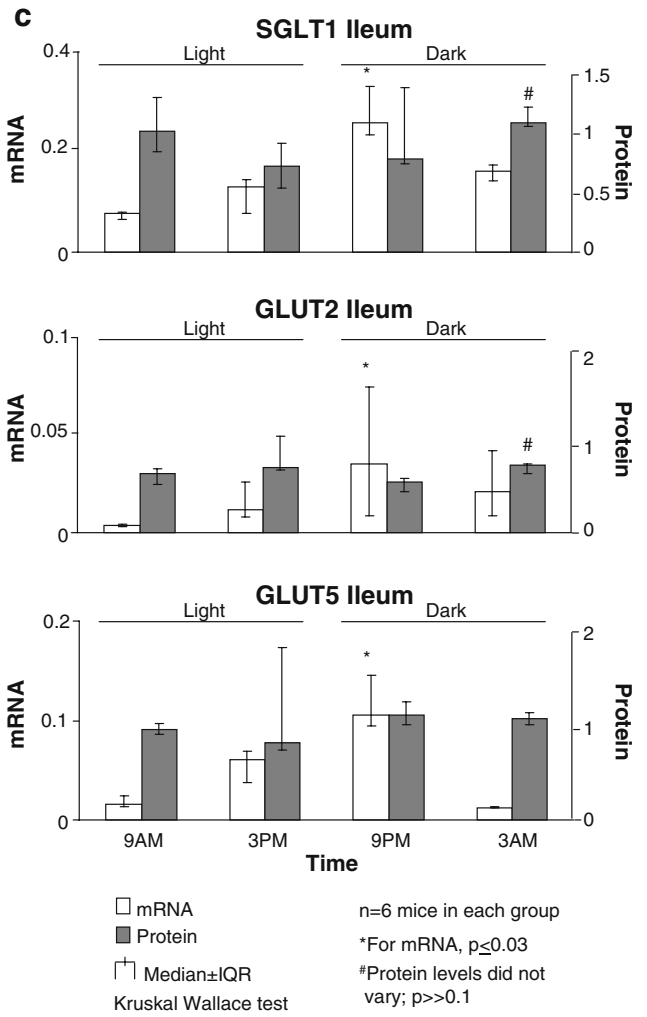

Fig. 1 (continued).

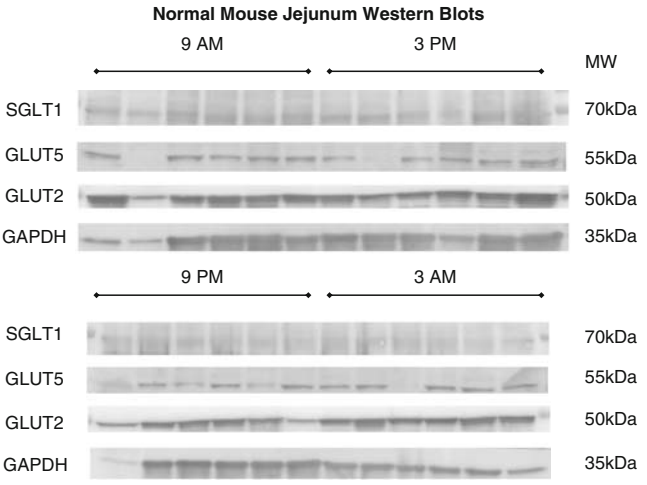

Figure 2 Representative Western blots for SGLT2, GLUT2, and GLUT5 in the jejunum; note that the calculations are based on expression of the transporter protein band compared to the band for GAPDH.

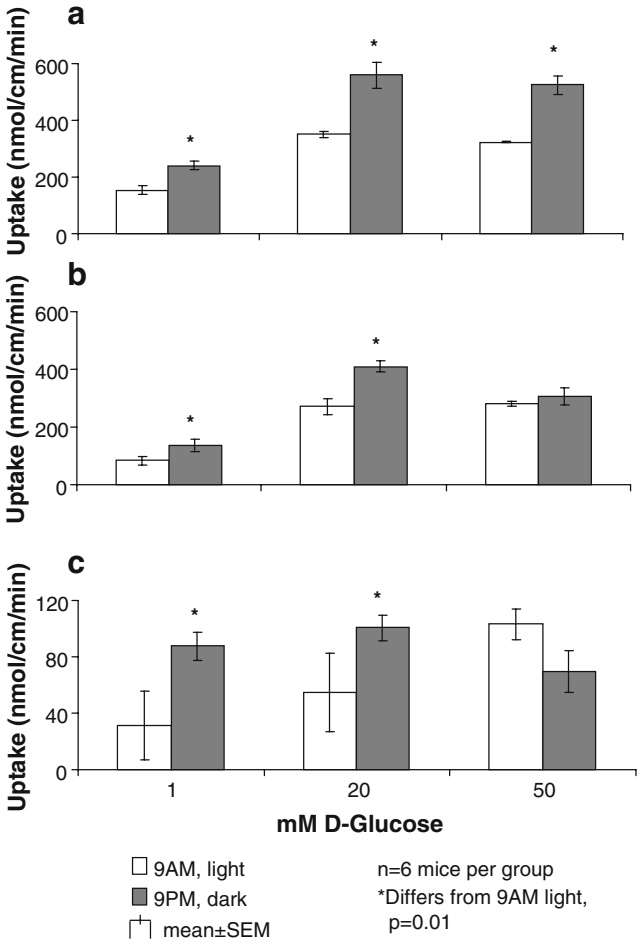

Figure 3 Difference in transporter-mediated glucose uptake in **a** duodenum, **b** jejunum, and **c** ileum at 9 AM vs 9 PM. Glucose uptake was greater at 9 PM than at 9 AM in all three intestinal segments.

substrate, remained unchanged in the jejunum, reinforcing the concept that the increased protein expression is not a result of a change in type of transporter or conformation rather an increase in the number of transporters expressed.

In the duodenum, transporter function (transport of glucose) showed a similar trend as in the jejunum, with a 1.8-fold increase in the V_{max} from 9 AM to 9 PM and no change in K_m; protein expression also had a diurnal trend; however, the peak expression occurred at 9 AM (during the early part of light cycle), at least as measured by our technique of isolation and semiquantitative Western blot. This relative peak in protein expression in mouse duodenum did not correlate with the timing of mRNA expression, transport activity as measured by the everted sleeve technique, maximal food intake, or the peak expression of protein in the rat duodenum.[6,10] We suggest that this apparent discrepancy, as measured by our technique of harvest and Western blot assay, may be an artifact related to the high activity of proteases expected to be present in the

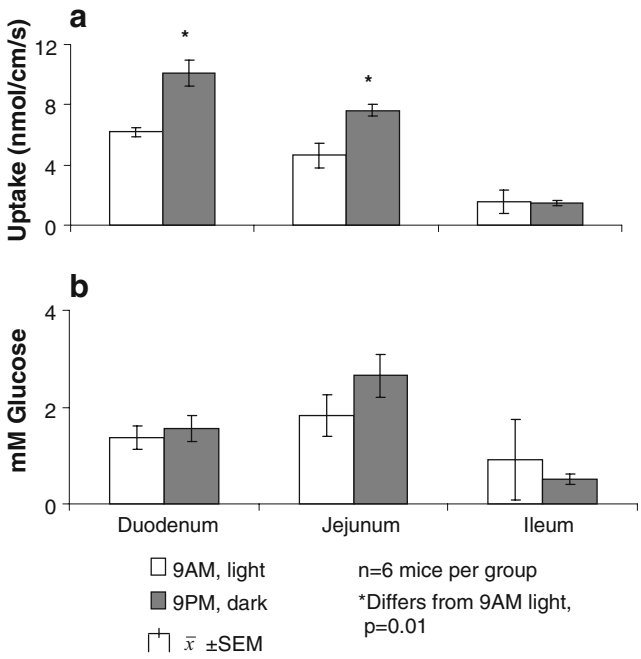

Figure 4 Variation in the **a** V_{max} and **b** K_m for each intestinal segment from 9 AM to 9 PM. In duodenum and jejunum, the mean V_{max} was greater at 9 PM than at 9 AM; K_m remained unchanged.

duodenal lumen at 9 PM and 3 AM during feeding, which may have led to degradation of these membrane transport proteins during tissue harvest. Western blot analysis requires cell lysis to allow the protein transporters to be recognized by the antibodies. Because the proteins are in solution, should any active proteases be present, degradation may occur. Despite the addition of protease inhibitors to the media, it is possible that high activities of proteases in the duodenal lumen during the nocturnal eating would affect the apparent levels of proteins (both transporters and the housekeeping gene GAPDH), making the measurements less reliable. Evidence for the latter is that in about 50% of mice, we were unable to measure any protein expression of the transporters or even the housekeeping gene GAPDH, suggesting a nonselective degradation of protein in the duodenal samples. These findings question the reliability of the measurements by Western blots of duodenal protein by this technique. The functional uptake studies of membrane-bound hexose transporters may not be as susceptible to these changes, explaining the increase in uptake at 9 PM.

Ileal mRNA levels of all three transporters in mice peaked during the early part of the dark cycle with a delay of 6 h from the peak times in the duodenum and jejunum, consistent with findings in the rat.[10] This temporal delay may be a function of the time needed for ingested food to reach the ileum, yet remaining consistent with the anticipation of food for all three transporters. Unlike in the duodenum and jejunum, however, the total cellular protein levels measured by Western blot analyses showed no variation with the time of the day. In large animals, most carbohydrate absorption occurs during transit through the duodenum and jejunum, with minimal intraluminal carbohydrate remaining for absorption in the ileum. Whether this occurs in the mouse is unknown, but this observation might explain the lack of a change in total cellular protein levels or number of transporters as depicted by function (V_{max}) in the ileal segment from 9 AM to 9 PM. This absence of a diurnal rhythm of total cellular protein expression and hexose transport in the ileum of mice also occurs in the rat.[10]

In contrast to total cellular levels of protein expression in the ileum, glucose uptake measured by the everted sleeve technique was increased at 9 PM compared to 9 AM with a similar trend as in duodenum and jejunum. The explanation of this increase in hexose transporter function cannot be further delineated by our study; however, several potential explanations are possible. Our techniques of measuring total cellular mRNA and protein levels do not necessarily reflect membrane expression or function. Indeed, considerable evidence suggests that there are cytoplasmic pools of preformed SGLT1 and GLUT2 protein that can be translocated rapidly to the apical membrane to increase functional uptake of luminal hexoses.[14,15] Evidence is strongest for GLUT2 translocation.[16–19] Such translocation of preformed cytoplasmic transporter protein(s) to the apical membrane would not be recognized by our techniques for measuring total cellular protein levels but would explain our findings. Further experiments will be necessary to elucidate the mechanisms of this diurnal variation in function of hexose transporters.

An interesting finding from our experiment was an apparent difference in the measured K_m of hexose transport in the ileum compared to the duodenum and jejunum. This difference in K_m was small and of questionable importance but does raise the question of whether there may be a different type or conformational change of the transporter present in the ileum, with a higher affinity for these sugars to allow more efficient absorption of any nutrients that remained in the lumen. This difference could be attributed to differences in the ratio of SGLT1 and GLUT2 expressed at the apical membrane as a result of lesser quantities of glucose in the ileal content, secondary to a change in conformation of the transporter(s) within the membrane, or possibly due to expression of a splice variant of transporters not recognized by our real-time PCR and Western blot assays. Further experiments will be required to differentiate these possibilities.

In summary, our study demonstrates that the mouse, similar to the rat, ingests food primarily at night during the dark cycle, and the expression and function of the hexose

transport proteins SGLT1, GLUT2, and GLUT5 follow a diurnal pattern. Expression of mRNA is anticipatory to feeding, while protein levels, at least in the jejunum, are increased during the time of maximal feeding. The peaks in both protein expression and transport function increase by 1.5- to twofold compared to the trough levels. Demonstration of this diurnal variation should facilitate investigation of molecular mechanisms regulating the expression of the transport proteins.

References

1. Affleck JA, Helliwell PA, Kellett GL. Immunocytochemical detection of GLUT2 at the rat intestinal brush-border membrane. J Histochem Cytochem 2003;51:1567–1574.
2. Au A, Gupta A, Schembri P, Cheeseman CI. 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.
3. Bell GI, Burant CF, Takeda J, Gould GW. Structure and function of mammalian facilitative sugar transporters. J Biol Chem 1993;268:19161–19164.
4. Castello A, Guma A, Sevilla L, Furriols M, Testar X, Palacin M, et al. Regulation of GLUT5 gene expression in rat intestinal mucosa: regional distribution, circadian rhythm, perinatal development and effect of diabetes. Biochem J 1995;309(Pt 1):271–277.
5. Corpe CP, Bovelander FJ, Hoekstra JH, Burant CF. The small intestinal fructose transporters: site of dietary perception and evidence for diurnal and fructose sensitive control elements. Biochim Biophys Acta 1998;1998(1402):229–238.
6. Corpe CP, Burant CF, Hoekstra JH. Intestinal fructose absorption: clinical and molecular aspects. J Pediatr Gastroenterol Nutr 1999;28:364–374. doi:10.1097/00005176-199904000-00004.
7. Corpe CP, Burant CF. Hexose transporter expression in rat small intestine: effect of diet on diurnal variations. Am J Physiol 1996;271:G211–G216.
8. Helliwell PA, Richardson M, Affleck J, Kellett GL. 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.
9. Helmrath MA, VanderKolk WE, Can G, Erwin CR, Warner BW. Intestinal adaptation following massive small bowel resection in the mouse. J Am Coll Surg 1996;183:441–449.
10. Houghton SG, Duenes JA, Fatima J, Iqbal CW, 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.
11. Houghton SG, Zarroug AE, Duenes JA, Fernandez-Zapico ME, Sarr MG. 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.
12. Karasov WH, Diamond JM. A simple method for measuring intestinal solute uptake in vitro. J Comp Physiol 1983;152:105–116.
13. Levin RJ. Digestion and absorption of carbohydrates—from molecules and membranes to humans. Am J Clin Nutr 1994;59:690S–698S.
14. Kellett GL. The facilitated component of intestinal glucose absorption. J Physiol 2001;531:585–595. doi:10.1111/j.1469-7793.2001.0585h.x.
15. Kellet GL, Helliwell PA. The diffusive component of intestinal glucose absorption is mediated by the glucose-induced recruitment of GLUT2 to the brush border. Biochem J 2000;350:155–162. doi:10.1042/0264-6021:3500155.
16. Kipp H, Khoursandi S, Scharlau D, Kinne RK. More than apical: distribution of SGLT1 in CaCO-2 cells. Am J Physiol 2003;285:C737–C749.
17. Pan X, Terada T, Okuda M, Inui K. The diurnal rhythm of the intestinal transporters SGLT1 and PEPT1 is regulated by the feeding conditions in rats. J Nutr 2004;134:2211–2215.
18. Rhoads DB, Rosenbaum DH, Unsal H, Isselbacher KJ, Levitsky LL. Circadian periodicity of intestinal Na+/glucose cotransporter 1 mRNA levels is transcriptionally regulated. J Biol Chem 1998;273:9510–9516. doi:10.1074/jbc.273.16.9510.
19. Tavakkolizadeh A, Berger UV, Shen KR, Levitsky LL, Zinner MJ, Hediger MA, et al. Whang EEl. Diurnal rhythmicity in intestinal SGLT-1 function, V(max), and mRNA expression topography. Am J Physiol 2001;280:G209–G215.

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ORIGINAL ARTICLE

How Uncommon are Isolated Lung Metastases in Colorectal Cancer? A Review from Database of 754 Patients Over 4 Years

Ker Kan Tan · Gilberto de Lima Lopes Jr. · Richard Sim

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Abstract
Background It is commonly thought that colon cancer metastases to the lungs without involvement of the liver are rare.
Methods We performed a retrospective review of all patients with colorectal cancer diagnosed between December 2003 and August 2007 in Singapore. Isolated lung metastases were determined as (1) Definite if there was confirmed histology or cytology of the lung lesion(s) in the absence of liver lesions on CT scan, and (2) Probable if there were only radiological evidence suggestive of lung metastases rather than lung primary also in the absence of liver lesions on CT scan.
Results There were 196 patients with rectal and 558 patients with colon cancer (369 left-sided and 189 right-sided). There were 13 definite isolated lung metastases, and the remaining 43 were probable. Twenty-three (12%) patients with rectal cancer and 33 (6%) patients with colon cancer had isolated lung metastases (OR 2.11, 95% CI 1.21–3.70). Patients with ≥pT3 lesions (OR 1.92, 95% CI 0.75–4.93) and ≥pN1 (OR 1.56, 95% CI 0.86– 2.83) were more likely to have isolated lung metastases.
Conclusion The true incidence of isolated lung without liver metastases in colorectal cancer is likely to lie between 1.7% and 7.2%. While the incidence of isolated lung metastases is twice as common in patients with rectal cancer, it is still significant in patients with colon cancer. The absence of liver involvement should not preclude a search for lung metastases.

Keywords Skipped metastases · Lung metastases · Colorectal cancer · Isolated

Introduction

The incidence of colorectal cancers is rising worldwide. Surgical resection is the primary treatment modality for colorectal cancers, and its outcome is most closely related to the extent of disease at presentation. However, metastases are present in up to 30% of patients with colorectal cancers at the time of presentation.[1] The commonest sites of involvement are the regional lymph nodes, liver, lungs, and peritoneum.[2] Most deaths from cancer are still due to metastases.[2]

As the venous drainage of the colon is via the portal system, the first site of hematogenous spread of malignancy has always been regarded as the liver. But metastases bypassing the liver have been mentioned in several reports over the years, including to the lungs and thyroid.[3–6]

Lung metastases are seen in about 10–15% of all colorectal cancer metastases, but only 10% of these are isolated in the absence of liver metastases.[3,4] The higher incidence of this isolated lung metastases in rectal compared to colonic carcinoma was attributed to the direct hematogenous spread into the systemic circulation via the inferior and middle rectal veins, bypassing the portal venous system.[3,7]

However, colon cancer with isolated metastases not involving the liver is considered very rare with only a few

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reports mentioning the existence of such an entity.[3,4] Our study aims to review the incidence of isolated lung metastases in all patients with colorectal cancers and to identify clinical factors that could be associated with this phenomenon.

Methods

Study Population

Tan Tock Seng Hospital is a single 1,300-bed hospital, the second largest in Singapore and provides secondary and tertiary medical care for about 1.5 million people. A retrospective review of the records of all patients diagnosed with colorectal cancers in our institution between December 2003 and August 2007 was performed. Data for this study was derived from a database of de-identified patient information.

Definition of Isolated Lung Metastases and Colon and Rectal Cancers

All patients with evidence of lung metastases without liver involvement were included in the review. Isolated lung metastases were determined as (1) Definite if there was confirmed histology or cytology of the lung lesion(s) in the absence of liver lesions on CT scan, and (2) Probable if there were only radiological evidence suggestive of lung metastases rather than lung primary also in the absence of liver lesions on CT scan. The findings on the CT scans were agreed upon by two independent radiologists. All scans were performed with intravenous contrast using a Siemens SOMATOM Sensation 64-slice CT scanner (Siemens AG, Wittelsbacherplatz, Muenchen, Germany) for the past 3 years.

Our institution's routine follow-up protocol for any patient with resected colorectal malignancy includes three monthly follow-up with CEA levels for the first 2 years and six monthly follow-up with CEA levels for the next 3 years with surveillance colonoscopy done 1 year after the surgery. CT scans of the abdomen and pelvis, and definitely thorax, is not routine and is only usually performed if there's a high index of suspicion or for monitoring of response of metastatic disease undergoing adjuvant therapy. Some of the histological features of the lung lesions that were suggestive of colorectal primary would include the presence of histological immunological markers such as Cytokeratin 20 (CK-20) and Villin, and in the absence of CK-7 and thyroid transcription factor 1 (TTF-1). Synchronous lung metastases were described as lesions arising within 6 months of the diagnosis of the primary, while metachronous metastases were lesions arising after 6 months.

We defined patients with rectal cancer in our study group as those located up to 15 cm from the anal verge excluding the rectosigmoid region. The location of the primary lesion in the colon cancer group commenced from the cecum until the rectosigmoid junction. These patients were also further subdivided into right- and left-sided lesions. Right-sided cancers were regarded if the primary was located from the cecum until the transverse colon, while left-sided cancers was located from the splenic flexure till the rectosigmoid junction.

Exclusion Criteria

Patients were excluded if there were any liver lesions suggestive of metastases within 6 months of diagnosis of the isolated lung metastases, but patients with liver metastases after 6 months from diagnosis of isolated lung metastases were included as it would indicate the progression of the dissemination of the malignancy. Patients were also excluded if the lung lesion(s) did not grow in the absence of adjuvant chemotherapy, indicating a higher probability that they were of infective or scar origins.

Statistical Analysis

For all the colorectal cancer patients reviewed for possible isolated lung metastases, differences in the age, gender, ethnic differences, and site of primary malignancy were tested using Chi square. Other association between the presence of isolated lung metastases and the tumor staging, nodal status of the resected specimens and the location of primary colonic lesions were also tested using Chi square. All results were presented with their Odds ratios (OR) and their 95% confidence interval (CI). All analyses were performed using the SPSS 13.0 statistical package (Chicago, IL, USA).

Results

There were 754 patients diagnosed with colorectal cancers in our institution from December 2003 until August 2007. Their mean age was 67.8 [standard deviation (SD) 12.6] years. A total of 196 (26.0%) patients had rectal cancers, while 558 (74.0%) had colon cancers, with 189 (25.1%) right-sided lesions and 369 (48.9%) left-sided ones. Table 1 illustrates the characteristics of all the 754 patients who had colorectal cancers.

Surgery was performed in 730 (96.8%) patients. The remaining 24 (3.2%) patients declined surgery. Emergency operation was performed in 181 patients (24.0%), and their indications were intestinal obstruction (133, 17.4%), bleeding (25, 3.3%), and perforation (25, 3.3). Details of the histology of the resected specimens are shown in Table 2.

Table 1 Characteristics of All 754 Patients who were Diagnosed with Colorectal Cancers

Characteristics	Results
Mean age (years)	67.8 (SD 12.6)
Gender	
Male	398 (52.8%)
Female	356 (47.2%)
Location of malignancy	
Right colon	189 (25.1%)
Caecum	41 (5.4%)
Ascending colon	54 (7.2%)
Hepatic flexure	36 (4.8%)
Transverse colon	58 (7.7%)
Left colon	369 (48.9%)
Splenic flexure	22 (2.9%)
Descending colon	59 (7.8%)
Sigmoid and rectosigmoid	288 (38.2%)
Rectum	196 (26.0%)

From the resected specimens, majority of the specimen showed an advanced T staging (T3/T4) in 83.6%, and positive nodal involvement (≥N1) in 54.8%, with a median of 17 (1–99) lymph nodes harvested. An overwhelming proportion of the malignancy were of moderate differentiation (n=679, 92.3%). Distant metastases was already present in 168 (22.3%) patients at presentation, with liver the most common organ involved in 15.0% (n=113). The median follow-up for all the patients was 21 (6–40) months.

There were a total of 56 patients with isolated lung metastases, 33 (59%) in patients with colon primary, and 23 (41%) in patients with rectal cancers. Of these 56 lung metastases, 13 (23.2%) were definite, (seven in colon cancers, six in rectal cancers) with the remaining 43 (76.8%) probable (26 in colon cancers, 17 in rectal cancers). Thirty (53.6%) patients had synchronous isolated lung metastases while the remaining 26 (46.4%) had metachronous lesions. The median time taken for isolated lung metastases to be diagnosed was 17 (4–36) months after diagnosis of the primary. Carcinoembryonic antigen (CEA levels) was only raised in 18 (32.1%) during follow-up. Table 3 shows the characteristics and details of the group of patients with isolated lung metastases.

Table 2 Histology of Resected Specimens

Tumor staging	
T1	33 (4.6%)
T2	84 (11.8%)
T3	405 (56.8%)
T4	191 (26.8%)
Median number of lymph nodes removed	17 (1–99 lymph nodes)
Nodal staging	
N0	322 (45.2%)
N1	214 (30.0%)
N2	177 (24.8%)
Grading of tumor specimen	
Well differentiated	26 (3.5%)
Moderately differentiated	679 (92.3%)
Poorly differentiated	31 (4.2%)
AJCC's classification staging	
I	79 (10.5%)
II	193 (25.6%)
III	289 (38.3%)
IV	168 (22.8%)
Number of patients with >1 metastases at diagnosis	32 (4.2%)

Table 3 Characteristics of the 56 Patients with Isolated Lung Metastases

Characteristics	Results
Median age (years)	65 (23–88)
Gender	
Male	28 (50.0%)
Female	28 (50.0%)
Location of colorectal malignancy	
Colon	33 (58.9%)
Right-sided	8 (14.3%)
Left-sided	25 (44.6%)
Rectum	23 (41.1%)
Tumor staging of resected specimen	
T1	0 (0.0%)
T2	5 (8.9%)
T3	29 (51.8%)
T4	18 (32.1%)
Nodal status of resected specimen	
N0	18 (32.1%)
N1	23 (41.1%)
N2	11 (19.6%)
Diagnosis of isolated lung metastases	
Definite	13 (23.2%)
Colon	7 (12.5%)
Rectum	6 (10.7%)
Probable	43 (76.8%)
Colon	26 (46.4%)
Rectum	17 (30.4%)
CEA levels of patients performed when isolated lung metastases was diagnosed:	
When isolated lung metastases was diagnosed at presentation	20 (35.7%)
Raised	15 (26.8%)
Normal	5 (8.9%)
When isolated lung metastases was diagnosed during follow up	36 (64.3%)
Raised	18 (32.1%)
Normal	18 (32.1%)
Timing of isolated lung metastases	
Synchronous lesions	30 (53.6%)
Metachronous lesions	26 (46.4%)
Median time for diagnosis of isolated lung metastases after diagnosis of the primary (months)	17 (4–36)

In the 13 patients with definite diagnosis, eight had cytological confirmation, while five had histological evidence, of which four underwent wedge resection of their lung metastases, while one had a core biopsy of the lesion. In these 13 patients, details of the immunohistochemistry were present in seven, for which all were positive for CK-20 and Villin and negative for CK-7 and TTF-1. Of all the patients who underwent chest X-ray preoperatively or during follow-up, only eight (14.3%) patients had features suggestive of lung metastases, and all underwent CT scans of the thorax subsequently. In the group of patients with probable lung metastases, 27 had bilateral lung lesions, while 16 had unilateral nodules. Figure 1 summarised the above findings.

In the 33 patients with colonic primary, 13 had adjuvant chemotherapy, whereas in the 23 patients with rectal primary, four had neoadjuvant chemoradiation therapy, four had adjuvant radiotherapy, while nine have adjuvant chemotherapy.

Patients with rectal cancers were strongly associated with the presence of isolated lung metastases (OR 2.11, 95% CI 1.21–3.70, p=0.011) compared to colon cancer patients (Table 4). Analysis of the subgroup of patients with colonic primary showed that isolated lung metastases were slightly more commonly seen in left-sided colon cancers compared to right sided ones (OR 1.64, 95% CI 0.73–3.72, p=0.260; Table 5), though not statistically significant. More advanced T-staging, ≥T3 lesions (OR 2.44, 95% CI 0.57–10.43, p=0.291) seems to be associated with isolated lung metastases in colon cancers. Whereas in rectal cancers, the presence of nodal disease (OR 3.03, 95% CI 0.97–9.48, p=0.055) appears to be more strongly associated with isolated lung metastases (Table 6).

Discussion

Reports decades ago showed that pulmonary parenchyma metastases happened in about 10–15% of all colorectal cancers with an approximately 10% of these cases being isolated to the lung.[3,4] It has been reported that the lungs could be the only site of metastasis when the primary tumor is in the rectum, with incidence of up to 12%.[4,8,9] The high incidence of systemic recurrence in rectal carcinoma was attributed to direct spread into the systemic circulation via the inferior and middle rectal veins.[3,7,10]

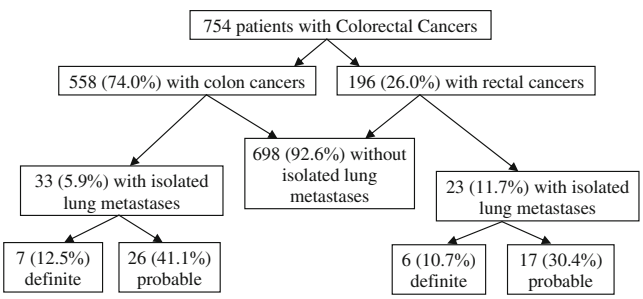

Figure 1 Flowchart describing the outcome of the 754 patients with reference to isolated lung metastases.

The present series supports this hypothesis as those patients with rectal cancers were shown to have a much higher incidence of isolated pulmonary metastases than those with colon cancers: 12% vs. 6%, respectively. This sizeable percentage rate of isolated lung metastases in rectal cancers has a rather serious implication in its management. CT scans of the thorax should be routinely carried out for patients with rectal cancers for staging and surveillance since around half of these lesions in the present series occurred at diagnosis or within 6 months of presentation. This is especially so as reports have shown favorable long-term results even after repeated surgical resection for lung metastases from colorectal primaries.[11,12]

However, there has never been any postulation for the rationale associating colon cancer with isolated lung metastases, unlike that of rectal cancer. As the venous drainage of the colon is via the portal system, the first site of hematogenous spread of malignancy has always been regarded as the liver. But metastases bypassing the liver have been mentioned in several reports over the years, involving the lungs and/or thyroid only.[3–7] The incidence of isolated lung without liver metastases in colon cancer patients ranged from 1% to 3.8% and was only mentioned in a few reports over the decades[3,4] compared to 5.9% in the present series.

The precise mechanism accounting for this phenomenon of skip metastasis bypassing the first draining solid organ or the sentinel node through the hematogenous and lymphatics route is unclear. Various reports cite nonanatomic spread to any draining lymph node or solid organ and nonsequential spread within the lymphatic bed or hematogenous sites as possible explanations. These features could be related to the differences in tumor biology among various patients, tumor types, or even within a given tumor,[13–15] supporting the "seed and soil" hypothesis.

The authors feel that the increased presence of isolated lung metastases in patients with advanced T and N disease is not surprising and has been highlighted in other reports,[16–19] even though the result was statistically not significant. This tendency may perhaps reflect the increased likelihood of skipped metastases through nonanatomical, nonsequential channels after surgery for locally advanced tumors, for which further studies would be required. But isolated lung metastases also occurred in a significant proportion of patients with T2 and N0 disease. These features reinforced a heightened awareness at all times in detecting metastatic disease during the management of all

Table 4 Comparing Colon Ca Against Rectal Ca in Association with Isolated Lung Metastases

Variables	Absence of Isolated Lung Metastases	Presence of Isolated Lung Metastases	OR (95% CI) *p* value
Site of primary malignancy			
Colon	525	33	1.00
Rectal	173	23	2.11 (1.21 – 3.70)* *p*: 0.011

*p=0.011

patients with colorectal malignancy regardless of the stage of their primary cancers.

CEA has not been used as a screening test for detecting primary colorectal malignancy due to its insufficient specificity or sensitivity.[20] But its utilization as a tool to detect recurrent disease in patients following curative resection of colorectal cancers has been well documented.[21–24] However, in this current series, only half of the patients with isolated lung metastases were found to have elevated CEA levels during follow-up after initial curative surgery. This was not surprising, as CEA levels were shown to be especially useful in the detection of recurrent disease in the liver with sensitivity of up to 80%, while CEA was much less reliable at predicting recurrent disease in other locations.[23,25,26]

Recent reports have recommended the regime of annual CT scan for the first 3 years after resection for AJCC stage

Table 6 Analysis of Variables for Isolated Lung Metastases in the Patients with Rectal Primary

Variables	Absence of Isolated Lung Metastases	Presence of Isolated Lung Metastases	OR (95% CI)
Age group			
≤65	83	11	1.00
≥66	90	12	1.01 (0.42–2.40) p=1.00
Gender			
Male	102	13	1.00
Female	71	10	1.11 (0.46 – 2.66) p=0.825
Tumor staging of resected specimen			
T1/T2	44	3	1.00
T3/T4	117	16	2.01 (0.56–7.22) p=0.409
Nodal status of resected specimen			
N0	69	4	1.00
N1/N2	91	16	3.03 (0.97–9.48) p=0.055

Table 5 Analysis of Variables for Isolated Lung Metastases in the Patients with Colonic Primary

Variables	Absence of Isolated Lung Metastases	Presence of Isolated Lung Metastases	OR (95% CI) *p* value
Age group			
≤65	197	16	1.00
≥66	328	17	0.64 (0.32–1.29) p=0.267
Gender			
Male	268	15	1.00
Female	257	18	1.25 (0.62–2.54) p=0.592
Location of malignancy in the colon			
Right Colon	181	8	1.00
Left Colon	344	25	1.64 (0.73–3.72) p=0.260
Comparing malignancy in the sigmoid colon versus rest of colon			
Sigmoid Colon	254	16	1.00
Rest of Colon	271	17	1.00 (0.49–2.01) p=1.00
Tumor staging of resected specimen			
T1/T2	68	2	1.00
T3/T4	432	31	2.44 (0.57–10.43) p=0.291
Nodal status of resected specimen			
N0	234	15	1.00
N1/N2	265	19	1.12 (0.56–2.25) p=0.859

II and III disease.[27,28] But neither the role of CT scan nor CEA can be used alone. Evaluation of each patient must include a thorough clinical evaluation, colonoscopy, CEA, and the necessary imaging modalities.[29,30]

All the above points brought out an important message in the current practice. As we tend to focus only on patients with stage III or high risk stage II disease during the follow-up with the aid of CEA levels, we may have already missed several patients with resectable metastatic disease. In view of the unpredictability of metastatic potential in each colorectal malignancy in every patient, the authors feel that the role of tumor genetic profiling may help to predict the outcome and hopefully prognosticate the disease in the future.

In our series, only four patients (7.1%) with isolated lung metastasis underwent metastasectomy, for which two are still alive currently (>3 years since the lung surgery), while the other two have passed away since. It has been shown in the literature that early diagnosis of colorectal pulmonary metastases is of paramount importance, as several reports have highlighted the survival benefits of pulmonary metastasectomy.[31–34] If the metastases could be completely removed, the cumulative 5- and 10-year (total) survival could be as high as 44% and 22%, respectively.

The majority of patients with isolated lung metastasis in our series were not suitable for resection due to several reasons. These included bilateral and multiple lung lesions, control of primary disease, inadequate pulmonary reserve after the planned resection, comorbid conditions, and patients' decisions. These are similar to the criteria mentioned in the literature of suitability for resection of pulmonary metastases.[31–34] After resection, improved survival was shown to be related to various factors such as smaller number and sizes of metastases, lower intrapulmonary tumor load, long disease-free interval, normal serum CEA level, and the absence of concomitant liver metastases and mediastinal lymph node spread. Pulmonary metastasectomy can even be performed effectively in patients with recurrent disease after prior hepatic resection for colorectal metastases, and prolonged survival can still be achieved.

As with most studies, there were several limitations in the present study. This series of patients was enrolled from a single institution, and the data was retrospectively reviewed. The small number of patients with isolated lung metastases may also mask several other important factors that could be accountable. Another significant point was that not all diagnosed lung metastases in this series were diagnosed through confirmed histology or cytology of the lung lesion(s). As such, some of the cases included may have had lung primaries or just post-infective lung scarring. We also do not use PET scan routinely, so some cases classified as isolated lung metastases may actually have other occult metastases as well. The fact that CT scan of the thorax was also not routinely performed for all patients was very significant, as it is possible that other patients with isolated lung metastases may be missed as a consequence, especially since rise in CEA was not present in half of the patients with isolated lung metastases during follow-up. Considering these limitations, the true incidence of isolated lung metastases may range from 3.1% to 11.7% in patients with rectal cancers, and from 1.3% to 5.9% in patients with colon cancers.

Although these limitations are significant, this study remains important in highlighting the presence and extent of isolated lung metastases in colorectal malignancy. It also attempted to identify factors that could aid in the detection of patients with isolated lung metastases earlier and perhaps allow proper interventions to be instituted.

Conclusion

The true incidence of isolated lung without liver metastases in colorectal cancer could lie between 1.7% and 7.2%. While the incidence of isolated lung metastases is twice as common in patients with rectal cancer, it is still significant in patients with colon cancer. Search for lung metastases should be included in the staging and surveillance of all patients with rectal cancer. The absence of liver involvement should not preclude a search for lung metastases.

References

1. Eisenberg B, Decosse JJ, Harford F, Michalek J. Carcinoma of the colon and rectum: the natural history reviewed in 1704 patients. Cancer 1982;49(6):1131–1134. doi:10.1002/1097-0142(19820315)49:6<1131::AID-CNCR2820490611>3.0.CO;2-T.
2. Galandiuk S, Wieand HS, Moertel CG, Cha SS, Fitzgibbons RJ Jr, Pemberton JH, Wolff BG. Patterns of recurrence after curative resection of carcinoma of the colon and rectum. Surg Gynecol Obstet 1992;174(1):27–32.
3. Pihl E, Hughes ES, McDermott FT, Johnson WR, Katrivessis H. Lung recurrence after curative surgery for colorectal cancer. Dis Colon Rectum 1987;30:417–419. doi:10.1007/BF02556487.
4. McCormack PM, Attiyeh FF. Resected pulmonary metastases from colorectal cancer. Dis Colon Rectum 1979;22:553–556. doi:10.1007/BF02587003.
5. Hanna WC, Ponsky TA, Trachiotis GD, Knoll SM. Colon cancer metastatic to the lung and the thyroid gland. Arch Surg 2006;141(1):93–96. doi:10.1001/archsurg.141.1.93.
6. Phillips JS, Lishman S, Jani P. Colonic carcinoma metastasis to the thyroid: a case of skip metastasis. J Laryngol Otol 2005;119(10):834–836. doi:10.1258/002221505774481273.
7. Scheele J, Altendorf-Hofmann A, Stangl R, Gall FP. Pulmonary resection for metastatic colon and upper rectum cancer. Is it useful? Dis Colon Rectum 1990;33(9):745–752. doi:10.1007/BF02052319.
8. Goya T, Miyazawa N, Kondo H, Tsuchiya R, Naruke T, Suemasu K. Surgical resection of pulmonary metastases from colorectal cancer. 10-year follow-up. Cancer 1989;64(7):1418–1421. doi:10.1002/1097-0142(19891001)64:7<1418::AID-CNCR2820640709>3.0.CO;2-N.

9. Wilkins EW Jr, Head JM, Burke JF. Pulmonary resection for metastatic neoplasms in the lung: experience at the Massachusetts Hospital. Am J Surg 1978;135:480–483. doi:10.1016/0002-9610(78)90023-5.
10. Akasu T, Yamaguchi T, Fujimoto Y, Ishiguro S, Yamamoto S, Fujita S, Moriya Y. Abdominal sacral resection for posterior pelvic recurrence of rectal carcinoma: analyses of prognostic factors and recurrence patterns. Ann Surg Oncol 2007;14(1):74–83. doi:10.1245/s10434-006-9082-0.
11. Welter S, Jacobs J, Krbek T, Krebs B, Stamatis G. Long-term survival after repeated resection of pulmonary metastases from colorectal cancer. Ann Thorac Surg 2007;84(1):203–210. doi:10.1016/j.athoracsur.2007.03.028.
12. Ishikawa K, Hashiguchi Y, Mochizuki H, Ozeki Y, Ueno H. Extranodal cancer deposit at the primary tumor site and the number of pulmonary lesions are useful prognostic factors after surgery for colorectal lung metastases. Dis Colon Rectum 2003;46(5):629–636. doi:10.1007/s10350-004-6623-0.
13. Merrie AE, Phillips LV, Yun K, McCall JL. Skip metastases in colon cancer: assessment by lymph node mapping using molecular detection. Surgery 2001;129(6):684–691. doi:10.1067/msy.2001.113887.
14. Herrera-Ornelas L, Justiniano J, Castillo N, Petrelli NJ, Stulc JP, Mittelman A et al. Metastases in small lymph nodes from colon cancer. Arch Surg 1987;122:1253–1256.
15. Tang R, Wang JY, Chen JS et al. Survival impact of lymph node metastasis in TNM stage III carcinoma of the colon and rectum. J Am Coll Surg 1995;180:705–712.
16. Read TE, Mutch MG, Chang BW, McNevin MS, Fleshman JW, Birnbaum EH, Fry RD, Caushaj PF, Kodner IJ. Locoregional recurrence and survival after curative resection of adenocarcinoma of the colon. J Am Coll Surg 2002;195(1):33–40. doi:10.1016/S1072-7515(02)01224-3.
17. Radespiel-Tröger M, Hohenberger W, Reingruber B. Improved prediction of recurrence after curative resection of colon carcinoma using tree-based risk stratification. Cancer 2004;100(5):958–967. doi:10.1002/cncr.20065.
18. Zlobec I, Baker K, Minoo P, Jass JR, Terracciano L, Lugli A. Node-negative colorectal cancer at high risk of distant metastasis identified by combined analysis of lymph node status, vascular invasion, and Raf-1 kinase inhibitor protein expression. Clin Cancer Res 2008;14(1):143–148. doi:10.1158/1078-0432.CCR-07-1380.
19. Park YJ, Park KJ, Park JG, Lee KU, Choe KJ, Kim JP. Prognostic factors in 2230 Korean colorectal cancer patients: analysis of consecutively operated cases. World J Surg 1999;23(7):721–726. doi:10.1007/PL00012376.
20. Hine KR, Leonard JC, Booth SN, Dykes PW. Carcinoembryonic antigen concentrations in undiagnosed patients. Lancet 1978;2:1337–1340. doi:10.1016/S0140-6736(78)91975-X.
21. Devesa JM, Morales V, Enriquez JM et al. Colorectal cancer. The bases for a comprehensive follow-up. Dis Colon Rectum 1988;31:636–652. doi:10.1007/BF02556803.
22. Beart RW, Metzger PP, O'Connell MJ, Schutt AJ. Postoperative screening of patients with carcinoma of the colon. Dis Colon Rectum 1981;24:585–589. doi:10.1007/BF02605750.
23. Rocklin MS, Senagore AJ, Talbott TM. Role of carcinoembryonic antigen and liver function tests in the detection of recurrent colorectal carcinoma. Dis Colon Rectum 1991;34:794–797. doi:10.1007/BF02051073.
24. Barillari P, Bolognese A, Chirletti P, Cardi M, Sammartino P, Stipa V. Role of CEA, TPA, and Ca 19-9 in the early detection of localized and diffuse recurrent rectal cancer. Dis Colon Rectum 1992;35(5):471–476. doi:10.1007/BF02049405.
25. Hine FR, Dyke PW. Serum CEA testing in the postoperative surveillance of colorectal carcinoma. Br J Cancer 1984;49:689–693.
26. McCall JL, Black RB, Rich CA, Harvey JR, Baker RA, Watts JM, Toouli J. The value of serum carcinoembryonic antigen in predicting recurrent disease following curative resection of colorectal cancer. Dis Colon Rectum 1994;37(9):875–881. doi:10.1007/BF02052591.
27. Desch CE, Benson AB 3rd, Somerfield MR, Flynn PJ, Krause C, Loprinzi CL, Minsky BD, Pfister DG, Virgo KS, Petrelli NJ, American Society of Clinical Oncology. Colorectal cancer surveillance: 2005 update of an American Society of Clinical Oncology practice guideline. J Clin Oncol 2005;23(33):8512–8519. doi:10.1200/JCO.2005.04.0063.
28. Chau I, Allen MJ, Cunningham D, Norman AR, Brown G, Ford HE, Tebbutt N, Tait D, Hill M, Ross PJ, Oates J. The value of routine serum carcino-embryonic antigen measurement and computed tomography in the surveillance of patients after adjuvant chemotherapy for colorectal cancer. J Clin Oncol 2004;22(8):1420–1429. doi:10.1200/JCO.2004.05.041.
29. Staib L, Schirrmeister H, Reske SN, Beger HG. Is (18)F-fluorodeoxyglucose positron emission tomography in recurrent colorectal cancer a contribution to surgical decision making? Am J Surg 2000;180(1):1–5. doi:10.1016/S0002-9610(00)00406-2.
30. Sarikaya I, Bloomston M, Povoski SP, Zhang J, Hall NC, Knopp MV, Martin EW Jr. FDG-PET scan in patients with clinically and/or radiologically suspicious colorectal cancer recurrence but normal CEA. World J Surg Oncol 2007;5:64. doi:10.1186/1477-7819-5-64.
31. Warwick R, Page R. Resection of pulmonary metastases from colorectal carcinoma. Eur J Surg Oncol 2007. 33(Suppl 2):S59–S63. doi:10.1016/j.ejso.2007.09.018.
32. Zink S, Kayser G, Gabius HJ, Kayser K. Survival, disease-free interval, and associated tumor features in patients with colon/rectal carcinomas and their resected intra-pulmonary metastases. Eur J Cardiothorac Surg 2001;19(6):908–913. doi:10.1016/S1010-7940(01)00724-2.
33. Joosten J, Bertholet J, Keemers-Gels M, Barendregt W, Ruers T. Pulmonary resection of colorectal metastases in patients with or without a history of hepatic metastases. Eur J Surg Oncol 2008;34(8):895–899. doi:10.1016/j.ejso.2008.01.009.
34. Labow DM, Buell JE, Yoshida A, Rosen S, Posner MC. Isolated pulmonary recurrence after resection of colorectal hepatic metastases–is resection indicated? Cancer J 2002;8(4):342–347. doi:10.1097/00130404-200207000-00011.

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ORIGINAL ARTICLE

Is Gum Chewing Useful for Ileus After Elective Colorectal Surgery? A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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Abstract
Background The evaluation of the usefulness of gum chewing for postoperative ileus has given inconclusive results. We evaluated the efficacy of gum chewing in the treatment of ileus after elective colorectal surgery.
Materials and Methods We performed a meta-analysis of randomized clinical trials comparing the effect of gum chewing+ standard treatment vs. standard treatment on ileus after colorectal surgery. MEDLINE, EMBASE, the Cochrane Controlled Trial Register, and the Cochrane Database of Systematic Reviews were searched until August 2008. Primary outcomes were time to first flatus, time to first passage of feces, and length of hospital stay. The mean difference (MD) in hours was calculated with the random effects model to assess the effect of gum chewing on the outcomes.
Results Six trials including 244 patients were analyzed. Time to first flatus was significantly reduced with gum chewing+ standard treatment compared to standard treatment alone (MD −14 h, 95% confidence interval [95%CI] −23.5 to −4.6). Time to first passage of feces was significantly reduced (MD −25 h, 95%CI −42.3 to −7.7), but the length of hospital stay was only marginally reduced (MD −26.2 h, 95%CI −57.5 to 5.2) with gum chewing.
Conclusion In patients with ileus after colonic surgery, gum chewing in addition to standard treatment significantly reduces the time to first flatus and the time to first passage of feces when compared to standard treatment alone. There is also a trend to reduce the length of hospital stay. Gum chewing should be added to the standard treatment of these patients.

Keywords Gum chewing · Ileus · Colorectal surgery · Randomized clinical trials · Meta-analysis

Introduction

Postoperative ileus is a major health care problem and an important cause of prolonged hospital stay.[1–3] It is known that the most prolonged ileus occurs in colonic surgery, especially when this is open.[1–5]

Normal bowel motility depends on several physiologic mechanisms, which include the autonomous nervous system, gastrointestinal hormones, and inflammatory mediators.[4,5] The surgical procedure and the use of some drugs may alter some of these mechanisms.[1–5]

Multimodal approaches to treat postoperative ileus in colorectal surgery include early feeding, avoidance of unnecessary use of nasogastric tube, thoracic epidural analgesia, unspecific pharmacologic agents such as water-soluble contrast (gastrografin),[6] specific agents such as alvimopan, a selective μ receptor opioid antagonist, and lately, gum chewing.[1–7]

Gum chewing is a form of sham feeding which stimulates the cephalic phase of digestion. This produces the release of neurohormonal mediators and the increase of gastrointestinal motility and glandular secretion (salivary, gastric, biliopancreatic). These events may clinically translate into a faster recovery of gas and feces transit, as well as

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a better tolerance to oral ingestion and a shortening of the length of hospital stay.[1,4,5]

Recently, several randomized clinical trials with limited number of patients reported contradictory clinical outcomes of gum chewing in the management of postoperative colonic ileus.[8–13] Lately, Chan and Law[14] and Purkayastha et al.[15] published nearly identical meta-analyses of five of these trials, including 158 patients, and concluded that gum chewing reduces postoperative ileus after colorectal surgery.

We performed an updated systematic review and a meta-analysis of randomized clinical trials that investigated the effects of gum chewing on ileus after elective colonic surgery.

Materials and Methods

Identification of Trials

We searched MEDLINE (January 1966 through August 1, 2008), EMBASE (1974 through August 1, 2008), the Cochrane Controlled Trials Register, and the Cochrane Database of Systematic Reviews (Cochrane Library, Issue 1, 2008) for randomized trials dealing with gum chewing for ileus after colorectal surgery. All searches used the key words *colon* or *colonic surgery*, *ileus*, and *gum chewing* in conjunction with each of the following words: *postoperative*, *postsurgery*, *postsurgical*, *randomised controlled trials*, and *randomised clinical trials*. We reviewed the bibliographies of relevant studies (trials and nontrials) to search for additional eligible randomized trials. We also searched for abstracts of randomized trials from conference proceedings available in major surgery journals in the last 10 years. Only data accessible in peer-reviewed journals were included, and we were not masked with regard to authors or journal.

Inclusion and Exclusion Criteria

Inclusion criteria were: prospective, parallel group, phase III clinical trials with random assignment to either gum chewing±standard treatment or standard treatment/placebo, patients with postoperative ileus after colonic or colorectal cancer or other type of colorectal disease (e.g., diverticulitis), and patients with elective open or laparoscopy-assisted surgery, which included right hemicolectomy, transverse colectomy, left hemicolectomy, sigmoidectomy, anterior resection, and/or abdominoperianal resection. We included main clinical trial reports or trial abstracts with complete information, written in the English language, and with patients older than 15 years. Trials with time to first flatus as primary outcome were included. Other outcomes were time to first passage of feces and/or length of hospital stay. There was no restriction about the number of patients included or the treatment duration. We excluded non-randomized studies, surgery other than colonic, and other types of treatment or interventions other than gum chewing.

Data Extraction

One author (WV) screened the titles and abstracts to exclude nonhuman studies, retrieved potentially relevant manuscripts for detailed evaluation, and selected publications compliant with the inclusion and exclusion criteria. Jointly with another author (AVH), both researchers reassessed the inclusion and exclusion criteria. Clinical trial quality was evaluated with respect to four strictly predefined criteria: allocation concealment, blinding, intention to treat analysis, and completeness of follow-up (http://www.consort-statement.org). Each of these criteria was judged as good or unknown. Differences in judgement of the criteria were resolved by discussion until a consensus was reached. We were not masked to authors or journals, and some bias may have been introduced.

If all the necessary data to perform a meta-analysis (e.g., standard deviations of outcomes) were not specified within the articles, authors were contacted. The primary author of the study was contacted and asked for the additional data. We only needed to contact one lead author and he provided the requested information.

Statistical Analysis

Primary outcomes of the study were time to first flatus, time to first passage of feces and length of hospital stay. The mean difference (MD) and its 95% confidence interval (95%CI) were calculated as a measure of effect size because outcome measurements in all trials were made in the same scale (i.e., hours). MD is the simple mean difference between the mean time to first flatus with gum chewing±standard treatment and the mean time to first flatus with standard treatment/placebo.[16] MD was calculated using the inverse variance method and the random effects model, which was described by DerSimonian and Laird.[17] The data were analyzed using the Cochrane Review Manager 5 software. To test heterogeneity across trials, we used the chi-square test with a p value <0.1 required to determine significant statistical heterogeneity. To test the overall effect of gum chewing on the time of flatus, we used the conventional Z test. To assess the risk of publication bias, we built a funnel plot by graphically showing the relation between effect size and statistical weight for each trial. A symmetric and funnel-shaped plot supports the lack of significant publication bias, whereas a strongly asymmetric plot suggests the underlying presence of publication bias. Publication bias, if not recognized and

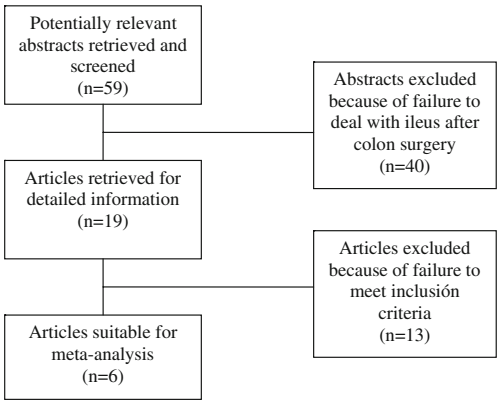

Figure 1 Identification of randomized clinical trials available for analysis.

acknowledged, can lead to meta-analyses with biased and overly optimistic findings and should thus be actively investigated and appraise.[16] Using time to first flatus as outcome, subgroup analyses per type of colorectal disease (cancer vs. cancer+nonmalignant disease) and type of elective surgery (open vs. laparoscopic) were also performed. Subgroup analyses were exploratory in nature and underpowered to detect true subgroup effects.

Results

The initial search identified 59 potential studies on gum chewing and colon surgery (Fig. 1). Hand searching of retrieved articles yielded no additional clinical trials.

Included Studies

The systematic review revealed six randomized clinical trials (Table 1),[8–13] involving 244 patients, published between 2002 and 2006. Four trials showed a significant reduction in the time to first flatus.[8,10,11,13] In contrast, only two trials showed a significant reduction in the time to first passage of feces,[8,11] and in the length of hospital stay.[10,13] Gum was sugar-free in five trials,[8–12] but no reasons were given about this selection. Gum chewing was consistently given three times a day from the first postoperative morning until first passage of flatus or bowel movements starts again. Each chewing lasted between 5 and 60 min.[9,12] Passage of flatus was used as time to start feeding in all trials. The perioperative standard care of patients included thoracic epidural analgesia, early drinking of water, and early deambulation. Two studies only performed surgery of the left colon and rectum.[9,10]

Asao et al.[8] reported in 2002 a trial evaluating gum chewing in patients with colorectal cancer who underwent laparoscopic surgery. Besides a significant shortening of the time to first flatus by 1 day, they also showed that the time to first passage of feces was significantly reduced by 65 h (74 vs. 139 h). However, they we not able to demonstrate a significant reduction of length of hospital stay. The same group published 4 years later another trial in patients with colorectal cancer who underwent open surgery.[11] The time to first flatus was significantly reduced by 35 h, and the time to first passage of feces was significantly reduced by 52 h (85 vs. 136 h).

In 2006, Quah et al.[9] studied patients with cancer of the left colon and rectum. These patients did not benefit from gum chewing: the time to first flatus was about 60 h in both groups and the length of hospital stay was about 10 days in both groups. Interestingly, the group of patients who chewed gum had a better sensation of well-being in comparison to the standard treatment group. Another study dealing with patients who underwent left colonic surgery was published in the same year.[10] However, these inves-

Table 1 General Characteristics of Randomized Clinical Trials Included in the Meta-Analysis

Author/Year[ref.]	*N* per arm (gum±standard/ standard–placebo)	Outcomes	Colorectal pathology	Type of colorectal surgery
Asao/2002[8]	10/9	Time to flatus, time to feces, length of stay	Cancer	Laparoscopic
Quah/2006[9]	19/19	Time to flatus, time to feces, length of stay	Cancer	Open
Schuster/2006[10]	17/17	Time to flatus, time to first bowel movement, time to hunger, length of stay	Cancer and nonmalignant conditions	Open
Hirayama/2006[11]	11/11	Time to flatus, time to feces	Cancer	Open
Matros/2006[12]	22/21	Time to flatus, time to first bowel movement, time ready for discharge, length of stay	Cancer and nonmalignant conditions	Open
McCormick/2005[13]	18/19	Time to flatus, time to first bowel movement, length of stay	Cancer and nonmalignant conditions	Open
	35/16	Time to flatus, time to first bowel movement, length of stay	Cancer and nonmalignant conditions	Laparoscopic

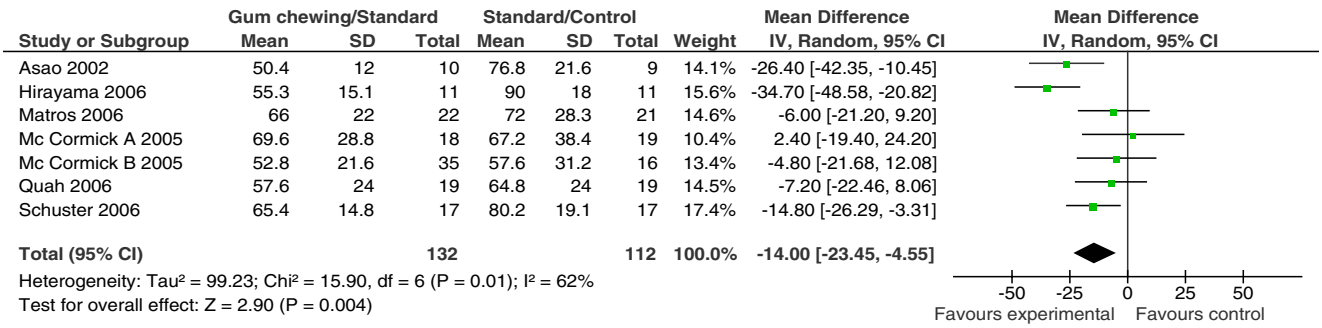

Figure 2 MD and 95%CI of difference in time to first flatus between gum chewing±standard treatment and standard–placebo treatment groups. The size of the data markers (*squares*) is approximately proportional to the statistical weight of each trial. *McCormick A* refers to the open colectomy patients and *McCormick B* refers to the laparoscopic colectomy patients.

tigators also included patients with recidivant diverticulitis. Gum chewing significantly reduced the time to first flatus by 25 h (65 vs. 80 h), the time to first bowel movement by 26 h (63 vs. 89 h), and the length of hospital stay by 60 h (103 vs. 163 h).

Matros et al.,[12] in 2006, compared three arms in cancer and nonmalignant disease patients: gum chewing+standard treatment, standard treatment, and placebo (acupressure wrist bracelet). There was no significant reduction in the time to first flatus among these three groups (60 vs. 67 vs. 72 h, respectively). The length of hospital stay was not significantly reduced either (105 vs. 102 vs. 98 h, respectively).

In a multicenter trial, McCormick et al.[13] compared gum chewing for 15 min QID vs. swallowing of a small amount of water (sips of water) in patients in immediate postoperative care due to elective colorectal surgery. The authors studied patients with both open and laparoscopic surgery. They showed that gum chewing in contrast to control treatment shortened the postoperative ileus period (2.6 vs. 3.3 days, p=0.0047) and hospital stay (4.0 vs. 5.3, p=0.029) in patients with laparoscopic colectomy, but not in patients with open surgery.

Most of the trials were not of good quality. Allocation concealment was good in three trials.[9,10,12] It was not known from three trials whether they performed allocation concealment.[8,11,13] Blinding was good in two trials,[9,12] but the other four did not specify if this was performed or if it was not possible. Intention to treat analysis was used in two trials only.[9,12] Completeness of follow-up was reported in four trials.[8–10,12]

Meta-Analysis

Time to first flatus was significantly reduced with gum chewing and standard treatment compared to the standard treatment alone (MD −14 h, 95%CI −23.5 to −4.6; p=0.001) (Fig. 2). Six trials were suitable for this analysis (n=244), and they were heterogeneous with respect to this outcome (p=0.01).

The time to first passage of feces was significantly reduced with gum chewing and standard treatment compared to the standard treatment alone (MD −25 h, 95%CI −42.3 to −7.7; p=0.01) (Fig. 3). Four trials were used for this analysis (n=167),[8,9,11,13] and they were also heterogeneous with respect to this outcome (p=0.05).

The length of hospital stay was reduced with gum chewing and standard treatment compared to the standard treatment alone, although the difference was not significant (MD −26.2 h, 95%CI −57.5 to 5.2; p=0.1) (Fig. 4) with strong evidence of heterogeneity across trials (p<0.0001). Five trials were used for this analysis (n=222).[8–10,12,13]

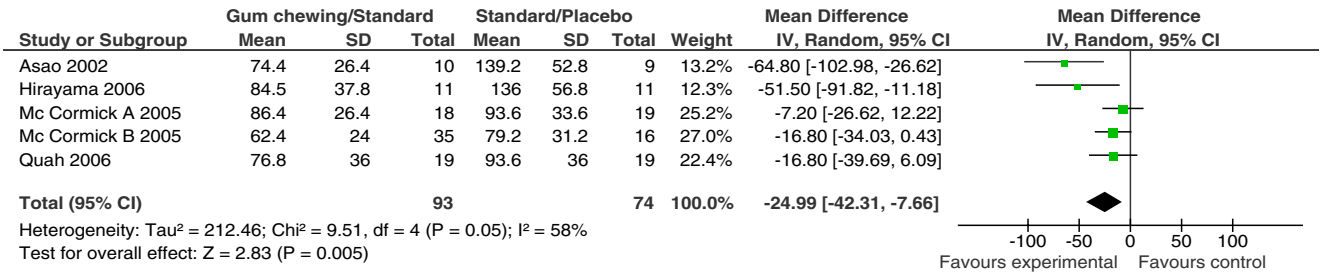

Figure 3 MD and 95%CI of difference in time to first passage of feces between gum chewing±standard treatment and standard–placebo treatment groups. The size of the data markers (*squares*) is approximately proportional to the statistical weight of each trial.

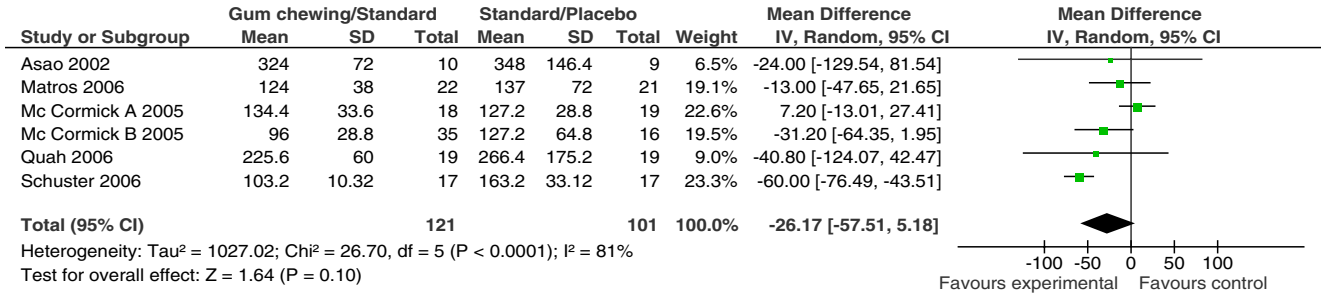

Figure 4 MD and 95%CI of difference in length of hospital stay between gum chewing±standard treatment and standard–placebo treatment groups. The size of the data markers (*squares*) is approximately proportional to the statistical weight of each trial.

The funnel plot showed no evidence of publication bias for the analysis of the time to first flatus (Fig. 5). No evidence of publication bias was found for the time to first passage of feces or length of hospital stay.

Subgroup Analysis

Time to first flatus was consistently reduced across different types of colorectal disease, and this reduction was significantly larger in trials which included cancer patients[8,9,11] than in trials which included cancer and nonmalignant disease patients (p=0.01) (Fig. 6). Time to first flatus was also reduced in patients with both open and laparoscopic surgery, but the effect was only significant in the open surgery subgroup (Fig. 7). However, no differences in gum chewing effects were observed between the open and laparoscopic surgery subgroups (p=0.8).

Discussion

This meta-analysis demonstrates that, in patients who underwent elective colorectal surgery, gum chewing significantly improved postoperative ileus by reducing the time to first flatus by 14 h, the time to first feces by 25 h, and the length of hospital stay by 26 h in comparison with standard treatment. Reductions of the time to first flatus were also observed in subgroups defined by type of colorectal disease and type of surgery.

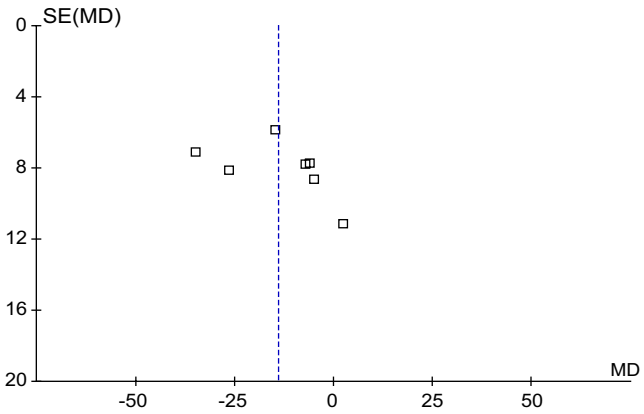

Figure 5 Funnel plot of the six trials included in the meta-analysis. The standard error of MD of each trial was plotted against the MD for time to first flatus (primary outcome for all trials). No skewed distribution was observed, suggesting no publication bias.

Postoperative ileus is the delay of the resumption of normal gastrointestinal motility after surgical stress. The clinical expression includes the absence of flatus and feces transit, abdominal distension, nausea, and vomiting. Each segment of the digestive tube resumes its motility after surgery at different times. The small intestine has the shortest time of ileus (between 8 and 12 h). The stomach has a longer ileus (between 1 and 2 days), and the colon has the longest time of ileus (between 3 and 5 days).[18–20]

Postoperative ileus is a consequence of the interaction of several factors. Probably the most important factor is the sympathetic hyperstimulation, which inhibits gastrointestinal motility. Some neurohormones of the enteric nervous system such as substance P, vasoactive intestinal peptide, and nitric oxide can also contribute to the duration of ileus.[5,19,20] Moreover, surgical aggression may stimulate the inflammatory cascade with liberation of interleukins (IL-6, IL-1b) and chemokines (MCP-1, ICAM-1), which further inhibit gastrointestinal motility.[19,20] Some drugs may also contribute to postoperative ileus. For instance, anesthetic drugs such as atropine, halothane, and enflurane may have a transitory effect, while opioid analgesics used during surgery and in the postoperative period may have a more prolonged effect.[21–23]

After surgery the myoelectric activity of the gastrointestinal tract is disorganized and this is translated into lack of propulsion. The electrical activity of the colon is the last to recover. Colon motility is diminished or absent until approximately the third postoperative day. At the fourth day, the colonic electrical activity consists of disorganized bursts, and later, a coordinated motor response is able to propagate. This allows the passage of flatus, the first indicator of the ileus resolution process. The passage of feces occurs within 1 or 2 days after the first flatus, and it does not necessarily mean the final resolution of the ileus.

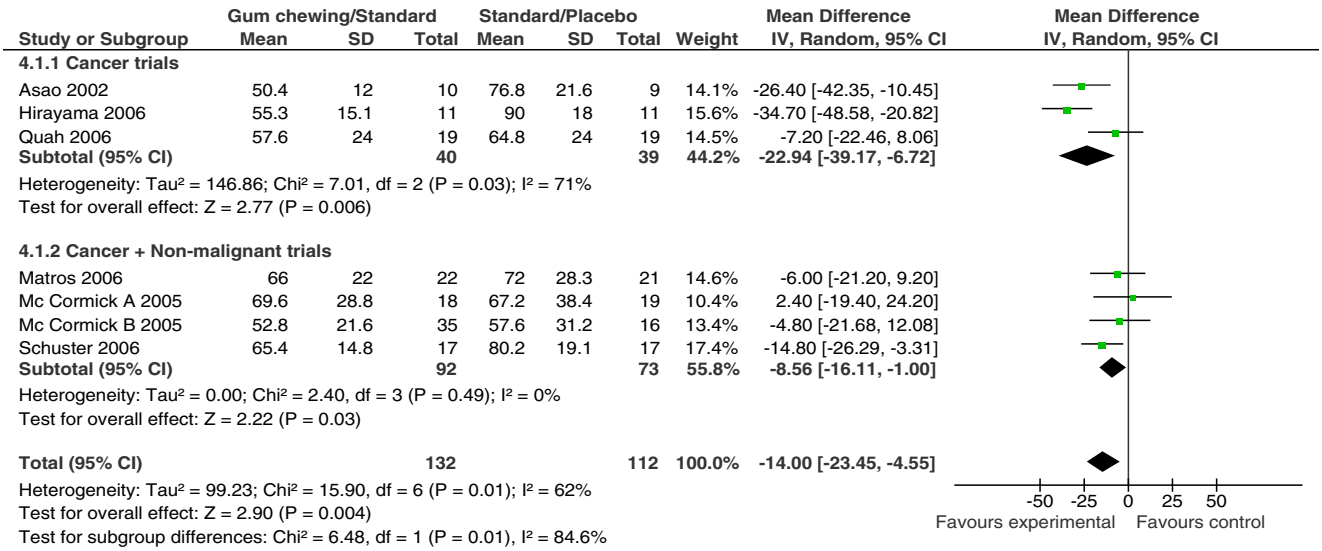

Figure 6 Subgroup analysis of the difference in time to first flatus by type of colorectal disease.

The passage of feces depends on the type of surgical procedure, the condition and content of the intestine prior to surgery, dietetic factors, and the usual intestinal frequency of the patient.[5,20,21]

Shortening of hospital stay by almost 26 h with gum chewing in comparison to standard care is translated into better well-being of patients, early return to the preoperative functional status, and especially, reduction of hospital costs.[24–26] To our knowledge, there are no specific studies evaluating the reduction of costs by using gum chewing in patients undergoing colorectal surgery. Additional advantages of gum chewing include stimulation of appetite and sensation of well-being during the postoperative period.

Two decades ago, it was described that replication of the cephalic phase of digestion through sham feeding stimulated the electrical, motor, and secretory activities of the gastrointestinal tract through neurohormonal and vagal pathways. In humans, sham feeding produces a significant increase of gastrin and neurotensin release and a partial alteration of the myoelectrical pattern of the gastrointestinal tract during fasting, also known as interdigestive migrating motor complex. Gum chewing is a type of sham feeding and was lately proposed as an activator of these various mechanisms.[27,28]

An open colorectal surgery has a more prolonged postoperative ileus than a laparoscopic-assisted colorectal surgery, probably due to a longer visceral manipulation and environmental exposure and higher use of analgesic drugs to control postoperative pain.[29–31] We found that gum chewing especially benefited patients who underwent open surgery. Gum chewing can also extend the benefits of the

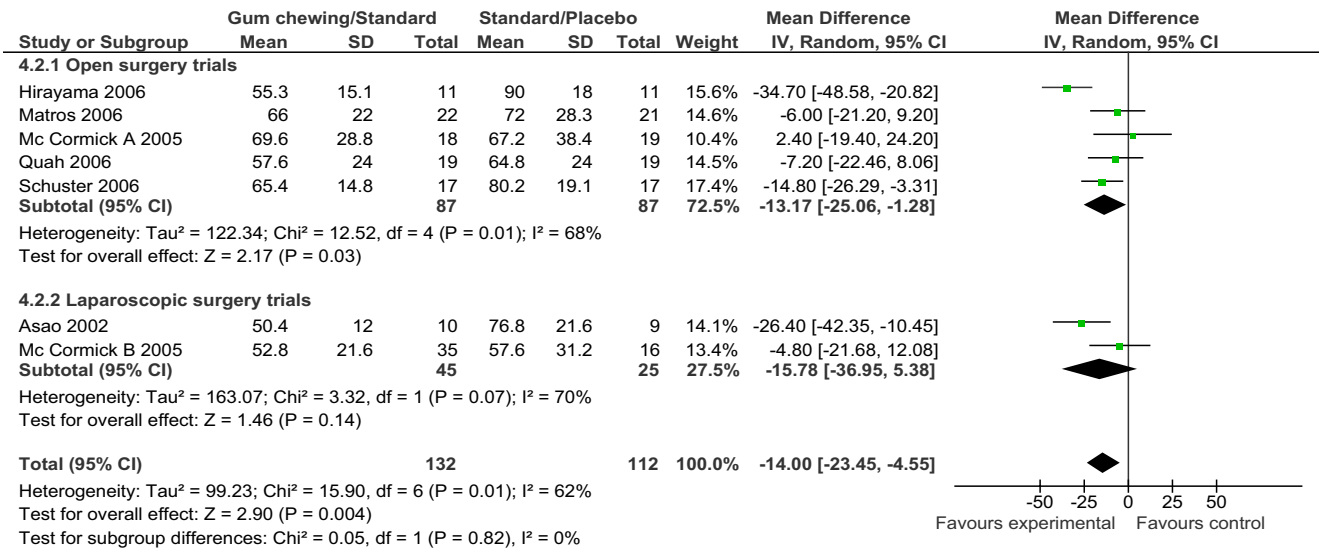

Figure 7 Subgroup analysis of the difference in time to first flatus by type of surgery.

minimally invasive laparoscopic surgery.[8] Moreover, the larger benefit of gum chewing in the subgroup that included patients with colorectal cancer alone can be important, given that these patients usually have a moderate to bad nutritional state and a shorter hospitalization can avoid in-hospital complications.[32,33]

Our meta-analysis is different than two recently published meta-analyses[14,15] in several ways. Our meta-analysis included six trials with 244 patients, 50% more patients than the other studies (five trials, $n=158$). We did not restrict the language of the studies; one of the other studies focused on English language studies.[14] The period of our systematic review was until August 2008, longer than the other periods (January 2007[14] and July 2006[15]). Finally, we focused on randomized controlled trials, not on nonrandomized comparative studies.[14]

Multimodal fast-track perioperative care programs in colorectal surgery are oriented to a fast recovery of patients, as well as to a shortened hospital stay. These programs include: adequate patient information about specific procedures, no bowel preparation, no sedative premedication, intake of small quantities of carbohydrate-enriched liquids within 2 h before surgery, epidural thoracic analgesia and short half-life anesthetics, restriction of intravenous perioperative fluids, use of minimally invasive surgery, use of nonopioid systemic analgesic drugs, avoidance of the routine use of drainages or nasogastric tube, early withdrawal of urinary probe, early intake of small quantities of liquid, and early deambulation. All these measures have demonstrated favorable results such as shorter hospitalization, better patient comfort, reduction of in-hospital mortality, and reduction of postoperative costs.[1–3,34] Gum chewing should become part of the multimodal fast-track perioperative care program in colorectal surgery.

It is not known whether gum chewing also has a favorable effect in postoperative ileus in abdominopelvic surgery, such as transperitoneal aortic surgery,[35] cesarean section, hysterectomy with abdominal access,[36] and radical cystectomy.[37,38]

Our study has some limitations. First, the total number of patients ($n=244$) included in the meta-analysis was relatively small. However, this meta-analysis is the largest available meta-analysis that adds about 90 patients more than recently published meta-analyses.[14,15] We performed a formal systematic review of all clinical trials published until August 1, 2008 and our analysis did not show evidence of publication bias. Second, we did not have access to original source data (i.e., individual patient data) for any of these clinical trials. Thus, we based the analysis on available data from published studies or directly from authors. Third, clinical trials included in the meta-analysis can be regarded as poorly controlled as far as use of opiates and other analgesics, postoperative feeding, epidural analgesia, fast-track, or other standard and nonstandard protocols. However, those controls reflected what authors considered their current clinical practice. We expect that a tightly controlled randomized trial will show a smaller clinical effect. Fourth, a meta-analysis may be considered less convincing than a large prospective trial designed to assess the outcome of interest. However, given the lack of an appropriately sized clinical trial evaluating gum chewing for postoperative ileus in colorectal surgery, a well-designed and well-performed meta-analysis is the best option available to answer this clinical question.

Conclusion

Gum chewing is a cheap, physiological, and secure intervention that significantly improves ileus after elective colorectal surgery. This intervention should be included in the multimodal approach of postoperative colorectal ileus. A tightly controlled, multicenter randomized clinical trial with a substantial number of patients is necessary to confirm the efficacy of gum chewing in patients with elective colorectal surgery.

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References

1. Wind J, Hofland J, Preckel B et al. Perioperative strategy in colonic surgery, laparoscopy and/or fast track multimodal management versus standard care (LAFA trial). BMC Surg 2006;6:16. doi:10.1186/1471-2482-6-16.
2. Jakobsen DH, Sonne E, Andreasen J, Kehlet H. Convalescence after colonic surgery with fast-track vs conventional care. Colorectal Dis 2006;8:683–687. doi:10.1111/j.1463-1318.2006.00995.x.
3. Basse L, Jakobsen DH, Bardram L et al. Functional recovery after open versus laparoscopic colonic resection. A randomized, blinded study. Ann Surg 2005;241:416–423. doi:10.1097/01.sla.0000154149.85506.36.
4. Mattei P, Rombeau JL. Review of the pathophysiology and management of postoperative ileus. World J Surg 2006;30:1382–1391. doi:10.1007/s00268-005-0613-9.
5. Miedema BW, Johnson JO. Methods for decreasing post operative gut dismotility. Lancet Oncol 2003;4:365–372. doi:10.1016/S1470-2045(03)01118-5.
6. Chen JH, Hsieh CB, Chao PC et al. Effect of water-soluble contrast in colorectal surgery: a prospective randomized trial. World J Gastroenterol 2005;11:2802–2805.
7. Harms BA, Heise CP. Pharmacologic management of post operative ileus: the next chapter in GI surgery. Ann Surg 2007;245:364–365. doi:10.1097/01.sla.0000256394.97313.fb.
8. Asao T, Kuwano H, Nakamura J, Morinaga N, Hirayama I, Ide M. Gum chewing enhances early recovery from postoperative ileus after laparoscopic colectomy. J Am Coll Surg 2002;195:30–32. doi:10.1016/S1072-7515(02)01179-1.

9. Quah HM, Samad A, Neathey AJ, Hay DJ, Maw A. Does gum chewing reduce postoperative ileus following open colectomy for left-sided colon and rectal cancer? A prospective randomized controlled trial. Colorectal Dis 2006;8:64–70. doi:10.1111/j.1463-1318.2005.00884.x.
10. Schuster R, Grewal N, Greaney GC, Waxman K. Gum chewing reduces ileus after elective open sigmoid colectomy. Arch Surg 2006;141:174–176. doi:10.1001/archsurg.141.2.174.
11. Hirayama I, Suzuki M, Ide M, Asao T, Kuwano H. Gum-chewing stimulates bowel motility after surgery for colorectal cancer. Hepatogastroenterology 2006;53:206–208.
12. Matros E, Rocha F, Zinner M et al. Does gum chewing ameliorate postoperative ileus? Results of a prospective, randomized, placebo-controlled trial. J Am Coll Surg 2006;202:773–778. doi:10.1016/j.jamcollsurg.2006.02.009.
13. McCormick JT, Garvin R, Cuashaj P et al. The effects of gum-chewing in bowel function and hospital stay after laparoscopic vs. open colectomy: a multi-institution prospective randomized trial. J Am Coll Surg 2005;201:S66–S67. doi:10.1016/j.jamcollsurg.2005.06.152.
14. Chan MK, Law WL. Use of chewing gum in reducing postoperative ileus after elective colorectal resection: a systematic review. Dis Colon Rectum 2007;50:2149–2157. doi:10.1007/s10350-007-9039-9.
15. Purkayastha S, Tilney HS, Darzi AW, Tekkis PP. Meta-analysis of randomized studies evaluating chewing gum to enhance postoperative recovery following colectomy. Arch Surg 2008;143:788–793. doi:10.1001/archsurg.143.8.788.
16. Clarke M, Oxman AD. Cochrane Reviewers Handbook 4.2.6 (updated software, updated September 2006). The Cochrane Library, Issue 1. Oxford. 2007.
17. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–788. doi:10.1016/0197-2456(86)90046-2.
18. Mc Fadden DW, Zinner MI. Manifestations of gastrointestinal disease. In Schwartz SI, ed. Principles of Surgery. New York: McGraw-Hill, 1994.
19. Helton WS, Fisichella PM. Intestinal obstruction. In American College of Surgeons ACS Surgery Principles and Practice. New York: WebMD, 2005.
20. Luckey A, Livingston E, Tache Y. Mechanism and treatment of postoperative ileus. Arch Surg 2003;138:206–214. doi:10.1001/archsurg.138.2.206.
21. Person B, Wexner SD. The management of postoperative ileus. Curr Probl Surg 2006;43:6–65. doi:10.1067/j.cpsurg.2005.10.003.
22. Jørgensen H, Wetterslev J, Møiniche S, Dahl JB. Epidural local anaesthetics versus opioid-based analgesic regimens for postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. Cochrane Database Syst Rev 2001; Issue 1, Art. No. CD001893. doi:10.1002/14651858.CD001893.
23. Hudcova J, McNicol E, Quah C, Lau J, Carr DB. Patient controlled opioid analgesia versus conventional opioid analgesia for postoperative pain. Cochrane Database Syst Rev 2006; Issue 4, Art. No. CD003348. doi:10.1002/14651858.CD003348.pub2.
24. Noblett SE, Horgan AF. A prospective case-matched comparison of clinical and financial outcomes of open versus laparoscopic colorectal resection. Surg Endosc 2007;21:404–408. doi:10.1007/s00464-006-9016-8.
25. Aihara H, Kawamura YJ, Konishi F. Reduced medical costs achieved after elective oncological colorectal surgery by early feeding and fewer scheduled examinations. J Gastroenterol 2003;38:747–750. doi:10.1007/s00535-002-1140-1.
26. King PM, Blazeby JM, Ewings P et al. The influence of an enhanced recovery programme on clinical outcomes, cost and quality of life after surgery for colorectal cancer. Colorectal Dis 2007;9:281–282.
27. Stern RM, Crawford HE, Stewart WR, Vasey MW, Koch KL. Sham feeding. Cephalic vagal influences on gastric myoelectric activity. Dig Dis Sci 1989;34:521–527. doi:10.1007/BF01536327.
28. Soffer EE, Adrian TE. Effect of meal composition and sham feeding on duodenojejunal motility in humans. Dig Dis Sci 1992;37:1009–1014.
29. Schwenk W, Haase O, Neudecker J, Müller JM. Short term benefits for laparoscopic colorectal resection. Cochrane Database Syst Rev 2005; Issue 2, Art. No. CD003145. doi:10.1002/14651858.CD003145.pub2.
30. Paraskeva PA, Aziz O, Darzi A. Laparoscopy surgery for colon cancer. Surg Clin North Am 2005;85:49–60.
31. Noel JK, Fahrbach K, Estok R et al. Minimally invasive colorectal resection outcomes: short-term comparisons with open orocedures. J Am Coll Surg 2007;204:291–307.
32. Braga M, Vignali A, Zuliani W et al. Laparoscopic versus open colorectal surgery. Cost–benefit analysis in a single-center randomized trial. Ann Surg 2005;242:890–896.
33. Lacy AM, García-Valdecasas J, Delgado S et al. Laparoscopy assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomized trial. Lancet 2002;359:2224–2229.
34. Zhou T, Wu XT, Zhou YJ, Huang X, Fan W, Li YC. Early removing gastrointestinal decompression and early oral feeding improve patients rehabilitation after colorectostomy. World J Gastroenterol 2006;12:2459–2463.
35. Miedema BW, Schillie S, Simmons JW, Burgess SV, Liem T, Silver D. Small bowel motility and transit after aortic surgery. J Vasc Surg 2002;36:19–24.
36. Satji B. Evaluation of gum chewing on the return of bowel function in cesarean-delivery patients. Obstet Gynecol 2006;107 (4Suppl):10S.
37. Chang SS, Baumgartner RG, Wells N, Cookson MS, Smith JR. Causes of increased hospital stay after radical cystectomy in a clinical pathway setting. J Urol 2002;167:208–211.
38. Kouba EJ, Wallen EM, Pruthi RS. Gum chewing stimulates bowel motility in patients undergoing radical cystectomy with urinary diversion. Urology 2007;70:1053–1056.

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ORIGINAL ARTICLE

Postoperative Morbidity Following Chemoradiation for Locally Advanced Low Rectal Cancer

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Abstract
Background Postoperative morbidity remains a significant clinical problem and may alter long-term outcome particularly after neoadjuvant chemoradiation in patients with locally advanced low rectal cancer. The aim of the present study was to identify a potential long-term effect of postoperative morbidity.
Methods Analysis of prospectively collected data of 90 consecutive patients who underwent neoadjuvant chemoradiation and curative mesorectal excision for locally advanced (cT3/4, Nx, M0/1) adenocarcinoma of the mid and lower third of the rectum during a 7-year period (1996–2002).
Results Major postoperative complications occurred in 17.8% and minor complications in 26.6% of patients. Hospital mortality and 30-day mortality was 0%. Infectious complications were seen in 34.5%. The leading causes of infectious complications were anastomotic leakage and perineal wound infection. Postoperative morbidity was statistically significantly associated with gender ($P<0.05$), pre-therapeutic haemoglobin level ($P<0.05$), ASA score ($P<0.05$), hospitalisation ($P<0.001$) and clinical long-time course ($P<0.01$). Moreover, early postoperative morbidity was proven as an independent prognostic factor concerning disease-free ($P<0.05$) and overall survival ($P<0.05$).
Conclusion Early postoperative morbidity in patients with preoperative chemoradiation due to locally advanced low rectal cancer is demonstrated as an independent prognosticator. Gender, pre-therapeutic haemoglobin level and ASA score indicate patients at risk for early postoperative complications and may therefore serve as predictive features.

Keywords Postoperative morbidity · Preoperative chemoradiation · Locally advanced rectal cancer · Survival

Introduction

Progress in the treatment of locally advanced rectal cancer was mainly contributed by the development of new surgical procedures (i.e. total mesorectal excision; TME[1,2]), better staging methods (i.e. MRI[3]), the regular use of radiotherapy[4–6] and new chemotherapeutic agents.[7–10] In Europe, preopera-

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tive treatment either as short-course radiation[5] or as combined chemoradiation followed by surgery is the current standard of treatment in patients with locally advanced rectal cancer.[4,6,11] Patients responding to combined chemoradiation as seen by histopathologic downstaging are those who benefit most.[12–16]

It is well known that these extensive therapeutic strategies in rectal cancer result in an increase of postoperative complication rates, which remain a severe clinical problem. Usually, rectal cancer surgery is associated with a higher risk for anastomotic leakage, delayed perineal wound closure and other (e.g. pelvic sepsis, intra-abdominal abscess formation) postoperative infectious complications.[17–24] Furthermore, it is assumed that postoperative complications are associated with a significant increase in loco-regional recurrence and worse long-term survival rates.[17–19] The risks of any wound complications, either major perineal or pelvic sepsis, are reported to be doubled[25,26] in patients with preoperative chemoradiation. These infectious complications could be due to a significant reduction on collagen accumulation and an impaired leukocyte production.[27] Also, an impaired immune system status following major surgical procedures and/or pre-treatment may have a relevant influence on postoperative surgical infections.[28] Furthermore, one may speculate that postoperative morbidity is linked to the primary condition of the patient. Nevertheless, several studies showed that pre-treatment of locally advanced rectal cancer did not influence postoperative complications, but improved outcome with a higher number of complete resections and sphincter-preserving operative procedures and enhanced local tumour control.[29,30]

This study was performed to identify a potential long-term effect of early postoperative morbidity with a focus on infectious complications in patients with locally advanced low rectal cancer and neoadjuvant chemoradiation. Various clinico-pathological features were analysed regarding their influence on the postoperative clinical course. In addition, disease-free, cancer-specific and overall survival was determined for groups of patients with and without postoperative morbidity.

Patients and Methods

Patient Population

Ninety consecutive patients (male 57, female 33) with a mean age of 60.5 years (from 34 to 80 years) who underwent curative treatment between 1996 and 2002 at the Department of Surgery, Innsbruck Medical University, due to locally advanced and histological confirmed adenocarcinoma of the mid and lower third of the rectum were included in this study. Patients' characteristics and clinico-pathological data are given in Table 1. All data regarding date and cause of death were confirmed by the "Tumorregister Tirol", a cancer register maintained by the Tyrolean government. Additionally, patients were followed every 3 months for the first 3 years, biannual for up to 5 years, every 12 months thereafter or until death. Follow-up evaluations included outpatient visit, blood chemistry/CEA test, abdominal ultrasound, CT scan of the thorax and abdomen and colonoscopy/rectoscopy according to a predetermined plan. The post-treatment surveillance period ranged from at least 5 to at most 125 months, giving a mean follow-up of 59 months. Only six patients were lost to follow-up.

Preoperative staging comprised colonoscopy to assess the distance of the distal edge of the tumour from the dentate line, length and circumferential involvement of the cancer and to examine the entire colon. Endorectal ultrasound for determination of the depth of the tumour infiltration was performed in all patients. Moreover, 25.6% of patients underwent additional MRI examination of the pelvic region for the same purpose.[31] Rectal digital examination was performed in all patients, but was not the basis for staging the tumour. Only cT3 or cT4 tumours regardless of their lymph node status were considered for pre-treatment. CT scan of the thorax and abdomen was used to rule out or to localise distant metastasis.

Preoperative combined chemoradiation according to the *study protocol #01* of the "*Tyrolean Oncology Working Group"*, as described elsewhere,[32] was used in all patients. Pre-treatment consisted in a total radiation dose of 45 Gray (Gy) in fractionated doses—1.8 Gy per day—or 2×1.1 Gy per day hyper-fractionated for 5 weeks. Radiation fields in a three-field technique included the rectal canal when APE was considered and was not included when the sphincter was planned to be preserved. 5-Fluorouracil (350 mg/m^2 body surface per day) in continuous infusion during 120 h within 5 weeks was administered. Patients were scheduled for surgery in the third week after completion of pre-treatment.

Surgical procedures consisted of a low anterior resection (LAR) with a colo-anal or colo-rectal pouch anastomosis (double stapled technique), abdominal perineal excision (APE) or Hartmann's procedure, respectively. Total meso-rectal excision (TME) was performed in all patients. In LAR, a diversion stoma (loop ileostomy 45.5%, colostomy 9%) or a tube caecostomy (45,5%) was carried out in all but one patient. Stoma closing was performed within 63 days (from 8 to 482 days) in all except one patient who died prior to the scheduled intervention. Over the given period of time, none of the patients were treated with laparoscopic approach and unexceptionally preoperative mechanical bowel preparation was carried out. Mean hospitalisation was 20.3 days (from 4 to 73 days).

Prophylactic antibiotic treatment was administered immediately before anaesthesia induction and consisted of a

Table 1 Patients (N=90) Characteristics and Clinico-pathological Features

	Mean	Min–max	N	%
Age (years)	60.5	34–80		
Gender				
Female			33	37
Male			57	63
ASA score[a]				
1			4	5
2			44	49
3			39	43
4			3	3
5			0	0
Distance from the dentate line (cm)	5.9	0–16		
Pre-therapeutic haemoglobin (g/dl)	12.8	5.8–16.9		
Pre-therapeutic anaemia (<11 g/dl)			17	19
Operative procedure				
LAR			56	62
APE			33	37
Hartmann's procedure[b]			1	1
Cumulative 5FU dose (mg/m^2)	7,483	3,800–13,300		
Cumulative RT dose (Gy)	43.4	38.3–45.4		
Hospitalisation (days)	20.3	4–73		
Tumour stage				
ypT0			9	10
1			5	6
2			28	31
3			42	46
4			6	7
ypN0			59	66
1			19	21
2			12	13
M0			88	98
1			2	2
UICC-stage 0			9	10
I			25	28
II			22	24
III			32	36
IV			2	2
R stage				
R0			85	95
R1			5	5
Tumour differentiation				
G1–2			80	89
G3–4			10	11
Response				
pCR			9	10
Downstaging[c]			45	50
Clinical course				
Uneventful			57	63
Poor[d]			33	37
Loco-regional failure			3	3
Distant metastases			22	24
Loco-regional failure and distant metastases			8	9
Death during follow-up			28	31
Lost during follow-up			6	7
Overall observation time (months)	59	5–125		

min–max lowest and highest value, *LAR* low anterior resection, incl. inter-sphincteric resection (N=1), *APE* abdomino-perineal excision, *5FU* 5-fluorouracil, *RT* radiotherapy, *pCR* pathological complete response, *Gy* Gray

[a] *ASA* American Society of Anesthesiology, http://www.asahq.org/clinical/physicalstatus.htm

[b] In one male patient, cardiac arrest during surgical procedure due to anaphylactic reaction following intraoperative resuscitation necessitated change in the surgical plan and Hartmann's procedure was carried out

[c] cT4→ypT0–3; cT3→ypT0–2

[d] Poor clinical course—development of loco-regional and/or distant relapse

beta-lactam substance in combination with either metronidazol or clindamycin for anaerobic organisms. Antibiotic prophylaxis was used in all patients for an average of 2.59 days (from 0 to 13 days), single shot antibiotic prophylaxis was carried out in 47.7% (N=43) of patients.

Early postoperative complications were defined as any deviation from the normal postoperative course, as defined and classified by Dindo et al.,[33] requiring medical treatment, surgical, endoscopic or radiological interventions during the hospital stay of the patient or at least within 30 days after surgery. Major infectious complications were defined as anastomotic leakage, intra-abdominal abscess(es) or wound infections requiring drainage and/or re-operation and delayed wound healing (>1 month). Minor infectious complications comprised urinary tract infections, pneumonia, wound and perineal infections with healing within 1 month and central venous line sepsis.

Statistical Analysis

All data were prospectively collected in the context of the study protocol and entered in an audit capable database (ChiBASE). Categorical data are reported as absolute numbers and percentage; continuous data are summarised as the sample mean, 95% confidence interval and/or minimum and maximum values, respectively. Accordingly, chi-squared test or one-way analysis of variance was used for analytical statistics. Survival rates were calculated using the Kaplan–Meier method and respective groups were compared with the log rank test. Cox regression model was calculated to determine in a backward stepwise manner independent prognostic factors. Statistical significance was defined as $P<0.05$. SPSS for Macintosh 16.0 software (Chicago, IL, USA) was used for all statistical analyses.

Table 2 Infectious Complications Following Surgery of Low Rectal Cancer with Pre-treatment in 31 Patients

	Grade I–II	Grade IIIa–IVb
Fever of unknown origin	2	–
Thrombophlebitis	1	–
Erysipelas	1	–
Central venous line sepsis	3	–
Pneumonia	3	–
Urinary tract infection	7	–
Wound infection		
Abdominal	5	–
Perineal[a]	4	1
Intra-abdominal infection		
Abscess	–	4
Pelvic sepsis	–	6
Anastomotic leakage	–	7
Total	26	18

[a] After APE

Table 4 Non-infectious Complications in 16 Patients

	Grade I–II	Grade IIIa–IVb
Haematological		
Leucopenia	11	–
Respiratory system		
Pleural effusion	–	2
Respiratory insufficiency	1	–
Urinary tract		
Urinary retention	9	–
Surgical		
Bleeding[a]	–	1
Central nervous system		
Cerebral apoplexy	1	–
Transitory psychotic syndrome	1	–
Acute hearing loss	1	–
Total	14	3

[a] After APE

Results

A total of 61 postoperative complications were seen in 40 (44.4%) patients. Out of these patients, 21 had more than one deviation from regular postoperative course. The majority of patients with postoperative morbidity showed infectious secondary disease (seen in 31 patients; 34.4% out of all patients; see Table 2), followed by postoperative prolonged urinary retention (N=9; 10%). Additional antibiotic treatment was used postoperatively in 34.4% (N=31) due to bacterial infections. The spectrum of pathogens isolated is shown in Table 3. Detailed description of all non-infectious postoperative complications is given in Table 4. Twenty-four (26.7%) patients developed merely infectious complications; in seven (7.8%) patients, infectious and non-infectious secondary disease and in nine (10%) patients, solely non-infectious morbidity was noticed. The leading and at the same time most severe cause of infectious complications was anastomotic dehiscence (N=7; 12.5% of all patients in whom LAR was performed) with or without pelvic sepsis and/or intra-abdominal abscess(es) formation (N=10; 11%). Patients with APE showed wound healing problems in the perineal region (N=5; 15%) with delayed wound closure. Postoperative hospital mortality was 0%. Classification of complications according to the proposal of

Table 3 Isolated Pathogens with Regard to their Infectious Site

Isolated pathogens	Abdominal wound	Perineal wound	Intra-abdominal	Pelvic	Urinary tract	Respiratory tract	Central venous line
E. coli	4	2	6	1	3	1	0
Enterococci	1	0	7	2	3	0	0
Enterobactericae	2	0	0	1	3	0	1
Pseudomonas	1	0	1	1	2	0	0
Citrobacter	0	0	0	0	1	0	0
Acinetobacter	0	0	2	0	0	0	0
MRSA	1	0	2	1	0	1	1
Staphylococcus aureus	0	0	2	1	0	0	2
Klebsiella	1	0	3	1	1	0	0
CNS	1	1	3	1	0	0	2
Proteus	1	0	1	0	0	1	0
Bacteroides	1	0	3	0	0	0	0
Corynebacterium	0	0	1	0	0	0	0
Candida	0	0	1	0	0	2	0
Total	13	3	42	9	13	5	6

MRSA methicillin-resistant *Staphylococcus aureus*, *CNS* coagulase-negative *Staphylococcus*

Table 5 Relationship Between Postoperative Complications and Various Clinico-pathological Parameters

	Complications			Grade III–IV		
	No	Yes	*P*	No	Yes	*P*
Age (years)	58.8 (56.1–61.5)	62.6 (58.9–66.3)	n.s.	59.9 (57.5–62.3)	63.3 (57.1–69.5)	n.s.
Gender						
Male	37	20	<0.05	49	8	n.s.
Female	13	20		25	8	
ASA Score						
1	2	2	<0.05	3	1	n.s.
2	31	13		40	4	
3	16	23		29	10	
4	1	2		2	1	
Distance of the distal edge from the dentate line (cm)	6.1 (5.0–7.1)	5.7 (4.7–6.8)	n.s.	5.9 (5.1–6.7)	6.3 (4.3–8.3)	n.s.
Pre-therapeutic haemoglobin (g/dl)	13.27 (12.7–13.8)	12.28 (11.6–12.9)	<0.05	13.1 (12.6–13.5)	11.7 (10.6–12.8)	<0.01
Pre-therapeutic anaemia						
No	43	30	n.s.	63	10	<0.05
Yes (<11 g/dl)	7	10		11	6	
Operative procedure						
LAR	33	23	n.s.	46	10	n.s.
APE	16	17		27	6	
Hartmann's procedure[a]	1	0		1	0	
Cumulative 5FU dose (mg/m^2)	7,780 (7,281–8,279)	7,128 (6,756–7,500)	n.s.	7,564 (7,187–7,943)	7,119 (6,596–7,641)	n.s.
Cumulative RT dose (Gy)	43.4 (42.8–44.1)	43.2 (42.6–43.9)	n.s.	43.4 (43.0–43.9)	42.9 (41.8–44.0)	n.s.
Hospitalisation (days)	15.3 (14.0–16.7)	26.6 (22.1–31.0)	<0.001	17.6 (15.7–19.5)	33.0 (34.8–41.2)	<0.001
Single shot antibiotic prophylaxis						
No	25	22	n.s.	37	10	n.s.
Yes	25	18		37	6	
Tumour stage						
ypT0	5	4	n.s.	7	2	<0.05
1	4	1		5	0	
2	17	11		26	2	
3	23	19		34	8	
4	1	5		2	4	
ypN0	34	25	n.s.	49	10	n.s.
1	10	9		15	4	
2	6	6		10	2	
M0	48	40	n.s.	72	16	n.s.
1	2	0		2	0	
UICC-stage 0	5	4	n.s.	7	2	n.s.
I	16	9		23	2	
II	11	11		16	6	
III	16	16		26	6	
IV	2	0		2	0	
R stage						
R0	49	36	n.s.	72	13	<0.05
R1	1	4		2	3	
Tumour differentiation						
G1–2	44	36	n.s.	67	13	n.s.
G3–4	6	4		7	3	
Response						
pCR						
No	5	4	n.s.	7	2	n.s.
Yes	45	36		44	37	
Downstaging[b]						

Table 5 (continued)

	Complications			Grade III–IV		
	No	Yes	*P*	No	Yes	*P*
No	28	17	n.s.	41	4	<0.05
Yes	22	23		33	12	
Clinical long-time course						
Uneventful	38	19	<0.01	49	8	n.s.
Poor[c]	12	21		25	8	
Loco-regional failure						
No	48	31	<0.01	66	13	n.s.
Yes	2	9		8	3	
Distant metastases						
No	38	22	<0.05	51	9	n.s.
Yes	12	18		23	7	
Death during follow-up						
No	41	21	<0.01	54	8	n.s.
Yes	9	19		20	8	
Overall observation time (months)	77.4 (67.6–87.2)	59.7 (49.0–70.3)	<0.05	71.6 (63.5–79.7)	59.8 (42.0–77.7)	n.s.

Continuous data are given as mean values with respective 95% CI in parentheses; nominal data are given as absolute counts
ASA American Society of Anesthesiology, *LAR* low anterior resection, incl. inter-sphincteric resection (*N*=1), *APE* abdomino-perineal excision, *5FU* 5-fluorouracil, *RT* radiotherapy, *pCR* pathological complete response, *Gy* Gray
[a] In one male patient, cardiac arrest during surgical procedure due to anaphylactic reaction following intraoperative resuscitation necessitated change in the surgical plan and Hartmann's procedure was carried out
[b] cT4→ypT0–3; cT3→ypT0–2
[c] Poor clinical course—development of loco-regional and/or distant relapse

Dindo et al. showed nine (22.5% out of 40 patients with postoperative complications) grade I, 15 (37.5%) grade II, four (10%) grade IIIa, seven (17.5%) grade IIIb, four (10%) Grade IVa and one (2.5%) grade IVb cases.

In female patients, postoperative complications occurred statistically significantly (χ^2=4.3; *df*=1, *P*<0.05) more often (58%) than in male patients (35%). Development and severity of complications (grade III–IV) were statistically significantly associated with the pre-therapeutic haemoglobin level (see Table 5). Patients who developed postoperative complication had statistically significantly (*F*=4,8; *df*=1, *P*<0.05) lower pre-therapeutic haemoglobin counts (mean=12.28; 95% CI=11.64–12.94) when compared with patients with an uneventful postoperative course whilst on hospitalisation (mean=13.27; 95% CI=12.70–13.76). Furthermore, postoperative complications were statistically significantly associated with the ASA score (χ^2=7.9; *df*=3, *P*<0.05) and with length of hospital stay (*F*=28,7; *df*=1, *P*<0.001). Patients with complications showed a prolonged hospitalisation of an average of 26.6 days (95% CI=22.13–31.04), whereas patients without complications stayed 15.3 days (95% CI=14.04–16.71) days in the hospital. Additionally, patients with complication were statistically significantly (χ^2=8.7; *df*=1, *P*<0.01) at higher risk for tumour relapse (54% vs. 23.5%) or death (46% vs. 20%, χ^2=7.3; *df*=1, *P*<0.01) during long-term follow-up. With regard to severity of postoperative complications (grade III–IV), a statistically significant relationship between ypT stage (χ^2=13.2; *df*=4, *P*<0.05), downstaging of the tumour (χ^2=4.9; *df*=1, *P*<0.05), pre-therapeutic anaemia (χ^2=4.4; *df*=1, *P*<0.05) or haemoglobin levels (*F*=6,7; *df*=1, *P*<0.01), hospitalisation (*F*=33,0; *df*=1, *P*<0.001) and *R* classification (χ^2=6.5; *df*=1, *P*<0.05) was found. All data are summarised in Table 5.

Univariate survival analysis concerning disease-free (DFS), cancer-specific (CSS) and overall survival (OS) showed that development of postoperative complications has a strong effect on survival (see Table 6). Patients with postoperative complications showed statistically significantly shorter survival rates at 5 years (DFS=44% vs. 76%; CSS=65% vs. 81%; OS=61% vs. 79%) and 10 years (DFS=42% vs. 76%; CSS=55% vs. 79%; OS=43% vs. 77%) when compared with patients with an uneventful immediate postoperative course (Fig. 1). Additional statistically significant prognosticators concerning clinico-pathological features are given in Table 6.

In multivariate survival analysis, downstaging of the tumour, tumour differentiation and development of postoperative complications were demonstrated as independent prognostic factors. Patients with postoperative complications had a 2.2-fold (95% CI=1.08–4.56) higher risk of developing progressive disease and a 2.7-fold (95% CI=1.06–7.00) higher relative risk of dying (see Table 7).

Table 6 Univariate Survival Analysis of Various Clinico-pathological Features and Postoperative Complications

	DFS		CCS		OS	
	χ^2	*P*	χ^2	*P*	χ^2	*P*
Age (years)						
Continuous	2.2	n.s.	1.7	n.s.	2.3	n.s.
≤60 years vs. >60 years	1.5		0.8	n.s.	1.1	n.s.
Gender						
Female vs. male	0.1	n.s.	0	n.s.	0.3	n.s.
ASA score						
1 vs. 2 vs. 3 vs. 4	10.7	<0.05	6.9	n.s.	5.7	n.s.
Distance from the dentate line (cm)						
Continuous	0.3	n.s.	0.4	n.s.	0.5	n.s.
≤4 cm vs. >4 cm	0.2	n.s.	0.1	n.s.	0.5	n.s.
Pre-therapeutic haemoglobin (g/dl)						
Continuous	0.5	n.s.	1.7	n.s.	3.8	<0.05
≤11 g/dl vs. >11 g/dl	1.3	n.s.	1.5	n.s.	1.8	n.s.
Operative procedure						
LAR vs. APE	12.7	n.s.	12.7	n.s.	11.4	n.s.
Cumulative 5FU dose (mg/m^2)	0.1	n.s.	0.1	n.s.	0.7	n.s.
Cumulative RT dose (Gy)	0.1	n.s.	0.7	n.s.	2.2	n.s.
Hospitalisation (days)						
Continuous	8.8	<0.01	2.6	n.s.	1.3	n.s.
≤14 days vs. >14 days	6.5	<0.05	4.1	<0.05	7.5	<0.01
Tumour stage						
ypT0 vs. 1 vs. 2 vs. 3 vs. 4	16	<0.01	10.2	<0.05	12.2	<0.05
ypN0 vs. 1 vs. 2	11.4	<0.01	11.8	<0.01	8.3	<0.05
M0 vs. M1	0.1	n.s.	0.4	n.s.	0.6	n.s.
UICC-stage						
0 vs. I vs. II vs. III vs. IV	14.4	<0.01	11.5	<0.05	13.1	<0.05
R stage						
R0 vs. R1	14.9	<0.05	111.4	<0.01	19	<0.01
Tumour differentiation						
G1–2 vs. G3–4	128.9	<0.001	114.6	<0.001	111.9	<0.01
Response						
pCR						
No vs. yes	2.4	n.s.	3.6	0.05	3.8	0.05
Downstaging[a]						
No vs. yes	16.1	<0.001	11.1	<0.01	11.3	<0.01
Postoperative complications						
No vs. yes	9.2	<0.01	4.3	<0.05	9.4	<0.01
No vs. grade I vs. II vs. III vs. IV	16.8	<0.01	4.3	n.s.	9.8	<0.05
Severe (Grade III–IV) no vs. yes	1.9	n.s.	1.3	n.s.	3.5	n.s.
Infectious no vs. yes	4.5	<0.05	2.1	n.s.	4.9	<0.05

ASA American Society of Anesthesiology, *LAR* low anterior resection, incl. inter-sphincteric resection (*N*=1), *APE* abdomino-perineal excision, incl. Hartmann's procedure (*N*=1), *5FU* 5-fluorouracil, *RT* radiotherapy, *pCR* pathological complete response, *Gy* Gray, *DFS* disease-free survival, *CSS* cancer-specific survival, *OS* overall survival

[a] cT4→ypT0–3; cT3→ypT0–2

Discussion

Our study shows in a very distinct group of patients, namely in patients with locally advanced stages (i.e. cT3 or cT4) determined unexceptionally by endorectal ultrasound and in one quarter of patients additionally by MRI, that postoperative morbidity is frequent while nearly half of patients (44.4%) are affected. The proportion of postoperative complications in our series is slightly higher when compared with published data[6,17,18] and remains a serious clinical problem in patients with preoperative chemoradiation and consecutive surgery. Out of all postoperative complications, 18% (16 out of all patients) were classified as severe (i.e. grade IIIa to IVb according to the proposal of

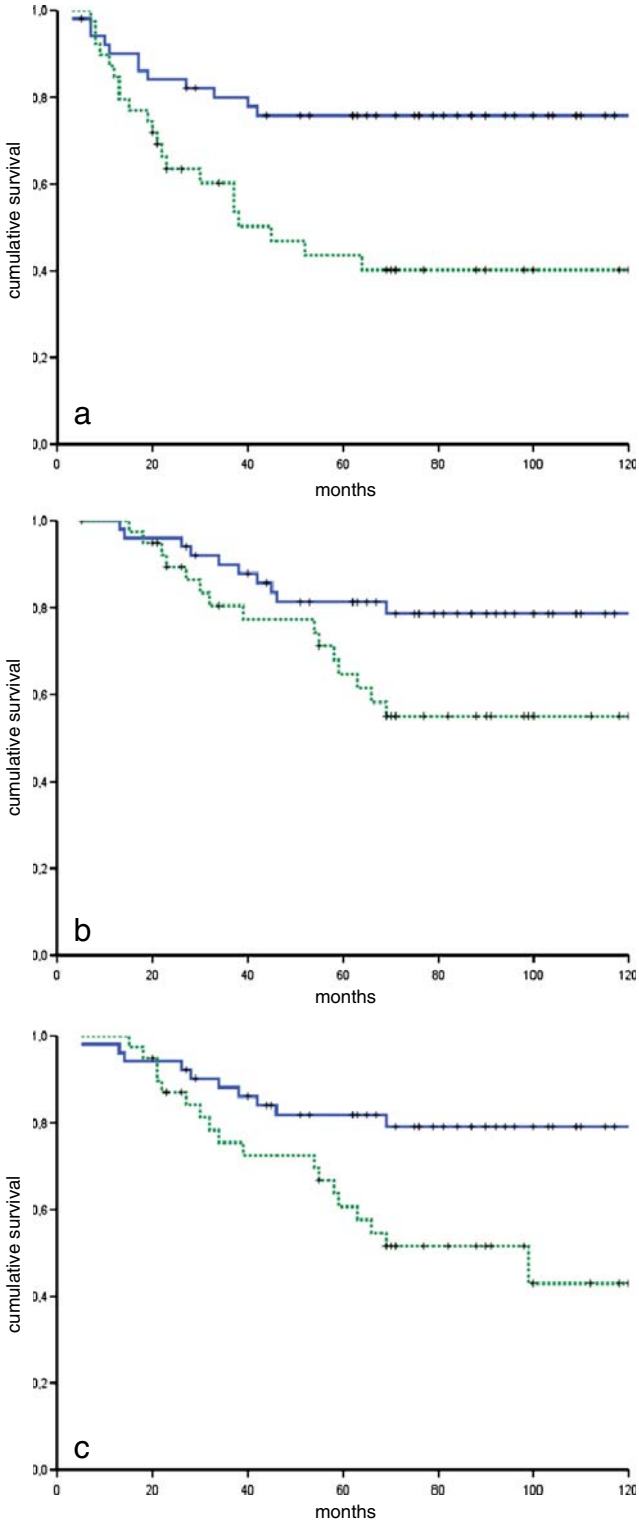

Figure 1 Kaplan–Meier curves for **a** disease-free, **b** cancer-specific and **c** overall survival in patients with preoperative chemoradiation: correlation with postoperative morbidity (*continuous line*) patients without postoperative complications; (*dotted line*) patients with postoperative complications. Percentages indicate survival rates at 5 and 10 years + . . . patients at risk.

Dindo et al.) requiring intervention in general anaesthesia or were life threatening. Nevertheless, none of the patients died during hospital stay.

The majority (77.5%; 31 out of 40 patients with complications) of postoperative complications were infectious secondary disease. Unsurprisingly, the spectrum of pathogens comprised mainly those of the large bowel. The leading cause of infectious complications was anastomotic dehiscence (12.5%; seven out of 56 LAR) or delayed perineal wound healing when APE was performed (15%; five out of 33 APE). Although wound healing problems were overall easily manageable, in one case, a perineal wound infection after APE led to severe clinical problems with renal failure and the need of re-operation. An anastomotic leakage, which is in contrary one of the most feared complications, occurred in 12.5% of all sphincter-preserving resections, which is in the range reported so far.[6,34,35] In this situation, diversion stoma at primary operation turned out to be extremely helpful in managing this life-threatening condition. In five out of the seven patients with anastomotic dehiscence, only tube caecostomy had been performed and in all but one patient re-laparotomy with resection of the anastomosis following terminal colostomy had to be carried out. The remaining two patients had a diversion stoma. In these patients and in additional three, in whom an abscess in the sacral cavity was evident and a minor leakage has to be assumed, solely interventional drainage of the abscess had to be carried out to control morbidity. Due to this observation, which is in contrary to our findings in non-pre-treated patients,[36] from the beginning of the year 2000, protective loop ileostomy was declared as the mandatory routine procedure at our department in pre-treated patients with low anterior or inter-sphincteric resection.

Possible explanations for increased rates of postoperative complications after preoperative chemoradiation and the negative influence of postoperative morbidity on disease-free and overall survival may be found in an impaired immune system regarding both anti-infectious and anti-tumour immunity. Prall et al. demonstrated a negative impact on anti-tumour immunity with impaired effects on CD4 (T-helper cells), CD8 (cytotoxic T-cells), CD83 (mature dendritic cells) and CD57 (natural killer cells).[37] Moreover, a limited immune system function may last at least over the entire preoperative treatment period of 5 weeks and the treatment-free interval might be too short for adequate recovery. Another important factor seems to be the abnormal tumour vascularisation itself and the extracellular matrix effects following preoperative radiation responsible for delayed wound healing.[38] The impact of postoperative complications, especially anastomotic leakage on immediate postoperative mortality and local recurrence, is well recognised.[39,40,17,28,41] Its impact on long-term

Table 7 Multivariate Survival Analysis Regarding DFS and OS

	DFS		CSS		OS	
	RHR (95% CI)	*P*	RHR (95% CI)	*P*	RHR (95% CI)	*P*
Tumour differentiation						
G3–4 vs. G1–2	14.24 (1.92–9.39)	<0.000	3.03 (1.16–7.91)	<0.05	2.49 (1.00–6.29)	0.05
Postoperative complications						
Yes vs. no	2.20 (1.08–4.56)	<0.05	1.46 (0.56–3.85	n.s.	2.73 (1.06–7.00)	<0.05
Downstaging						
No vs. yes	3.19 (1.34–7.57)	<0.01	2.27 (0.51–10.15)	n.s.	2.10 (0.56–7.92)	n.s.

DFS disease-free survival, *CSS* cancer-specific survival, *OS* overall survival, *RHR* relative hazard ratio, *CI* confidence interval

outcome is still a matter of debate due to the fact that, in most studies, the number of patients is too small to draw binding conclusions[39,40] and/or the effect on postoperative mortality cannot be ruled out.[42,43] In our series, none of the patients died postoperatively during hospitalisation or at least 30 days after surgery, resulting in a possible stronger effect of early postoperative morbidity on survival. We could clearly show that patients with postoperative complications showed statistically significantly shorter survival rates ($P<0.01$) and higher proportions of tumour recurrence with regard to both loco-regional failure ($P<0.01$) and distant metastasis ($P<0.01$). However, severity of complications were not related with the clinical course. The mechanism by which postoperative complications, especially anastomotic leakage, adversely affect survival remains to be elucidated. In our opinion, local implantation of viable tumour cells by anastomotic leakage that leads to loco-regional recurrence cannot entirely explain the phenomenon. The biological behaviour of occult hepatic metastases at the time of potentially curative resection that determines the likelihood of dying from metastatic disease may be influenced by inflammatory response as already discussed before. Raised concentrations of C-reactive protein and also reduced levels of interleukin 6, tumour necrosis factor alpha (TNF-alpha) and interferon gamma (IF-gamma) are reported.[28,44] Release of pro-inflammatory cytokines and growth factors in case of intra-abdominal sepsis together with the associated immunosuppression also may have a direct effect on the growth of residual tumour cells.[17,37,45,44,41] It might therefore be hypothesised that patients who subsequently develop postoperative infectious secondary disease have either more residual tumour or inflammatory response may influence the behaviour of occult tumour cells. An altered disease-free survival at 2 or 3 years after curative resection may therefore theoretically support this assumption. In accordance with this hypothesis, we were actually able to demonstrate that the presence of postoperative infectious complications predicts disease-free survival. On the other hand, our working group clearly showed a significant correlation between disseminated tumour cells in the peripheral blood and response to pre-treatment.[32] A re-evaluation regarding the correlation of secondary disease, which was not carried out in the original work, underlines our speculation, showing that, in two out of three patients with anastomotic dehiscence, disseminated tumour cells in the peripheral blood during the perioperative course could be demonstrated directly (proofed by both CEA mRNA and CK20 mRNA) and indirectly (detection of free DNA).[46]

In our study, early postoperative complications were also statistically significantly ($P<0.05$) associated with the pre-therapeutic haemoglobin level. Moreover, red blood counts, gender and ASA scores turned out to be clinical feature capable of predicting postoperative complications. As described recently by our working group,[47] pre-therapeutic anaemia is an additional independent prognosticator in gastrointestinal malignancies, too. In our opinion, pre-therapeutic haemoglobin levels have to be interpreted as a mirror of the general condition of the oncologic patient and therefore associated with the clinical long-time course. It remains speculative to what extent pre-therapeutic transfusion or the administration of growth hormones together with surgical techniques that are known to reduce blood loss like laparoscopic approach with TME[48,49] is able to prevent postoperative complications.

Urinary retention (22.5% out of all complications) was recognised as the most common non-infectious problem. All of them were temporary and were manageable with means of replacement of urinary catheter and in men additionally by administration of alpha-1a antagonists. Due to the fact that urinary retention lasts for only a limited period of time, we assume that the reversible damage of the nerves was more due to pre-treatment than by operative procedure, which was moreover carried out by nerve-preserving technique with respect to the principles of the so-called TME. Due to the design of the study concerning the immediate postoperative course, we could not assess further two important postoperative complications, namely

sexual dysfunction and anal incontinence. On the strength of our past experience, faecal incontinence after closure of the diversion stoma continues to exist for at least half a year and is coped in almost all patients within 1 year.[50,51]

In conclusion, we could demonstrate that postoperative complications are important factors influencing clinical outcome and long-term survival in patients with locally advanced cancer of the mid and lower rectum in whom preoperative combined chemoradiation was carried out. Especially in infectious complications, which are mainly due to anastomotic leakage in LAR and delayed perineal wound healing in APE, the results are consistent with the hypothesis that the inflammatory response might play a significant role in altering the behaviour of occult residual tumour cells. Pre-therapeutic haemoglobin levels, gender and ASA scores were highlighted as predictors of postoperative complications. Urinary retention is the most common non-infectious complication and is due to its reversibility of inferior clinical relevance.

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References

1. Heald RJ, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978–1997. Arch Surg 1998;133:894–899. doi:10.1001/archsurg.133.8.894.
2. Martling A, Holm T, Rutqvist LE, Johansson H, Moran BJ, Heald RJ, Cedermark B. Impact of a surgical training programme on rectal cancer outcomes in Stockholm. Br J Surg 2005;92:225–229. doi:10.1002/bjs.4834.
3. Beets-Tan RGH, Beets GL. Rectal cancer: review with emphasis on MR imaging. Radiology 2004;232:335–346. doi:10.1148/radiol.2322021326.
4. Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, Daban A, Bardet E, Beny A, Ollier JC, EORTC Radiotherapy Group Trial 22921. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006;355:1114–1123. doi:10.1056/NEJMoa060829.
5. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, Rutten HJ, Pahlman L, Glimelius B, van Krieken JH, Leer JW, van de Velde CJ, Dutch Colorectal Cancer Group. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345:638–646. doi:10.1056/NEJMoa010580.
6. Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, Martus P, Tschmelitsch J, Hager E, Hess CF, Karstens JH, Liersch T, Schmidberger H, Raab R, German Rectal Cancer Study Group. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731–1740. doi:10.1056/NEJMoa040694.
7. Lay GC, Caraul B, Dessì M, Orrù S, Murtas R, Deidda MA, Farigu R, Farci D, Maxia L, Casula G, Amichetti M. Phase II study of preoperative irradiation and chemotherapy with capecitabine in patients with locally advanced rectal carcinoma. J Exp Clin Cancer Res 2007;26:61–70.
8. Öfner D, DeVries A, Thaler J, Eisterer W, Greil R, Lukas P, Rabl H, Samonigg H, Kapp K, Gnant M, ABCSG 95 Investigators. Preoperative oxaliplatin (O), capecitabine (X), and external beam radiotherapy (RT) in patients (pts) with newly diagnosed, primary operable, locally advanced rectal cancer (LARC). J Clin Oncol 2007;25:14527.
9. Rödel C, Grabenbauer GG, Papadopoulos T, Hohenberger W, Schmoll HJ, Sauer R. Phase I/II trial of capecitabine, oxaliplatin, and radiation for rectal cancer. J Clin Oncol 2003;21:3098–3104. doi:10.1200/JCO.2003.02.505.
10. Rödel C, Sauer R. Integration of novel agents into combined-modality treatment for rectal cancer patients. Strahlenther Onkol 2007;183:227–235. doi:10.1007/s00066-007-9000-9.
11. Haustermans K, Roels S, Verstraete J, Depuydt T, Slagmolen P. Adaptive RT in rectal cancer: superior to 3D-CRT? A simple question, a complex answer. Strahlenther Onkol 2007;183(2):21–23.
12. Janjan NA, Crane C, Feig BW, Cleary K, Dubrow R, Curley S, Vauthey JN, Lynch P, Ellis LM, Wolff R, Lenzi R, Abbruzzese J, Pazdur R, Hoff PM, Allen P, Brown T, Skibber J. Improved overall survival among responders to preoperative chemoradiation for locally advanced rectal cancer. Am J Clin Oncol 2001;24:107–112. doi:10.1097/00000421-200104000-00001.
13. Theodoropoulos G, Wise WE, Padmanabhan A, Kerner BA, Taylor CW, Aguilar PS, Khanduja KS. T-level downstaging and complete pathologic response after preoperative chemoradiation for advanced rectal cancer result in decreased recurrence and improved disease-free survival. Dis Colon Rectum 2002;45:895–903. doi:10.1007/s10350-004-6325-7.
14. Valentini V, Coco C, Picciocchi A, Morganti AG, Trodella L, Ciabattoni A, Cellini F, Barbaro B, Cogliandolo S, Nuzzo G, Doglietto GB, Ambesi-Impiombato F, Cosimelli M. Does down-staging predict improved outcome after preoperative chemo-radiation for extraperitoneal locally advanced rectal cancer? A long-term analysis of 165 patients. Int J Radiat Oncol Biol Phys 2002;53:664–674. doi:10.1016/S0360-3016(02)02764-5.
15. Wheeler JM, Dodds E, Warren BF, Cunningham C, George BD, Jones AC, Mortensen NJ. Preoperative chemoradiotherapy and total mesorectal excision surgery for locally advanced rectal cancer: correlation with rectal cancer regression grade. Dis Colon Rectum 2004;47:2025–2031. doi:10.1007/s10350-004-0713-x.
16. Rosenberg R, Nekarda H, Zimmermann F, Becker K, Lordick F, Hofler H, Molls M, Siewert JR. Histopathological response after preoperative radiochemotherapy in rectal carcinoma is associated with improved overall survival. J Surg Oncol 2008;97:8–13. doi:10.1002/jso.20844.
17. McArdle CS, McMillan DC, Hole DJ. Impact of anastomotic leakage on long-term survival of patients undergoing curative resection for colorectal cancer. Br J Surg 2005;92:1150–1154. doi:10.1002/bjs.5054.
18. Law WL, Choi HK, Lee YM, Ho JW, Seto CL. Anastomotic leakage is associated with poor long-term outcome in patients after curative colorectal resection for malignancy. J Gastrointest Surg 2007;11:8–15. doi:10.1007/s11605-006-0049-z.
19. Varty PP, Linehan IP, Boulos PB. Intra-abdominal sepsis and survival after surgery for colorectal cancer. Br J Surg 1994;81:915–918. doi:10.1002/bjs.1800810641.
20. Branagan G, Finnis D, Wessex Colorectal Cancer Audit Working Group. Prognosis after anastomotic leakage in colorectal surgery. Dis Colon Rectum 2005;48:1021–1026. doi:10.1007/s10350-004-0869-4.
21. Artioukh DY, Smith RA, Gokul K. Risk factors for impaired healing of the perineal wound after abdominoperineal resection of rectum for carcinoma. Colorectal Dis 2007;9:362–367. doi:10.1111/j.1463-1318.2006.01159.x.

22. Lyall A, Mc Adam TK, Townend J, Loudon MA. Factors affecting anastomotic complications following anterior resection in rectal cancer. Colorectal Dis. 2007;9:801–807. doi:10.1111/j.1463-1318.2006.01197.x.
23. Kressner U, Graf W, Mahteme H, Påhlman L, Glimelius B. Septic complications and prognosis after surgery for rectal cancer. Dis Colon Rectum 2002;45:316–321. doi:10.1007/s10350-004-6174-4.
24. Smith RL, Bohl JK, McElearney ST, Friel CM, Barclay MM, Sawyer RG, Foley EF. Wound infection after elective colorectal resection. Ann Surg 2004;239:599–605, discussion 605–7. doi:10.1097/01.sla.0000124292.21605.99.
25. Bullard KM, Trudel JL, Baxter NN, Rothenberger DA. Primary perineal wound closure after preoperative radiotherapy and abdominoperineal resection has a high incidence of wound failure. Dis Colon Rectum 2005;48:438–443. doi:10.1007/s10350-004-0827-1.
26. Buie WD, MacLean AR, Attard JA, Brasher PM, Chan AK. Neoadjuvant chemoradiation increases the risk of pelvic sepsis after radical excision of rectal cancer. Dis Colon Rectum 2005;48:1868–1874. doi:10.1007/s10350-005-0154-1.
27. Johnson LB, Jorgensen LN, Adawi D, Blomqvist P, Asklöf GB, Gottrup F, Jeppsson B. The effect of preoperative radiotherapy on systemic collagen deposition and postoperative infective complications in rectal cancer patients. Dis Colon Rectum 2005;48:1573–1580. doi:10.1007/s10350-005-0066-0.
28. Koerner P, Westerholt A, Kessler W, Traeger T, Maier S, Heidecke CD. Surgical trauma and postoperative immunosuppression. Chirurg 2008;79:290–294. doi:10.1007/s00104-008-1465-2.
29. Korkolis DP, Plataniotis GD, Gondikakis E, Xinopoulos D, Koulaxouzidis GV, Katsilieris J, Vassilopoulos PP. Short-term preoperative radiotherapy is a safe approach for treatment of locally advanced rectal cancer. Int J Colorectal Dis 2006;21:1–6. doi:10.1007/s00384-005-0740-7.
30. Marijnen CA, Kapiteijn E, van de Velde CJ, Martijn H, Steup WH, Wiggers T, Kranenbarg EK, Leer JW, Cooperative Investigators of the Dutch Colorectal Cancer Group. Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial. J Clin Oncol 2002;20:817–825. doi:10.1200/JCO.20.3.817.
31. DeVries AF, Kremser C, Hein PA, Griebel J, Krezcy A, Öfner D, Pfeiffer KP, Lukas P, Judmaier W. Tumor microcirculation and diffusion predict therapy outcome for primary rectal carcinoma. Int J Radiat Oncol Biol Phys 2003;56:958–965. doi:10.1016/S0360-3016(03)00208-6.
32. Zitt M, Müller HM, Dinnewitzer AJ, Schwendinger V, Goebel G, De Vries A, Amberger A, Weiss H, Margreiter R, Öfner D, Oberwalder M. Disseminated tumor cells in peripheral blood: a novel marker for therapy response in locally advanced rectal cancer patients undergoing preoperative chemoradiation. Dis Colon Rectum 2006;49:1484–1491. doi:10.1007/s10350-006-0673-4.
33. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–213. doi:10.1097/01.sla.0000133083.54934.ae.
34. Vignali A, Fazio VW, Lavery IC, Milsom JW, Church JM, Hull TL, Strong SA, Oakley JR. Factors associated with the occurrence of leaks in stapled rectal anastomoses: a review of 1,014 patients. J Am Coll Surg 1997;185:105–113.
35. Smith JA, King PM, Lane RH, Thompson MR. Evidence of the effect of 'specialization' on the management, surgical outcome and survival from colorectal cancer in Wessex. Br J Surg 2003;90:583–592. doi:10.1002/bjs.4085.
36. Tschmelitsch J, Wykypiel H, Prommegger R, Bodner E. Colostomy vs tube cecostomy for protection of a low anastomosis in rectal cancer. Ann Surg 1999;134:1385–1388.
37. Prall F, Wöhlke M, Klautke G, Schiffmann L, Fietkau R, Barten M. Tumour regression and mesorectal lymph node changes after intensified neoadjuvant chemoradiation for carcinoma of the rectum. APMIS 2006;114:201–210. doi:10.1111/j.1600-0463.2006.apm_304.x.
38. Riedel F, Philipp K, Sadick H, Goessler U, Hörmann K, Verse T. Immunohistochemical analysis of radiation-induced non-healing dermal wounds of the head and neck. In Vivo 2005;19:343–350.
39. Petersen S, Freitag M, Hellmich G, Ludwig K. Anastomotic leakage: impact on local recurrence and survival in surgery of colorectal cancer. Int J Colorectal Dis 1998;13:160–163. doi:10.1007/s003840050158.
40. Fujita S, Teramoto T, Watanabe M, Kodaira S, Kitajima M. Anastomotic leakage after colorectal cancer surgery: a risk factor for recurrence and poor prognosis. Jpn J Clin Oncol 1993;23:299–302.
41. Grandis JR, Snyderman CH, Johnson JT, Yu VL, D'Amico F. Postoperative wound infection. A poor prognostic sign for patients with head and neck cancer. Cancer 1992;70:2166–2170. doi:10.1002/1097-0142(19921015)70:8<2166::AID-CNCR2820700826>3.0.CO;2-H.
42. Walker KG, Bell SW, Rickard MJ, Mehanna D, Dent OF, Chapuis PH, Bokey EL. Anastomotic leakage is predictive of diminished survival after potentially curative resection for colorectal cancer. Ann Surg 2004;240:255–259. doi:10.1097/01.sla.0000133186.81222.08.
43. Birkmeyer JD, Dimick JB, Staiger DO. Operative mortality and procedure volume as predictors of subsequent hospital performance. Ann Surg 2006;243:411–417. doi:10.1097/01.sla.0000201800.45264.51.
44. McMillan DC, Canna K, McArdle CS. Systemic inflammatory response predicts survival following curative resection of colorectal cancer. Br J Surg 2003;90:215–219. doi:10.1002/bjs.4038.
45. Abramovitch R, Marikovsky M, Meir G, Neeman M. Stimulation of tumour growth by wound-derived growth factors. Br J Cancer 1999;79:1392–1398. doi:10.1038/sj.bjc.6690223.
46. Zitt M, Müller HM, Rochel M, Schwendlinger V, Zitt M, Goebel G, deVries A, Margreiter R, Oberwalder M, Zeillinger R, Öfner D. Circulating cell-free DNA in plasma of locally advanced rectal cancer patients undergoing preoperative chemoradiation: a potential diagnostic tool for therapy monitoring. Dis Markers 2008 (in press).
47. Öfner D. Anemia in cancer patients undergoing surgery. In Weiss G, Gordeuk VR, Hershko C, eds. Anemia of chronic disease. Atlanta: Taylor and Francis, 2005, pp 607–613.
48. Heiss MM, Mempel W, Jauch KW, Delanoff C, Mayer G, Mempel M, Eissner HJ, Schildberg FW. Beneficial effect of autologous blood transfusion on infectious complications after colorectal cancer surgery. Lancet 1993;342:1328–1333. doi:10.1016/0140-6736(93)92247-Q.
49. Mynster T, Nielsen HJ, Harling H, Bülow S, Danish TME-group, RANX05-group. Blood loss and transfusion after total mesorectal excision and conventional rectal cancer surgery. Colorectal Dis 2004;6:452–457. doi:10.1111/j.1463-1318.2004.00712.x.
50. Ammann K, Kirchmayr W, Klaus A, Mühlmann G, Kafka R, Oberwalder M, De Vries A, Ofner D, Weiss H. Impact of neoadjuvant chemoradiation on anal sphincter function in patients with carcinoma of the midrectum and low rectum. Arch Surg 2003;138:257–261. doi:10.1001/archsurg.138.3.257.
51. Pegger C, Kafka R, Öfner D, Holzner B, Sperner-Unterweger B, Oberwalder M. Health related quality of life in patients operated on for colorectal cancer. Colorectal Dis 2002;4:29.

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ORIGINAL ARTICLE

Adenocarcinoma of the Appendix Is Rarely Detected by Colonoscopy

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Abstract
Introduction Appendiceal tumors represent a subset of colonic neoplasms that frequently defy early diagnosis only to present at advanced stage with peritoneal metastasis. Data on early detection by colonoscopy is limited to case reports or series. The aim of this study is to determine the diagnostic yield of colonoscopy in detecting appendiceal lesions in patients with appendiceal adenocarcinoma and pseudomyxoma peritonei.
Methods We reviewed clinicopathologic data on 121 consecutive patients with histologically confirmed appendiceal adenocarcinoma with pseudomyxoma peritonei presenting to our institution for intraperitoneal hyperthermic chemotherapy (IPHC) and cytoreductive surgery between February, 1993 and August, 2007, focusing on the colonoscopy findings.
Results Preoperative colonoscopic data were available on 64 patients (average age=51; 52 for IPHC patients). Abnormal findings included seven patients with appendiceal lesions (11%), 12 patients with cecal abnormalities (19%), and 28 patients with polyps (44%). Twenty-three patients (36%) had a normal colonoscopy. Malignancy was documented in two of the 64 (3.1%) patients on preoperative colonoscopy biopsies.
Conclusions Appendiceal abnormalities are infrequently seen on colonoscopy and rarely yield a diagnostic biopsy in patients with appendiceal carcinoma. We found that nearly 42% of patients with carcinoma of the appendix have synchronous colonic polyps, a much higher prevalence than would be expected, supporting a role for a perioperative colonoscopy.

Keywords Appendiceal adenocarcinoma · Pseudomyxoma · Colonoscopy · Intraperitoneal hyperthermic chemotherapy

Introduction

Appendiceal adenocarcinoma is a rare lesion, which is, unfortunately, seldom diagnosed early. Presenting symptoms can include right lower quadrant pain, appendicitis, early satiety, and changes in bowel habits or abdominal distention. It is not unusual for these lesions to be detected incidentally at surgery or by cross-sectional imaging. In the USA, there are 561,000 appendectomies performed annually with approximately 250,000 cases of appendicitis per year.[1] Mucinous distention of the appendix, or mucocele, is present in 0.2–0.3% of appendectomy specimens and may be a premalignant lesion if associated with adenomatous changes. The incidence of appendiceal adenocarcinoma ranges from 0.11–0.80% in appendectomy specimens.[2–5] According to the surveillance, epidemiology and end-results program, the incidence of appendiceal malignancies in the USA is 0.12 cases per 1,000,000 people per year,

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with adenocarcinoma accounting for the largest subset at 37% of total cases.[6] Histologic type predicts extent of disease,[7] with signet-ring cell carcinoma of the appendix having metastases at time of diagnosis in 93% of cases, mucinous adenocarcinoma having metastases at time of diagnosis in 71% of cases, and colonic type adenocarcinoma having metastases at time of diagnosis in 83% of cases.[6]

Pseudomyxoma peritonei is a distinct clinical entity characterized by gelatinous ascites originating from a mucinous appendiceal adenoma or adenocarcinoma. Ronnett et al. found that at least 87% of cases of pseudomyxoma peritonei or mucinous adenocarcinoma with peritoneal involvement were of appendiceal origin.[8] Additionally, Misdraji et al. found that 64% of cases of appendiceal mucinous neoplasms showed evidence of appendiceal rupture and peritoneal spread.[9] We have found that pseudomyxoma is rarely caused by nonappendiceal tumors.

Endoscopic detection of appendiceal adenoma and adenocarcinoma has been reported as case reports and limited case series in the medical literature.[10–20] Ponsky first described the detection of appendiceal mucocele by colonoscopy in 1976 as a yellowish, submucosal, lipoma-like mass.[21] In the largest series to date, Zanati et al. described seven patients with mucinous cystadenoma of the appendix detected on colonoscopy over a 14-year period at a single institution.[16] Lee et al. first described their abnormal colonoscopy findings in a patient with pseudomyxoma peritonei.[22] We are unaware of a large series that adequately describes the preoperative colonoscopic findings in patients presenting with appendiceal adenocarcinoma with pseudomyxoma peritonei. Thus, the aim of this study was to determine the diagnostic yield of colonoscopy in detecting previously diagnosed appendiceal adenocarcinoma with pseudomyxoma peritonei and to characterize the mucosal abnormalities associated with appendiceal adenocarcinoma with pseudomyxoma peritonei.

Methods and Materials

We retrospectively reviewed our experience in 191 patients, from 1993 to 2006, with pseudomyxoma peritonei related to primary appendiceal tumors, who were treated with cytoreductive surgery (CS) and intraperitoneal hyperthermic chemotherapy (IPHC); complete records were available in 121 patients and made up our cohort. Sixty-four patients had a complete colonoscopy either prior to surgery. The initial history and physical, colonoscopy reports, surgical pathology reports, and clinic notes were reviewed for record of colonoscopy performed prior to CS. Reference to prior colonoscopy as normal was deemed to have no appendiceal lesion and no colonic polyps. A total of 64 patients were selected for final review. Colonoscopy report findings of appendiceal lesions, cecal lesions, colonic polyps, and any other mucosal or submucosal defect were compiled. This study was approved by our institutional review board.

Results

Colonoscopy Findings

There were a total of 68 colonoscopies performed on 64 patients prior to IPHC/CS. The indications are summarized in Table 1. The leading indications for performing colonoscopy were new diagnosis of appendiceal adenocarcinoma with pseudomyxoma peritonei (26.6%), cancer of unknown primary source (15.6%), abdominal pain (14.1%), and abdominal mass (10.9%). There were two patients with colonoscopy performed for screening purposes only (3.1%). Indication for colonoscopy was not available in three of the 64 (4.7%) patients.

Patients were defined as having normal colonoscopies if a normal endoscopy report was available and/or if the initial history and physical within our medical record reported on a normal colonoscopy. Colonoscopy reports were available on 54 of the 64 patients (84%) and the initial history and physical was used to report "normal" findings in the remaining ten patients (16%). The average age at time of endoscopy was 51 (range 26–74 years), the average age at time of diagnosis was 50 (range 26–74 years), and the average age at time of IPHC C/S treatment was 52 (range 26–74 years). There were 36 males and 28 females. Colonoscopy was performed for an average of 182 days

Table 1 Indications for Colonoscopy in Patients Presenting for Treatment of Appendiceal Adenocarcinoma with Pseudomyxoma Peritonei

Indication for colonoscopy	Number of cases (%)
Appendiceal adenocarcinoma with pseudomyxoma peritonei	17 (26.6)
Cancer of unknown primary	10 (15.6)
Abdominal pain	9 (14.1)
Abdominal mass	7 (10.9)
Preoperative for IPHC C/S	4 (6.3)
Anemia/rectal bleeding	4 (6.3)
Ascites	3 (4.7)
Unknown indication	3 (4.7)
Weight loss/change in bowel habits	2 (3.1)
Diverticulosis	2 (3.1)
Screening colonoscopy	2 (3.1)
Ulcerative colitis	1 (1.6)

CS cytoreductive surgery, *IPHC* intraperitoneal hyperthermic chemotherapy

(range 1–1447 days, median 79 days) prior to CS/IPHC. Table 2 summarizes colonoscopic findings. In 23 patients, the colonoscopy was entirely normal (36%). Appendiceal lesions were detected in seven patients (11%). Abnormal findings of the cecum, usually a mass effect, were present in 12 patients (19%). Lesions of the appendix and/or cecum were present in 16 patients (25%). Overall, a malignant diagnosis was made on two of the 64 (3.1%) patients on the preoperative colonoscopic biopsies. Table 3 summarizes the clinicopathological findings of patients with abnormalities at the cecum or appendix. Disseminated adenomucinosis of the appendix is classified as a low grade malignant lesion.[7] Colonic polyps were present in 27 patients (42%); only nonhyperplastic polyps were considered significant both within and outside of the cecum. An extrinsic mass in the midascending colon ulcerating through the bowel wall into the lumen was detected concomitantly in one patient (2%). One patient had extensive pancolonic polyps suggestive of familial polyposis (2%).

Surgical Treatments Prior to Colonoscopy

Because many patients presenting for IPHC have prior surgical therapy, we investigated the effect of prior surgery on likelihood of abnormalities being detected with colonoscopy. Prior surgery is defined on a scale of 0–3. Prior surgical score (PSS) of 0 is defined as biopsy only or laparoscopy plus biopsy. PSS of 1 is defined as previous exploratory laparotomy. PSS of 2 is defined as exploratory laparotomy with some resection, usually greater omentectomy or greater omentectomy plus right colectomy. PSS of 3 is defined as extensive surgery with an attempt at complete cytoreduction. PSS was unknown in six patients. There were 16 patients (25%) with PSS of 0, 23 (40%) patients had PSS of 1, 16 (25%) patients had PSS of 2, and three patients had PSS of 3 (5%). The three patients with extensive cytoreduction had normal colonoscopies. Thirty-three of the 64 patients (52%) with colonoscopy prior to IPHC had prior appendectomy.

Forty-four percent of the subset of 16 patients with abnormal findings of the appendiceal orifice and/or cecum had appendectomy prior to colonoscopy. Five of these 16 had PSS of zero, six patients had PSS of 1, and four patients had PSS of 2. PSS was unknown on a single patient.

Table 2 Colonoscopy Results for Patients with Appendiceal Adenocarcinoma with Pseudomyxoma Peritonei

Colonoscopic findings	Number of cases (%)
Normal colonoscopy	23 (36)
Colonic polyps	27 (42)
Appendiceal lesions	7 (11)
Cecal lesions	12 (19)
Invasive ulcerated mass	1 (2)
Pancolonic polyposis	1 (2)

Discussion

We describe the colonoscopic findings of patients presenting to our institution for treatment of appendiceal adenocarcinoma with pseudomyxoma peritonei with intraperitoneal hyperthermic chemotherapy and cytoreductive surgery. This constitutes the single, largest cohort of patients with appendiceal carcinoma in which preoperative colonoscopic data exist. Our series is limited by the inherent limitations and weaknesses seen in retrospective database studies. Specifically, the time between colonoscopy and surgery (either CS or conventional) varied between a few days and 4 years. Further, the clinical impressions of the endoscopists beyond that included in their report were not queried. In addition, our analysis is limited by a highly selected subset of patients with appendiceal carcinoma associated with pseudomyxoma and not just appendiceal adenocarcinomas and as such is not generalizable. However, it is clear that colonoscopy rarely identifies cancer of the appendix, even when it is in an advanced stage.

Standard colonoscopy continues to be the gold-standard study to evaluate colonic mucosa for abnormalities; however, the predilection of appendiceal adenocarcinoma to spread to the peritoneum limits detection of endoluminal disease with colonoscopy. The general consensus of centers caring for patients with appendiceal adenocarcinoma with pseudomyxoma peritonei is that a colonoscopy is inconsequential in these individuals as they typically have stage IV disease. We found that a colonoscopy alone is poor at definitively diagnosing advanced appendiceal adenocarcinoma with peritoneal spread with only 10% of cases showing an appendiceal abnormality and virtually no masses noted intraluminally. Thus, a normal colonoscopy does not predict the absence of an appendiceal adenocarcinoma.

However, we found a high incidence of synchronous colonic polyps, with no synchronous colon cancer. Wolff and Ahmed reported metachronous colonic neoplasm present in 21.4% in patients with benign lesions of the appendix and a single case (4.8%) of metachronous colonic neoplasm in patients with adenocarcinoma of the appendix.[23,24] Colonoscopy is useful in detecting synchronous colonic polyps that may have a higher risk for malignant transformation in this patient population as synchronous colonic neoplasms have been reported in the literature. Nonetheless, the increased incidence of colonic polyps in our cohort (44%) compared to those noted in the age-matched screening population in which adenomas should

Table 3 Appendiceal and Cecal Lesions Detected by Colonoscopy in Patients with Appendiceal Adenocarcinoma with Pseudomyxoma Peritonei

Patient	Age at time of CS	Gender	Initial Chief complaint	Final pathologic diagnosis	Prior appendectomy	Indication for colonoscopy	Site of lesion (A, C, A+C)	Colonoscopic findings	CT findings
1	68	F	Right lower quadrant pain, perforated appendicitis	PMCA of appendix	Yes	Performed prior to IPHC/CS	A	Appendiceal orifice lesion in the lumen	Acute appendicitis; right lower quadrant mass
2	53	M	Right lower quadrant pain, perforated appendicitis	PMCA of appendix	Yes	Screening colonoscopy	A	Colonic mucosa with no abnormalities, benign lymphoid aggregates, small polyp in appendiceal orifice	Appendicitis, 5.6×4.0 cm periappendiceal fluid collection consistent with abscess
3	49	F	Intermittent abdominal pain	PMCA of appendix	Yes	Abdominal pain, evaluate for diverticulosis	A+C	Mild mucosal edema and inflammation at appendiceal orifice	Right lower quadrant mass 3–4 cm
4	32	F	Primary infertility and dysmenorrhea	DPAM of appendix	No	Adenocarcinoma of unknown primary found on laparoscopy with mucinous features	A	Localized area of erythema at appendiceal orifice. Appendiceal orifice appeared bulging with large amount of mucin. Pathology negative for malignancy	None—diagnosis by laparoscopy with evidence of diffuse peritoneal seeding
5	57	M	Unknown	PMCA of appendix	Unknown	Adenocarcinoma of the appendix and malignant ascites	A+C	Cecal deformity. Prominent appendiceal stump. Pathology negative for malignancy	Unknown
6	33	M	Right lower quadrant pain, bloating, right inguinal hernia	DPAM of appendix	Yes	Appendiceal cancer, prior to IPHC/CS	A+C	Small tuft of abnormal nodular tissue at the appendiceal orifice in the cecum. Pathology found focal adenomatous changes with areas of abnormal mucinous glandular epithelium	Right inguinal canal mass/hernia, large mass in region of appendix suggestive of appendiceal mucocele
7	36	M	Vague abdominal discomfort	Peritoneal mucinous adenocarcinoma of appendix	No	Abdominal pain	A	Suggestion of depression of AO from extrinsic compression	Peritoneal carcinomatosis, mass in the appendix, tumor involved extensively the left hemidiaphragm, spleen, right diaphragm, right colon
8	65	M	Inguinal hernia	Peritoneal mucinous adenocarcinoma of appendix	No	Right lower quadrant mass, mucinous tumor	C	4 mm sessile polyp in the cecum	Lesion in the appendix highly suggestive of a large adenoma with low-volume mucin scattered throughout the abdomen

Table 3 (continued)

Patient	Age at time of CS	Gender	Initial Chief complaint	Final pathologic diagnosis	Prior appendectomy	Indication for colonoscopy	Site of lesion (A, C, A+C)	Colonoscopic findings	CT findings
9	54	M	Bloating, lower abdominal pain, cramping	Peritoneal mucinous adenocarcinoma of appendix	Yes	Bloating, lower abdominal pain, cramping	C	Deformed cecum, mucinous exudate from cecum with inflammatory component, appendiceal orifice not well identified, dysplastic rectal polyp. Cecal biopsy found tubulovillous adenoma and adjacent adenocarcinoma could not be excluded, rectal biopsy found hyperplastic polyp	7.2×4.6×6 cm thick walled necrotic, cystic paracecal mass, appendix not identified
10	52	F	Increased abdominal girth, anorexia	Low grade cancer of the appendix	Yes	History of pseudomyxoma peritonei	C	Cecum was deformed, poorly distensible, no mucosal abnormalities	Abdominal ascites, superficial umbilical mass 25×14×28 cm, large cystic mass from pelvis to mid abdomen with pelvic ascites
11	59	F	Postmenopausal vaginal bleeding, free pelvic fluid, and increased CEA	Low grade cancer of the appendix	Yes	Abdominal fluid and increased CEA	C	Four hyperplastic polyps at splenic flexure, cecum, and transverse colon,	2×2.5 cm low attenuation lesion on right paracolic gutter above iliac crest adjacent to associated colon, free abdominal fluid, bulky uterus, intrauterine free fluid
12	27	F	Left upper quadrant abdominal pain	PMCA of appendix	No	Abnormal abdominal CT with thickened cecum	C	Multiple, pedunculated, and sessile, adenomatous polyps (estimated at 30–40) were seen scattered throughout the colon. In addition, there were three polypoidal masses seen: one in the cecum measured about 3 cm, one in the proximal transverse colon (with extensive central ulceration and an irregular surface) measured about 5 cm, and one in the distal sigmoid colon (also with an irregular surface and central ulceration) measured about 3×6 cm	Thickened cecum and irregular stomach wall, abdominal pain, weight loss, bilateral ovarian mass, bilateral adrenal enlargement, right lung nodule

13	43	M	Right lower quadrant abdominal pain for 3 months, developed acute appendicitis	PMCA of appendix	Yes	Follow-up of diagnosis of adenocarcinoma of the appendix	C	There were two small nodules/polyps in the terminal ileum with papillary projections. There was an erythematous irregular mucosa in the cecum. There was a 1–2-cm flat adenoma-like lesion in the sigmoid colon at 35 cm. Pathology found cecal lesion to be invasive moderately differentiated adenocarcinoma	Acute appendicitis
14	58	F	Right-sided abdominal pain, presumed diverticulitis	PMCA of appendix	Yes	Follow-up of diverticulosis	C	Large, friable, ulcerated, sessile mass in the cecum. A single sessile polyp in the ascending colon. A single small polyp in the midsigmoid colon. Large, irregular, pedunculated, polypoid mass in the sigmoid colon 25 cm from the anus. Pathology found lesions to be tubular adenomas	None performed
15	39	M	Right upper quadrant abdominal pain	PMCA of appendix	No	Anemia	C	Mass in the region of the cecum. Pathology found lesion to be suspicious for high-grade dysplasia	Mass in right lower quadrant, soft tissue nodules, question of peritoneal carcinomatosis, multiple low attenuating liver lesions that maybe cysts
16	66	M	Unknown	DPAM of appendix	Unknown	Carcinoma of undetermined origin	C	There was a 5-mm diminutive polyp in the cecum, 5 cm above the ileocecal valve. Pathology found lesion to be tubulovillous adenoma with moderate glandular dysplasia	Unknown

CS cytoreductive surgery, *A* appendiceal, *C* cecal, *A+C* appendiceal and cecal, *IPHC* intraperitoneal hyperthermic chemotherapy, *PMCA* peritoneal mucinous carcinomatosis, *DPAM* disseminated peritoneal adenomucinosis

be detected in ≥25% of men and ≥15% women suggests that these patients are most likely at a higher risk for developing colonic neoplasia.[25] Thus, the value of the colonoscopy is not so much in identifying an appendiceal carcinoma, but, moreover, in detecting colonic neoplasia. Although finding polyps in patients with stage IV disease typically has no effect on long-term survival, most patients with peritoneal dissemination from low-grade appendiceal tumors treated with cytoreductive surgery and IPHC have median survival beyond 5 years. Therefore, colonoscopy and polypectomy may be of value in selected patients being evaluated for surgery.

Conclusion

We examined the yield of colonoscopy in detecting appendiceal adenocarcinoma in a cohort of patients with advanced disease and pseudomyxoma peritonei. There was a low detection rate of 11% for appendiceal abnormalities and 19% for cecal abnormalities. Despite a priori knowledge of the patient's appendiceal carcinoma diagnosis, the endoscopist was able to document malignancy in only 3% of patients on preoperative colonic biopsies. This data represents the largest series of colonoscopic examinations in the literature. We confirm that the likelihood of finding early lesions of the appendix is rare using endoscopic evaluation. Indeed, a negative colonoscopy was commonly present in our cohort with advanced disease, indicating that a negative colonoscopy does not rule out appendiceal primary tumor. There was a higher than expected rate of synchronous colon polyps in our cohort. Colonoscopy should be performed in selected patients diagnosed with appendiceal adenocarcinoma with pseudomyxoma peritonei to evaluate for synchronous premalignant lesions. Endoscopists should be aware that colonoscopy is unlikely to detect advanced appendiceal adenocarcinoma. However, findings of a smooth, submucosal lesion in the cecum near the appendiceal orifice or free-flowing mucin from the appendiceal orifice should raise concern for appendiceal adenocarcinoma.

References

1. Addiss DG, Shaffer N, Fowler BS, Tauxe RV. The epidemiology of appendicitis and appendectomy in the United States. Am J Epidemiol 1990;132:910–925.
2. Collins DC. 71,000 human appendix specimens. A final report, summarizing forty years' study. Am J Proctol 1963;14:265–281.
3. Marudanayagam R, Williams GT, Rees BI. Review of the pathological results of 2660 appendicectomy specimens. J Gastroenterol 2006;41:745–749. doi:10.1007/s00535-006-1855-5.
4. Blair NP, Bugis SP, Turner LJ, MacLeod MM. Review of the pathologic diagnoses of 2,216 appendectomy specimens. Am J Surg 1993;165:618–620. doi:10.1016/S0002-9610(05)80446-5.
5. Connor SJ, Hanna GB, Frizelle FA. Appendiceal tumors: retrospective clinicopathologic analysis of appendiceal tumors from 7,970 appendectomies. Dis Colon Rectum 1998;41:75–80. doi:10.1007/BF02236899.
6. McCusker ME, Coté TR, Clegg LX, Sobin LH. Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program, 1973–1998. Cancer 2002;94:3307–3312. doi:10.1002/cncr.10589.
7. Bradley RF, Stewart JH, Russell GB, Levine EA, Geisinger KR. Pseudomyxoma peritonei of appendiceal origin: a clinicopathologic analysis of 101 patients uniformly treated at a single institution, with literature review. Am J Surg Pathol 2006;30:551–559. doi:10.1097/01.pas.0000202039.74837.7d.
8. Ronnett BM, Zahn CM, Kurman RJ, Kass ME, Sugarbaker PH, Shmookler BM. Disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis. A clinicopathologic analysis of 109 cases with emphasis on distinguishing pathologic features, site of origin, prognosis, and relationship to "pseudomyxoma peritonei". Am J Surg Pathol 1995;19:1390–1408. doi:10.1097/00000478-199512000-00006.
9. Misdraji J, Yantiss RK, Graeme-Cook FM, Balis UJ, Young RH. Appendiceal mucinous neoplasms: a clinicopathologic analysis of 107 cases. Am J Surg Pathol 2003;27:1089–1103. doi:10.1097/00000478-200308000-00006.
10. Hamilton DL, Stormont JM. The volcano sign of appendiceal mucocele. Gastrointest Endosc 1989;35:453–456.
11. Nakagawa T. Colonoscopic diagnosis of mucocele of the appendix. Gastrointest Endosc 1993;39:733–734.
12. Raijman I, Leong S, Hassaram S, Marcon NE. Appendiceal mucocele: endoscopic appearance. Endoscopy 1994;26:326–328. doi:10.1055/s-2007-1008979.
13. Mizuma N, Kabemura T, Akahoshi K, Yasuda D, Okabe H, Chijiiwa Y, Nawata H, Matsui N. Endosonographic features of mucocele of the appendix: report of a case. Gastrointest Endosc 1997;46:549–552. doi:10.1016/S0016-5107(97)70013-0.
14. Minagawa M, Ishikawa H, Date K, Kosugi S, Hatakeyama K, Endo K, Kimura K, Fukuda F. Mucus outflow from the appendiceal orifice due to an appendiceal mucocele. Gastrointest Endosc 2001;53:493. doi:10.1067/mge.2001.113584.
15. Shami VM, Yerian LM, Waxman I. Adenoma and early stage adenocarcinoma of the appendix: diagnosis by colonoscopy. Gastrointest Endosc 2004;59:731–733. doi:10.1016/S0016-5107(04)00008-2.
16. Zanati SA, Martin JA, Baker JP, Streutker CJ, Marcon NE. Colonoscopic diagnosis of mucocele of the appendix. Gastrointest Endosc 2005;62:452–456. doi:10.1016/j.gie.2005.04.018.
17. Qualia CM, Drugas GT, Jones LT, Rossi TM. Colonoscopic diagnosis of an appendiceal mucocele. J Pediatr Gastroenterol Nutr 2007;45:145–146. doi:10.1097/MPG.0b013e3180686da7.
18. Isaacs KL, Warshauer DM. Mucocele of the appendix: computed tomographic, endoscopic, and pathologic correlation. Am J Gastroenterol 1992;87:787–789.
19. Hu CC, Chang JJ, Chen TC, Yen CL, Chien RN. Colonoscopic feature of primary adenocarcinoma of the appendix. Intern Med 2008;47:255–257. doi:10.2169/internalmedicine.47.0192.
20. Itaba S, Akahoshi K, Araki Y, Nakamura K, Chijiiwa Y, Ohata Y, Shimura H, Nawata H. Preoperative colonoscopic diagnosis of minute appendicular adenoma: report of a case. Endoscopy 1998;30:S64. doi:10.1055/s-2007-1001331.
21. Ponsky JL. Endoscopic view of mucocele of appendix. Gastrointest Endosc 1976;23:42–43.
22. Lee Y, Wu H, Hung M, Lin S, Hwang Y, Huang M. Ruptured appendiceal cystadenoma presenting as right inguinal hernia in a

patient with left colon cancer: a case report and review of literature. BMC Gastroenterol 2006;6:32. doi:10.1186/1471-230X-6-32.
23. Wolff M, Ahmed N. Epithelial neoplasms of the vermiform appendix (exclusive of carcinoid). I. Adenocarcinoma of the appendix. Cancer 1976;37:2493–2510. doi:10.1002/1097-0142(197605)37:5<2493::AID-CNCR2820370543>3.0.CO;2-D.
24. Wolff M, Ahmed N. Epithelial neoplasms of the vermiform appendix (exclusive of carcinoid). II. Cystadenomas, papillary adenomas, and adenomatous polyps of the appendix. Cancer 1976;37:2511–2522. doi:10.1002/1097-0142(197605)37:5<2511::AID-CNCR2820370544>3.0.CO;2-L.
25. Rex DK, Petrini JL, Baron TH, Chak A, Cohen J, Deal SE, Hoffman B, Jacobson BC, Mergener K, Petersen BT, Safdi MA, Faigel DO, Pike IM. ASGE/ACG taskforce on quality in endoscopy. Quality indicators for colonoscopy. Am J Gastroenterol 2006;101:873–885.

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ORIGINAL ARTICLE

Colectomy in Patients with Acute Colitis: A Systematic Review

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Abstract
Background For patients with acute colitis, the decision when and how to operate is difficult in most cases. It was the aim of this systematic review to analyze early mortality and morbidity of colectomy for severe acute colitis in order to identify opportunities to improve perioperative treatment and outcome.
Methods A systematic review of the available literature in the Medline and PubMed databases from 1975 to 2007 was performed. All articles were assessed methodologically; the articles of poor methodological quality were excluded. Articles on laparoscopic colectomy for acute colitis were analyzed separately.
Results In total, 29 studies met the criteria for the systematic review, describing a total of 2,714 patients, 1,257 of whom were operated on in an acute setting, i.e., urgent or emergency colectomy. Reported in-hospital mortality was 8.0%; the 30-day mortality was 5.2%. Morbidity was 50.8%. The majority of complications were of infectious and thromboembolic nature. Over the last three decades, there was a shift in indications from toxic megacolon, from 71.1% in 1975–1984 to 21.6% in 1995–2005, to severe acute colitis not responding to conservative treatment, from 16.5% in 1975–1984 to 58.1% in 1995–2007. Mortality decreased from 10.0% to 1.8%. Morbidity remained high, exceeding 40% in the last decade. Mortality after laparoscopic surgery was 0.6%. Complication rate varies from 16–37%.
Conclusion Colectomy for acute colitis is complicated by considerable morbidity. The incidence of adverse outcome has substantially decreased over the last three decades, but further improvements are still required. The retrospective nature of the included studies allows for a considerable degree of selection bias that limits robust and clinically sound conclusions about both conventional and laparoscopic surgery.

Keywords Abdominal surgery · Colectomy · Inflammatory bowel disease · Ulcerative colitis · Crohn's disease · Treatment outcome

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Introduction

About 25% of patients with inflammatory bowel disease (IBD) complicated by an acute colitis will undergo an acute colectomy either as an emergency or an urgent procedure. Emergency colectomy is indicated in case of life-threatening complications as toxic megacolon, perforation, or severe hemorrhage. Ongoing acute colitis despite optimal medical therapy requires urgent colectomy, to prevent further

deterioration. In these urgent cases, the optimal timing of surgery remains difficult. Conservative treatment may save the colon. However, prolonged unsuccessful medical treatment may harm the patient: Delayed surgery may increase the risk of postoperative complications in these seriously ill, immunocompromised, malnourished, and deteriorating patients.[1–5] Conversely, early surgery will expose too many patients to risky emergency surgery.[6–11] It was the aim of this systematic review to analyze the causes of early mortality and morbidity after colectomy for acute colitis in order to identify opportunities to improve the results of treatment. Because of the changes in the long period of time studied, results were stratified for the time era in periods of 10 years.

Since laparoscopy is gaining territory in colorectal surgery, a subgroup analysis was made in order to analyze outcome after laparoscopic subtotal colectomy with the construction of an ileostomy for severe acute colitis. Primary outcome measures were mortality and morbidity and secondary outcome measures were hospital stay, readmission rate, and subsequent restorative procedures.

Methods

Identification of Studies

A systematic review was undertaken with searches performed in Medline and PubMed databases for the period 1975 to 2007, using the following keywords (MESH terms): inflammatory bowel disease, ulcerative colitis, Crohn's, toxic megacolon, surgery, colectomy, treatment outcome, morbidity, mortality, and complications. Studies with data on patients undergoing emergency and urgent (procto-) colectomy for inflammatory bowel disease were included. Language was limited to English, German, Dutch, French, and Italian.

The PubMed database was searched to identify articles on outcome of laparoscopic colectomy for severe acute colitis. The used terms were laparoscop*, colitis, and colectomy. Criteria of exclusion were studies in children only, construction of an ileoanal pouch, surgery for carcinoma in inflammatory bowel disease, long-term outcome only, case reports, and reviews.

Eligibility of Studies

To assess methodological quality, each article was subjected to the methodological index for nonrandomized studies (MINORS) according to Slim et al.[12] Independently, two authors (PT and MS) scored all publications. The results were discussed with two senior authors (AB and RB) if no consensus about the score was reached. Definite scores were established when consensus was reached between all authors. Since data on short-term follow-up and specified early mortality and morbidity are of main importance regarding the aim of our study, accurate specification of short-term outcome was mandatory for selection. A maximum of 17 points could be obtained. To be selected, publications had to score at least one point on each item, reflecting an overall fair methodological quality and homogeneity. The three most relevant publications were selected to search for related articles, which were evaluated in an identical way (Table 1).

Data Extraction

After the initial assessment of the studies for eligibility, two authors (PT and MS) independently extracted the following data: number and demographic data of patients, pre- and postoperative diagnosis, type of surgery, indications for surgery, mortality, and morbidity. Morbidity contained several items: small bowel obstruction/ileus, peritonitis, intra-abdominal abscess, wound infection, fascia dehiscence, rectal stump blowout, hemorrhage, stoma complications, perforation, wound infection, pneumonia, deep venous

Table 1 Modified Methodological Index for Nonrandomized Studies

Criteria		
1. A clearly stated aim	Not reported	0
	Partially reported, no clear aim	1
	Clear aim	2
2. Inclusion of consecutive patients	Not reported	0
	Patients in a certain time period	1
	Consecutive patients + characteristics	2
3. Methods	Not reported	0
	Incomplete	1
	Reported clearly, appropriate to aim	2
4. Evaluation criteria for endpoints	Not reported	0
	No clear description	1
	Clear explanation of chosen endpoints	2
5. Eligibility of endpoints	Not reported	0
	Mortality and/or morbidity	1
	Specified mortality and morbidity	2
	As previous + adequate statistical analysis	3
6. Short-term follow-up	Not reported	0
	Several days	1
	30 day/in-hospital	2
7. Loss to follow-up	Not reported	0
	Incomplete	1
	Clear	2
8. Overall judgment	Lack of comprehension	0
	Little argumentation	1
	Adequate argumentation and discussion	2
Total		17

thrombosis, pulmonary embolism, renal insufficiency, adrenal insufficiency, esophagitis, sepsis, pericarditis, myocardial infarction, urinary tract infection/retention, coagulopathy, nerve damage/compression, and iatrogenic damage. For complications requiring surgical intervention, the number of reoperations was scored.

Operations were classified as either elective or acute (i.e., urgent or emergency), in accordance with the description in the individual articles. Only results on acute operations were extracted. Main outcome measures were 30-day mortality, in-hospital mortality, and morbidity. Colectomy and proctocolectomy, the two main types of operative procedure, were evaluated separately regarding morbidity and mortality. All items were classified according to the original authors' definitions. The desired homogeneity in representation of the adverse events was obtained by grouping complications in general categories as specified in the Tables 2, 3, and 4.

Analysis

The incidence of each item scored was calculated from the pooled patients data. For each specified item, only those articles were used that present accurately described details on the specific item. For each item, the total number of patients described in these articles is reported. The articles were divided into three decades according to the year of publication. The main outcome measures were specified for each decade separately.

Statistical assessment was performed using Fisher's exact test to calculate significance. In order to detect significant trends, the chi-square test was used for linear trend.

Results

The literature search resulted in a total of 414 articles from the PubMed search and 235 articles from Medline search. From the 649 abstracts studied, 13 met the inclusion criteria for this review. The related article search added 612 studies to be evaluated, leading to the inclusion of another 24. Exclusion of articles with MINORS score less than 1 point in any of the items left 29 studies to be included in this systematic review (Fig. 1).

The median MINORS score of these 29 studies was 12 (range 9–15) of 17. The total number included amounted 2,714 patients. Colectomy in the acute phase, the subject of this article, was performed in 1,257 patients. Preoperative diagnosis, mentioned in 942 of these cases, was ulcerative colitis (UC) in 76.9%, Crohn's disease (CD) in 17.2%, indeterminate colitis (IC) in 2.3%, and 3.6% had other preoperative diagnosis. Postoperative diagnoses, mentioned in 226, were similarly distributed: UC in 80.5%, CD in 15.0%, IC in 3.1%, and 1.3% other diagnoses. Indications for surgery were failure of medical therapy/acute colitis in 44.2% (95% confidence interval (CI) 41.0–47.5%), toxic megacolon in 42.2% (95% CI 39.0–45.5%), hemorrhage in 7.7% (95% CI 5.9–9.8%), perforation in 7.0% (95% CI 5.3–8.9%), and other in 2.3% (95% CI 1.4–3.4%). Over time, the incidence of indications for surgery changed. The incidence of toxic megacolon decreased from 71.1% (95% CI 65.3–76.4%) in the first decade to 21.6% (95% CI 17.3–21.3%) in the third decade. Success of conservative treatment causes a fall of acute life-threatening complications like toxic megacolon or hemorrhage. The remaining category of acute colitis not responding to conservative treatment to such extent that it warrants acute surgery therefore increased from 16.5% (95% CI 12.2–21.5%) in the first decade to 58.1% (95% CI 52.2–63.7%) in the last (Table 2). Both shifts were found to be significant (chi-square; $p<0.001$).

Studies that report 30-day mortality included 634 patients. Of these, 5.2% (95% CI 3.6–7.2%; Table 2) died within 30 day after operation. Reports on in-hospital mortality included 1,112 patients, 8.0% of whom died in the hospital after operation. Mortality decreased significantly over time (chi-square test; $p<0.001$) from 10.0 in the first decade to 1.8% in the last.

Two different surgical procedures have been used: subtotal colectomy (STC) or proctocolectomy (PC), both with construction of an ileostomy. In the pooled data, outcome measures were specified for STC in 411 patients and for PC in 265 patients. Mortality within 30 days after STC was 9.0%. After PC, mortality was 8.3%. Overall mortality was 11.1% and 9.8%, respectively (Table 4). Since 1995, no articles have been published reporting on PC.

Overall morbidity was 50.8% (Table 2). Morbidity significantly decreased over the three-decade time span (chi-square test; $p<0.001$) from 62.3% in the first decade to 40.1% in the last. Complications are listed in Table 3. Most frequent surgical complications were wound infection/dehiscence (18.4%), intra-abdominal abscess (9.2%), small bowel obstruction (6.2%), ileostomy-related complications (5.5%), and hemorrhage (4.6%). Specified iatrogenic injuries were found in 3.4%: ureter ($n=2$), vagina ($n=2$), and pelvic nerves ($n=2$). Splenectomy due to iatrogenic damage was mentioned in one case. Reoperation was inadequately documented in most studies. Medical complications comprised infectious and thromboembolic incidents. Twenty-five out of 139 (18.0%) cases developed septicemia. Pneumonia was reported in 11.2% of the cases and urinary tract infection in 4.3%. Thromboembolic complications comprised deep venous thrombosis (7.2%) and pulmonary embolism (7.0%). Other thromboembolic complications (3.4%) were arterial embolism ($n=1$) and portal vein thrombosis ($n=1$). In six cases, thromboembo-

Table 2 Indications, 30-Day Mortality, and Morbidity for Acute Colectomy in Colitis Specified for Time Span and Overall Results

Study		No. of patients	Toxic megacolon	Hemorrhage	Perforation	Acute colitis	Other	30-day mortality	Morbidity
Binder et al.[6]	1975	80	16	5	14	45	0	5	52
Koudahl and Kristensen[13]	1975	19	19	0	0	0	0	–	–
Koudahl and Kristensen[14]	1976	36	–	–	–	–	–	–	–
Mungas et al.[15]	1976	25	25	–	4	0	0	0	11
Strauss et al.[11]	1976	28	28	–	–	0	0	6	28
Patel and Stone[16]	1977	40	40	–	2	0	0	–	14
Roys et al.[9]	1977	10	10	–	3	0	0	–	9
Soyer and Aldrete[17]	1980	12	12	–	–	0	0	1	–
Beauchamp and Beliveau[18]	1981	25	10	7	8	0	0	5	–
Muscroft et al.[19]	1981	14	14	–	–	0	0	–	–
Jamart et al.[20]	1983	20	20	0	0	0	0	–	–
Subtotal (1975–1984)			194/273 (71.1%)	12/144 (8.3%)	31/219 (14.2%)	45/273 (16.5%)	0/273 (0%)	17/170 (10.0%)	114/183 (62.3%)
95% CI			65.3–76.4	4.4–14.1	9.8–19.6	12.2–21.5	0.0–1.3	5.9–15.6	54.7–69.4
Greenstein et al.[21]	1985	59	59	–	–	0	0	–	–
Jones et al.[22]	1987	19	5	0	0	14	0	–	–
Frykholm et al.[23]	1989	78	–	–	–	–	–	8	–
Leijonmarck et al.[24]	1989	185	50	11	0	124	0	–	–
Robert et al.[25]	1990	11	4	11	0	0	0	0	8
Leenen et al.[26]	1991	8	8	0	3	0	0	–	6
Kyle et al.[27]	1992	31	11	0	2	20	0	1	–
Mikkola and Jarvinen[28]	1992	33	18	3	2	7	3	2	19
Ng et al.[29]	1992	32	5	2	2	28	0	0	7
Chevalier et al.[30]	1994	18	0	0	0	16	2	–	–
Melville et al.[31]	1994	106	–	–	–	–	–	–	–
Subtotal (1985–1994)			160/396 (40.4%)	27/337 (8.0%)	9/337 (2.7%)	209/396 (52.8%)	5/396 (1.3%)	11/185 (5.9%)	40/84 (47.6%)
95% CI			35.4–45.4	5.3–11.5	1.2–5.0	47.7–57.8	0.4–2.9	3.0–10.4	36.6–58.9
Fleshner et al.[32]	1995	14	–	–	–	–	–	0	8
Wojdemann et al.[33]	1995	147	41	3	4	84	15	5	–
Almogy et al.[34]	2001	42	11	0	5	26	0	–	–
Hyde et al.[35]	2001	44	6	–	–	–	–	0	29
Alves et al.[36]	2003	40	17	17	6	0	0	–	15
Elton et al.[37]	2003	7	–	–	–	–	–	–	–
Hyman et al.[8]	2005	74	0	1	5	66	2	0	17
Subtotal (1995–2007)			75/347 (21.6%)	21/303 (6.9%)	20/303 (6.6%)	176/303 (58.1%)	17/303 (5.6%)	5/279 (1.8%)	69/172 (40.1%)
95% CI			17.3–21.3	4.3–10.4	4.1–10.0	52.2–63.7	3.3–8.8	0.6–4.1	32.6–48.0
Total		1,257	429/1,016 (42.2%)	60/784 (7.7%)	60/859 (7.0%)	430/972 (44.2%)	22/972 (2.3%)	33/634 (5.2%)	223/439 (50.8%)
95% CI			39.0–45.5	5.9–9.8	5.3–8.9	41.0–47.5	1.4–3.4	3.6–7.2	45.9–55.7

lism was not specified. No reliable data could be retrieved on renal insufficiency and myocardial infarction.

Morbidity specified for STC and PC is listed in Table 4. Overall morbidity for STC was 56.3% and for PC 67.2%. Abscesses were found after 13 (17.8%) out of 73 subtotal colectomies and after six (11.3%) out of 53 proctocolectomies. The number of wound infections after STC was 13 (18.6%) out of 79 and after PC was 14 (23.7%) out of 59. Hemorrhage occurred in zero (0%) out of 16 and three (14.3%) out of 21 cases, respectively. A rectal stump blow out was reported in 11 (6.7%) out of 163 (sub-) total colectomies.

Table 3 Surgical and Medical Complications After Colectomy for Acute Colitis

Morbidity	Number	% (95% CI)	Reoperation	% (95% CI)
Surgical complications				
Small bowel obstruction/ileus	36/580	6.2 (4.4–8.5)	5/18	27.8 (9.7–53.6)
Wound dehiscence	10/175	5.7 (2.8–10.3)	1/1	100 (2.5–100.0)
Fascia dehiscence	–	–	–	–
Anastomotic leakage	2/147	1.4 (0.2–4.8)	2/2	100 (15.8–100.0)
Hemorrhage	22/476	4.6 (2.9–6.9)	8/10	80.0 (44.3–97.5)
			2/8[a]	25.0 (3.2–65.1)
Stoma complication	15/273	5.5 (3.1–8.9)	6/14	42.9 (17.7–71.2)
Perforation	3/79	3.8 (0.8–10.7)	3/3	100 (29.2–100.0)
Peritonitis	8/191	4.2 (1.8–8.1)	5/5	100 (47.8–100.0)
Abscess	46/532	8.6 (6.4–11.4)	6/10	60.0 (26.2–87.8)
			3/6[b]	50.0 (11.8–88.2)
Wound infection	73/575	12.7 (10.0–15.8)	–	–
Iatrogenic injury	7/185	3.8 (1.5–7.7)	–	–
Medical complications				
Pneumonia	13/116	11.2 (6.1–18.4)		
Urinary tract infection/retention	7/161	4.3 (1.8–8.8)		
Septicemia	25/139	18.0 (12.0–25.5)		
Thromboembolic complications				
Deep venous thrombosis	12/166	7.2 (3.8–12.3)		
Pulmonary embolism	3/43	7.0 (1.5–19.1)		
Other thromboembolism	8/232	3.4 (1.5–6.7)		

[a] Conservative treatment with packed cells
[b] Radiological drainage

Seven reports on laparoscopic colectomy for severe acute colitis met the criteria for inclusion in this review. Mean operation time was 253 min. Six out of 174 (3.4%) laparoscopic procedures were converted to laparotomy. The main reasons for conversion were adhesions, complicated colitis, or the necessity of peritoneal lavage. One patient out of 174 (0.6%) died as a result of a fatal stroke. Morbidity varied from 16–37%. Main complications were small bowel obstruction (8.9%), surgical site infections (6.3%), high output ileostomy (5.7%), and other stoma-related complications (4.4%). Hospital stay was expressed in median as in mean values (Table 5). Readmission rate was only mentioned in two studies, being seven out of 36 (19.4%). A later subsequent restorative procedure (mostly construction of an ileoanal pouch) could be performed in 116 out of 137 patients (85%). Due to insufficient data available, no

Table 4 Indications, Mortality, and Morbidity for Acute Subtotal Colectomy and Proctocolectomy

	STC	%	PC	%
Toxic megacolon	141/248	56.9	66/176	37.5
Hemorrhage	18/171	10.5	15/137	10.9
Perforation	14/166	8.4	11/77	14.3
Acute colitis	87/228	38.2	86/171	50.3
Reported mortality	45/405	11.1	26/265	9.8
30-day mortality	13/144	9.0	15/181	8.3
Overall morbidity	54/96	56.3	41/61	67.2
Small bowel obstruction/ileus	2/10	20.0	–	–
Peritonitis	0/26	0	1/15	6.7
Abscess	13/73	17.8	6/53	11.3
Wound infection	13/70	18.6	14/59	23.7
Burst abdomen	–	–	–	–
Hemorrhage	0/16	0	3/21	14.3
Stoma complications	1/16	6.3	2/22	9.1
Septicemia	1/11	9.1	2/7	28.6
Pelvic nerve damage	–	–	2/15	13.3
Rectal stump blow out	11/163	6.7	–	–

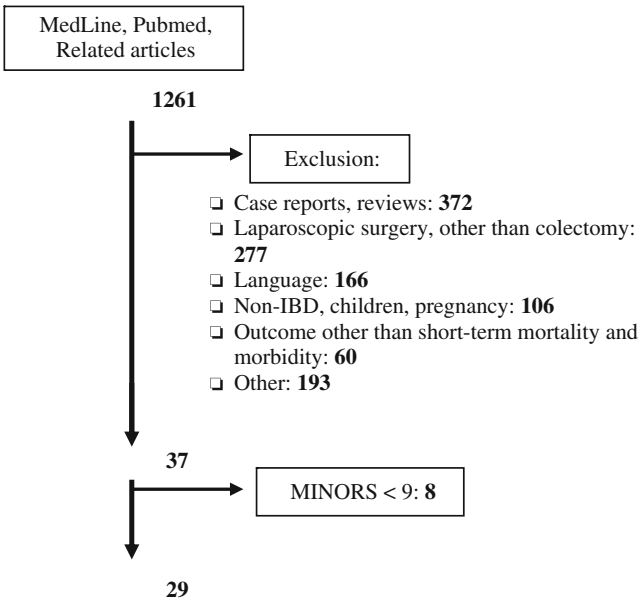

Figure 1 Algorithm article selection.

comparison between conventional and laparoscopic procedures could be made.

Discussion

Morbidity of colectomy in patients with acute colitis is high. Half of the patients develop one or more complications. Morbidity and mortality decreased considerably during the last three decades. In the earlier days, toxic megacolon was the most frequent indication for nonelective surgery. Over time, acute colitis not responding immunosuppressive therapy took over this role.

This review is mainly based on retrospective studies, with their generally known limitations. Mostly, definitions of indications and complications are not specified and, probably, not uniform. Performing subgroup analysis for ulcerative colitis and Crohn's disease is not possible. Pre- and postoperative diagnosis vary a lot and crossover, pathologic examination may not be uniform and complications are not reported related to diagnosis. The difference between urgent and emergency colectomy is not described in the reviewed literature. Therefore, it is impossible to define the difference in outcome between emergency and urgent colectomy. Inevitably, this causes heterogeneity in patient group composition in the various articles. Moreover, the retrospective literature may incorporate publication bias. However, in the absence of randomized prospective studies, this review represents the best level of evidence available.

After colectomy in the acute phase, the vast majority of complications are caused by surgical technical problems, infections, or thromboembolic sequelae. Efforts to improve the standard of care should therefore deal with these three major threats.

Surgical Complications

The frequency of most surgical complications as prolonged ileus (6.2%), wound dehiscence (5.7%), and anastomotic leakage (4.6%) is similar as in patients undergoing elective colectomy for other diagnosis. Iatrogenic bowel perforation is a feared complication in patients with toxic megacolon. Accidental perforations were observed in 3.8% of patients but insufficient data are available to determine whether this complication occurs more frequent as in patients undergoing acute abdominal surgery.

Blow out of the rectal stump was found in 6.7% after STC. According to some authors, the incidence of stump blow out is highest in patients with a short stump. Trickett et al. report an incidence of 33% of pelvic sepsis if a short intrapelvic stump is created, 6–12% in patients with an intraperitoneal stump, and in 3–4% of patients with a mucous fistula. Specification of the rectal stump length is lacking in all reviewed studies. The consequences of the reported cases of rectal stump blowout or preventive measures were not described. A minority of colorectal surgeons prefer to leave a rectal tube in the rectal stump, but there is no literature available to support or reject this practice.[45–48]

Since a subtotal colectomy with the construction of an ileostomy is the operation of choice, anastomotic leakage is only a relevant issue in ileorectal and ileoanal anastomosis. Most surgeons are reluctant to perform anastomosis because all patients with acute colitis receive high-dose corticosteroids, which is associated with an increased risk of anastomotic dehiscence. Moreover, most patients are malnourished and in a bad clinical condition. Primary anastomosis was reported in overall 147 patients. The anastomotic leakage rate was very low (1.4%; 95% CI 0.2–4.8) which may be a consequence of a selection bias.

Infectious Complications

Postoperative infections are the main cause of postoperative complications. Surgical site infections such as wound infections and intra-abdominal sepsis are found in 24% of patients. Distant infections such as pneumonia, urinary tract infections, and sepsis occurred in 32%. The causes of infectious complications and preventive measures, e.g., antibiotic prophylaxis, are not documented in the reviewed studies to the extent that conclusions can be drawn. Hence, optimal perioperative care must be based on extrapolation of data in related conditions. Several factors may contribute to the high infection rate.

Table 5 Studies on Laparoscopic Colectomy for Severe Acute Colitis

	Dunker et al.[38]	Marcello et al.[39]	Seshadri et al.[40]	Bell and Seymour[41]	Ouaïssi et al.[42]	Fowkes et al.[43]	Marceau et al.[44]
Publication year	2000	2001	2001	2002	2006	2007	2007
Study design	Retrospective	Case-control	Retrospective	Retrospective	Prospective	Prospective	Case-control
Patients	10	19	37	18	18	32	40
Diagnosis							
CU	8	16	20	18	15		26
CD	2	3	6	0	2		13
IC				0	1		1
Other			11				
Duration (min)	271	210	270	244–270	253	145	253
Conversion	0	0	3	0	0	1	2
Mortality	0	0	1	0	0	0	0
Morbidity (%)	30	16	25	33	28	37	35
Surgical							
Wound infection		2	0		1	3	0
Abscess	1			1			3
Hemorrhage			1	1			1
Stoma related	1				1		1
Bowel obstruction		1	3		1	5	3
High ileostomy output			0	3		2	
Other	3						
Medical							
Cardiopulmonary			0			3	2
Urinary tract			1				1
Thromboembolic			1	1	1		
Perioperative transfusion					1	4	7
Other medical	1						3
Hospital stay (days)	15[a]	4[b]	6[b]	5[a]	8[a]	7[b]	9[a]
Readmission				6	1		
Subsequent IPAA	6	13		17	18	26	36

Absolute numbers unless indicated otherwise
[a] Mean
[b] Median

In general, surgical site infections account for 15–25% of complications in patients with peritonitis. Prevention of perforation by well-timed surgery and proper surgical technique in handling the weakened colon may therefore contribute to diminish septic complications.

Wound infection is a frequent complication after abdominal surgery and occurred in 17.5% of patients, which is similar to patients undergoing abdominal surgery under clean contaminated and contaminated conditions. A major cause is peroperative contamination which may result from iatrogenic perforation or translocation of bacteria from the diseased and weakened colon. Moreover, standard antibiotic prophylaxis is likely to be inadequate. Motility disturbances of the gastrointestinal tract and treatment with antibiotics causes a change in the intestinal flora in patients with acute colitis.[49–51] Possibly, better results can be obtained with antibiotic prophylaxis directed against the altered intestinal flora, including antibiotics against hospital acquired bacteria.[50,52] Antibiotic profylaxis was not mentioned in the reviewed articles.

It is important to realize that the immune response in these seriously ill patients is compromised due to their general condition and the intensive use of immunomodulating agents. Patients with acute colitis are often in a poor condition due to hospitalization, nutritional deprivation, and extensive losses, e.g., diarrhea. Furthermore, the integrity of the colonic wall deteriorates in colitis. Diminished colonic wall integrity may lead to bacterial translocation, which increases the risk of infection. Medical therapy of acute colitis is focused on the suppression of the inflammatory response by high-dose corticosteroids and cyclosporine that are known to be detrimental to the patients' immune response to microorganisms. On the other hand, changes in medication contribute to a shift in presentation for acute surgery away from toxic megacolon and toward less severe conditions. Again, it should be noted that nomenclature in

the reviewed studies is probably not uniform. However, the changes in medical therapy might be an explanation for the improved outcome over the three decades studied, as found in the cited literature. Response rates after high dose intravenous corticosteroid therapy are 47–75% within 5 to 7 days.[53,54] Yet, 63% of these patients underwent a colectomy within 3 months. After 7 to 10 days, continuation of corticosteroid therapy in nonresponders has no benefit for the patient. Instead, it may cause harm to the patient by compromising the immune system, thus increasing the risk of complications after surgery.[53,55,56] In steroid failures, early decision about the next step is mandatory being either cyclosporine or surgery. Cyclosporine is a T-cell inhibitor with a rapid onset of action, not suppressing the activity of other stem cells or bone marrow.[53,57] The initial response rate is as high as 70–80%. However, in the longer term, a high rate of colectomies is reported in up to 70–88% of patients and no effect on survival has been documented.[58–62] New biological treatments such as cytokines or monoclonal antibodies against cytokines are still subject of study. In the development of newer additional medical therapies, the risk of an increase of perioperative morbidity must be taken into account, although in a recent review, no adverse effects on the outcome of surgery could be demonstrated of cyclosporine, methorexate, azathioprine, 6-mercaptopurine, and antitumor necrosis factor treatment in patients with inflammatory bowel disease.[63] Still prolonged ineffective medical treatment may worsen the condition of the patient and surgical outcome while postponing surgery for a short period only.

Thromboembolic Complications

Thromboembolic events are a cause of postoperative complications in 18% of the patients, most frequently deep venous thrombosis and pulmonary embolism. This is within the range of the incidence of thromboembolic events after colorectal surgery found in the literature which is 7–30%.[64,65] The understanding of the tendency of IBD patients to form arterial and venous clots is limited.[66] The reported incidence stresses the fact that thromboembolic prevention deserves scrutinous attention. In the literature evaluated, no information is given about preventive measures against thromboembolic complications in non-elective colectomy. Hence, optimal perioperative care must be based on extrapolation of data in related conditions. Based on the criteria of the American College for Chest Physicians, patients with inflammatory bowel diseases have a threefold increased risk in developing deep venous thrombosis or a pulmonary embolism.[67,68] Since acute medical illness and surgical intervention both are independent risk factors for venous thromboembolism, patients with severe acute colitis can be categorized in the highest risk level.[69] Recommendations for preventive measures have to be based on reliable data that are only available for patient populations with diagnoses other than acute colitis.

Subtotal Colectomy vs. Proctocolectomy

Subtotal colectomy and proctocolectomy are the procedures of choice in patients with acute colitis. Sixteen studies clearly reported mortality and/or morbidity specified in relation to the operation that was performed. All of these reports were published before 1995. This reflects a clinical practice from which urgent or emergency proctocolectomy virtually disappeared. Studies in 1995–2007 reported lower mortality and morbidity rates but did not specify for the type of operation. Data about the preoperative condition of the patients were not available. It is reasonable to assume that PC has been reserved for patients in a better condition. Therefore, a proper comparison between the two procedures from these retrospective studies is impossible. If a STC is performed, a long intraperitoneal stump is the best option because it has the lowest risk of stump leakage, proctectomy by laparotomy is more simple to perform, and the functional results of ileorectal anastomosis with a long rectal stump are superior to those with a short stump.[70] However, a long stump has the disadvantage that a proctectomy cannot be performed by a perineal approach alone as opposed to a very short stump. It appears to be safe to leave a closed rectal stump intraperitoneally or buried subcutaneously.[27,29,33,46,48] Elective proctectomy is performed in 57.6% of patients after STC. Morbidity of proctectomy comprises delayed wound healing in 20–60%, pelvic abscesses and perineal sinuses in 25–55%, urinary dysfunction in 25%, and sexual dysfunction in 15%.[71,72,74,75] No adequate data are available to outweigh the cumulative risk of one stage proctocolectomy against a two stage procedure.

A comparison between conventional open colectomy and laparoscopic colectomy is impossible because insufficient data are available to characterize both groups. Laparoscopic colectomy seems to be safe and feasible in inflammatory bowel disease. Possible advantages compared to open surgery are a reduced incidence of surgical site infections, incisional hernias, and an improved cosmesis. Laparoscopy is thought to be a less traumatic procedure, probably resulting in fewer adhesions and subsequent small bowel obstruction. Later, restorative procedures are not jeopardized by laparoscopic surgery. However, a couple of comments merit consideration. First, the population described in the studied articles is probably not uniform. Where Marcello and colleagues excluded patients with tachycardia, fever, marked leucocytosis, and peritonitis, Bell included patients with systemic manifestations of

inflammatory bowel disease. Furthermore, only Marceau et al.[44] described criteria for colectomy in detail. The decision to operate was based on clinical, laboratory, and colonoscopic findings. Finally, laparoscopic colectomy in IBD is technically demanding. The mesentery tends to be hypervascular, very friable and retroperitoneal planes may be difficult to divide. Cassilas and Delaney[73] state that it is justified to continue the development of laparoscopic surgery for IBD, but it should be performed by experienced surgeons only. Independent from the development of laparoscopy as a promising technique to treat these patients, it is important to realize that timing of surgery remains a key issue in order to further reduce unfavorable outcome.

Conclusion

In conclusion, the morbidity of acute colectomy for inflammatory bowel disease is relatively high. Surgical site infections, distant infections, and thromboembolic complications are the main opportunities to improve morbidity and mortality. If mortality and morbidity are lower in laparoscopic colectomy, then conventional open surgery remains unclear.

References

1. Jonsson K, Jiborn H, Zederfeldt B. Healing of anastomoses after obstruction of small intestine. Surg Gynecol Obstet 1988;167(4):324–330.
2. Tartter PI, Driefuss RM, Malon AM et al. Relationship of postoperative septic complications and blood transfusions in patients with Crohn's disease. Am J Surg. 1988;155(1):43–48. doi:10.1016/S0002-9610(88)80256-3.
3. Ballantyne KC, Sethia B, Reece IJ et al. Empyema following intra-abdominal sepsis. Br J Surg 1984;71(9):723–725. doi:10.1002/bjs.1800710929.
4. Greenhalgh DG, Gamelli RL. Is impaired wound healing caused by infection or nutritional depletion? Surgery 1987;102(2):306–312.
5. Hesp FL, Hendriks T, Lubbers EJ et al. Wound healing in the intestinal wall. Effects of infection on experimental ileal and colonic anastomoses. Dis Colon Rectum 1984;27(7):462–467. doi:10.1007/BF02555541.
6. Binder SC, Miller HH, Deterling RA. Emergency and urgent operations for ulcerative-colitis—procedure of choice. Arch Surg 1975;110(3):284–289.
7. Heppell J, Farkouh E, Dube S et al. Toxic megacolon—an analysis of 70 cases. Dis Colon Rectum 1986;29(12):789–792. doi:10.1007/BF02555345.
8. Hyman NH, Cataldo P, Osler T. Urgent subtotal colectomy for severe inflammatory bowel disease. Dis Colon Rectum 2005;48(1):70–73. doi:10.1007/s10350-004-0750-5.
9. Roys G, Kaplan MS, Juler GL. Surgical management of toxic megacolon. Am J Gastroenterol 1977;68(2):161–166.
10. Sirinek KR, Tetirick CE, Thomford NR et al. Total proctocolectomy and ileostomy—procedure of choice for acute toxic megacolon. Arch Surg 1977;112(4):518–522.
11. Strauss RJ, Flint GW, Platt N et al. Surgical management of toxic dilatation of colon—report of 28 cases and review of literature. Ann Surg 1976;184(6):682–688. doi:10.1097/00000658-197612000-00004.
12. Slim K, Nini E, Forestier D et al. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg 2003;73(9):712–716. doi:10.1046/j.1445-2197.2003.02748.x.
13. Koudahl G, Kristensen M. Toxic megacolon in ulcerative-colitis. Scand J Gastroenterol 1975;10(4):417–421.
14. Koudahl G, Kristensen M. Postoperative mortality and complications after colectomy for ulcerative-colitis. Scand J Gastroenterol 1976;11:117–122.
15. Mungas JE, Moossa AR, Block GE. Treatment of toxic megacolon. Surg Clin North Am 1976;56(1):95–102.
16. Patel SC, Stone RM. Toxic megacolon—results of emergency colectomy. Can J Surg 1977;20(1):36–38.
17. Soyer MT, Aldrete JS. Surgical-treatment of toxic megacolon and proposal for a program of therapy. Am J Surg 1980;140(3):421–425. doi:10.1016/0002-9610(80)90182-8.
18. Beauchamp G, Beliveau D, Archambault A. Death and complications after total colectomy for inflammatory bowel-disease. Can J Surg 1981;24(5):463.
19. Muscroft TJ, Asquith P, Warren PM et al. Toxic megacolon in ulcerative-colitis—a continuing challenge. Postgrad Med J 1981;57(666):223–227.
20. Jamart J, Boissel P, Debs A et al. Total colectomy with ileorectal anastomosis in surgical-management of toxic megacolon. Langenbecks Arch Chir 1983;360(3):159–165. doi:10.1007/BF01259232.
21. Greenstein AJ, Sachar DB, Gibas A et al. Outcome of toxic dilatation in ulcerative and Crohns colitis. J Clin Gastroenterol 1985;7(2):137–144. doi:10.1097/00004836-198504000-00007.
22. Jones HW, Grogono J, Hoare AM. Acute colitis in a district general-hospital. BMJ 1987;294(6573):683–684.
23. Frykholm G, Pahlman L, Enblad P et al. Early outcome after emergency and elective surgery for ulcerative colitis. Acta Chir Scand 1989;155:601–605.
24. Leijonmarck CE, Brostrom O, Monsen U et al. Surgical-treatment of ulcerative-colitis in Stockholm County, 1955 to 1984. Dis Colon Rectum 1989;32(11):918–926. doi:10.1007/BF0255 2266.
25. Robert JH, Sachar DB, Aufses AH et al. Management of severe hemorrhage in ulcerative-colitis. Am J Surg 1990;159(6):550–555. doi:10.1016/S0002-9610(06)80064-4.
26. Leenen LPH, Schoon E, Stuifbergen W et al. Surgical treatment of toxic megacolon. Ned Tijdschr Geneeskd 1991;135(22):992–996.
27. Kyle SM, Steyn RS, Keenan RA. Management of the rectum following colectomy for acute colitis. Aust N Z J Surg 1992;62(3):196–199. doi:10.1111/j.1445-2197.1992.tb05462.x.
28. Mikkola KA, Jarvinen HJ. Management of fulminating ulcerative-colitis. Ann Chir Gynaecol 1992;81(1):37–41.
29. Ng RLH, Davies AH, Grace RH et al. Subcutaneous rectal stump closure after emergency subtotal colectomy. Br J Surg 1992;79(7):701–703. doi:10.1002/bjs.1800790737.
30. Chevalier JM, Jones DJ, Ratelle R et al. Colectomy and ileorectal anastomosis in patients with Crohns-disease. Br J Surg 1994;81(9):1379–1381. doi:10.1002/bjs.1800810945.
31. Melville DM, Ritchie JK, Nicholls RJ et al. Surgery for ulcerative-colitis in the era of the pouch—the St-Marks-Hospital experience. Gut 1994;35(8):1076–1080. doi:10.1136/gut.35.8.1076.
32. Fleshner PR, Michelassi F, Rubin M et al. Morbidity of subtotal colectomy in patients with severe ulcerative-colitis unresponsive

to cyclosporine. Dis Colon Rectum 1995;38(12):1241–1245. doi:10.1007/BF02049146.
33. Wojdemann M, Wettergren A, Hartvigsen A et al. Closure of rectal stump after colectomy for acute colitis. Int J Colorectal Dis 1995;10(4):197–199. doi:10.1007/BF00346218.
34. Almogy G, Sachar DB, Bodian CA et al. Surgery for ulcerative colitis in elderly persons—changes in indications for surgery and outcome over time. Arch Surg 2001;136(12):1396–400. doi:10.1001/archsurg.136.12.1396.
35. Hyde GM, Jewell DP, Kettlewell MGW et al. Cyclosporin for severe ulcerative colitis does not increase the rate of perioperative complications. Dis Colon Rectum 2001;44(10):1436–1440. doi:10.1007/BF02234594.
36. Alves A, Panis Y, Bouhnik Y et al. Subtotal colectomy for severe acute colitis: a 20-year experience of a tertiary care center with an aggressive and early surgical policy. J Am Coll Surg 2003;197 (3):379–385. doi:10.1016/S1072-7515(03)00434-4.
37. Elton C, Makin G, Hitos K et al. Mortality, morbidity and functional outcome after ileorectal anastomosis. Br J Surg 2003;90(1):59–65. doi:10.1002/bjs.4005.
38. Dunker MS, Bemelman WA, Slors JFM et al. Laparoscopic-assisted vs open colectomy for severe acute colitis. Surg Endosc 2000;14:911–914. doi:10.1007/s004640000262.
39. Marcello PW, Milsom JW, Wong SK et al. Laparoscopic total colectomy for acute colitis. Dis Colon Rectum 2001;44:1441–1445. doi:10.1007/BF02234595.
40. Seshadri PA, Poulin EC, Schlachta CM et al. Does laparoscopic approach to total abdominal colectomy and proctocolectomy offer advantages? Surg Endosc 2001;15:837–842. doi:10.1007/s004640000356.
41. Bell RL, Seymour NE. Laparoscopic treatment of fulminant ulcerative colitis. Surg Endosc 2002;16:1778–1782. doi:10.1007/s00464-001-8300-x.
42. Ouaïssi M, Alves A, Bouhnik Y et al. Three-step ileal pouch-anal anastomosis under total laparoscopic approach for acute or severe colitis complicating inflammatory bowel disease. J Am Coll Surg 2006;202(4):637–642. doi:10.1016/j.jamcollsurg.2005.12.016.
43. Fowkes L, Krishna K, Menon A et al. Laparoscopic emergency and elective surgery for ulcerative colitis. Colorectal Dis 2008;10 (4):373–378. doi:10.1111/j.1463-1318.2007.01321.x.
44. Marceau C, Alves A, Ouaïssi M et al. Laparoscopic subtotal colectomy for acute or severe colitis complicating inflammatory bowel disease: a case-matched study in 88 patients. Surgery 2007;141(5):640–644. doi:10.1016/j.surg.2006.12.012.
45. Gurjar SV, Forshaw MJ, Ahktar N et al. Indwelling trans-anastomotic rectal tubes in colorectal surgery: a survey of usage in UK and Ireland. Colorectal Dis 2007;9(1):47–51. doi:10.1111/j.1463-1318.2006.00969.x.
46. McKee RF, Keenan RA, Munro A. Colectomy for acute colitis: is it safe to close the rectal stump? Int J Colorectal Dis 1995;10 (4):222–224. doi:10.1007/BF00346223.
47. Ozuner G, Strong SA, Fazio VW. Effect of rectosigmoid stump length on restorative proctocolectomy after subtotal colectomy 10. Dis Colon Rectum 1995;38(10):1039–1042. doi:10.1007/BF02133975.
48. Trickett JP, Tilney HS, Gudgeon AM et al. Management of the rectal stump after emergency sub-total colectomy: which surgical option is associated with the lowest morbidity? Colorectal Dis 2005;7(5):519–522. doi:10.1111/j.1463-1318.2005.00875.x.
49. Guarner F. The intestinal flora in inflammatory bowel disease: normal or abnormal? Curr Opin Gastroenterol 2005;21(4):414–418.
50. Guslandi M. Antibiotics for inflammatory bowel disease: do they work? Eur J Gastroenterol Hepatol 2005;17(2):145–147. doi:10.1097/00042737-200502000-00003.
51. Marteau P, Lepage P, Mangin I et al. Review article: gut flora and inflammatory bowel disease. Aliment Pharmacol Ther 2004;20 (Suppl 4):18–23. doi:10.1111/j.1365-2036.2004.02062.x.
52. Sartor RB. Therapeutic manipulation of the enteric microflora in inflammatory bowel diseases: antibiotics, probiotics, and prebiotics. Gastroenterology 2004;126(6):1620–1633. doi:10.1053/j.gastro.2004.03.024.
53. Jarnerot G, Rolny P, Sandberg-Gertzen H. Intensive intravenous treatment of ulcerative colitis. Gastroenterology 1985;89(5):1005–1013.
54. Truelove SC, Willoughby CP, Lee EG et al. Further experience in the treatment of severe attacks of ulcerative colitis. Lancet 1978;2 (8099):1086–1088. doi:10.1016/S0140-6736(78)91816-0.
55. Meyers S, Sachar DB, Goldberg JD et al. Corticotropin versus hydrocortisone in the intravenous treatment of ulcerative colitis. A prospective, randomized, double-blind clinical trial. Gastroenterology 1983;85(2):351–357.
56. Rutgeerts P, Sandborn WJ, Feagan BG et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005;353(23):2462–2476. doi:10.1056/NEJMoa050516.
57. Lichtiger S, Present DH, Kornbluth A et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. N Engl J Med 1994;330(26):1841–1845. doi:10.1056/NEJM199406303302601.
58. Arts J, D'Haens G, Zeegers M et al. Long-term outcome of treatment with intravenous cyclosporin in patients with severe ulcerative colitis. Inflamm Bowel Dis 2004;10(2):73–78. doi:10.1097/00054725-200403000-00002.
59. Carbonnel F, Boruchowicz A, Duclos B et al. Intravenous cyclosporine in attacks of ulcerative colitis: short-term and long-term responses. Dig Dis Sci 1996;41(12):2471–2476. doi:10.1007/BF02100145.
60. Cohen RD, Stein R, Hanauer SB. Intravenous cyclosporin in ulcerative colitis: a five-year experience. Am J Gastroenterol 1999;94(6):1587–1592. doi:10.1111/j.1572-0241.1999.01149.x.
61. Moskovitz DN, Van AG, Maenhout B et al. Incidence of colectomy during long-term follow-up after cyclosporine-induced remission of severe ulcerative colitis. Clin Gastroenterol Hepatol 2006;4(6):760–765. doi:10.1016/j.cgh.2006.04.001.
62. Stack WA, Long RG, Hawkey CJ. Short- and long-term outcome of patients treated with cyclosporin for severe acute ulcerative colitis. Aliment Pharmacol Ther 1998;12(10):973–978. doi:10.1046/j.1365-2036.1998.00396.x.
63. Subramanian V, Pollok RC, Kang JY et al. Systematic review of postoperative complications in patients with inflammatory bowel disease treated with immunomodulators. Br J Surg 2006;93 (7):793–799. doi:10.1002/bjs.5375.
64. Alizadeh K, Hyman N. Venous thromboembolism prophylaxis in colorectal surgery. Surg Technol Int 2005;14:165–170.
65. Stender MT, Nielsen TS, Frokjaer JB et al. High preoperative prevalence of deep venous thrombosis in patients with colorectal cancer. Br J Surg 2007;94(9):1100–1103. doi:10.1002/bjs.5754.
66. Fichera A, Cicchiello LA, Mendelson DS et al. Superior mesenteric vein thrombosis after colectomy for inflammatory bowel disease—a not uncommon cause of postoperative acute abdominal pain. Dis Colon Rectum 2003;46(5):643–648. doi:10.1007/s10350-004-6625-y.
67. Bernstein CN, Blanchard JF, Houston DS et al. The incidence of deep venous thrombosis and pulmonary embolism among patients with inflammatory bowel disease: a population-based cohort study. Thromb Haemost 2001;85(3):430–434.
68. Miehsler W, Reinisch W, Valic E et al. Is inflammatory bowel disease an independent and disease specific risk factor for thromboembolism? Gut 2004;53(4):542–548. doi:10.1136/gut.2003.025411.

69. Geerts WH, Pineo GF, Heit JA et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126 Suppl(3):338S–400S. doi:10.1378/chest.126.3_suppl.338S.
70. van DP, Slors JF, Taat CW et al. Functional outcome after colectomy and ileorectal anastomosis compared with proctocolectomy and ileal pouch-anal anastomosis in familial adenomatous polyposis. Ann Surg 1999;230(5):648–654. doi:10.1097/00000658-199911000-00006.
71. Lubbers EJ. Healing of the perineal wound after proctectomy for nonmalignant conditions. Dis Colon Rectum 1982;25(4):351–357. doi:10.1007/BF02553614.
72. Tompkins RG, Warshaw AL. Improved management of the perineal wound after proctectomy. Ann Surg 1985;202(6):760–765. doi:10.1097/00000658-198512000-00016.
73. Cassilas S, Delaney CP. Laparoscopic surgery for inflammatory bowel disease. Dig Surg 2005;22(3):135–142. doi:10.1159/000087130.
74. Oakley JR, Fazio VW, Jagelman DG et al. Management of the perineal wound after rectal excision for ulcerative colitis. Dis Colon Rectum 1985;28(12):885–888. doi:10.1007/BF02554295.
75. Zeitels JR, Fiddian-Green RG, Dent TL. Intersphincteric proctectomy. Surgery 1984;96(4):617–623.

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ORIGINAL ARTICLE

Abdominal Surgery Impact Scale (ASIS) is Responsive in Assessing Outcome Following IPAA

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Abstract
Purpose Various generic and disease-specific quality of life instruments are available to assess outcome following surgery. However, they may not be sensitive to changes in outcome in the early postoperative period, which is important when assessing changes in surgical technique and perioperative care. The Abdominal Surgery Impact Scale (ASIS) is a validated instrument designed to assess short-term outcome following surgery. Thus, the aims of this study were to assess the impact of surgery on patients undergoing ileal pouch anal anastomosis (IPAA), assess factors which might impact on outcome, and lastly, further evaluate the reliability and internal consistency of the ASIS.
Methods Patients over the age of 18 who had an IPAA between March 2005 and October 2007 completed the ASIS on postoperative day 3 and at the time of discharge. The ASIS contains 18 items within six domains with possible scores ranging from 18 to 126. Demographic, clinical and surgical data, postoperative complications, and length of stay were also recorded. Internal reliability of the ASIS was measured using Cronbach's alpha coefficient.
Results Ninety-two patients (36 female, 56 male, mean age=36.8±10.8) completed the ASIS at two time intervals (mean 3 days and mean 7 days postoperatively). Forty-seven patients had an IPAA performed with an ileostomy; 11 patients had the IPAA performed laparoscopically. The mean hospital stay was 10.8 days. The overall mean ASIS score significantly increased over the two time periods (mean 56.9±18.3 vs. 81.8±17.3, $p<0.001$). Patients who had an ileostomy had a significantly lower mean score at discharge (77.32 vs. 86.82), secondary to lower scores on the physical limitations, functional impairment, and visceral function domains. Seven (7.8%) patients had ileo-anal anastomotic leaks, and seven (7.8%) patients had small bowel obstructions. These patients had an increased length of stay, whereas patients having laparoscopic surgery had a significantly shorter length of stay (8.8 days vs. 11.1 days), but there was no significant difference in mean ASIS scores. Cronbach's alpha coefficient was 0.94 overall and ranged from 0.69 to 0.91 for subscales indicating internal reliability.

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Conclusions ASIS is a valid instrument for measuring quality of life in the postoperative period and is responsive to changes over time. Although quality of life increases postoperatively during hospital stay, at discharge, patients with IPAA still have decreased quality of life. Patients with ileostomies have further decreased scores.

Keywords Quality of life · Restorative proctocolectomy · IPAA · Abdominal surgery impact scale

Introduction

Restorative proctocolectomy or ileal pouch anal anastomosis was first described in 1978.[1] This procedure is a technically challenging operation, and as a result, both the complication and failure rates were high in early reported series.[2,3] However, due to modifications in technique and greater experience with the procedure, both the reported early complication rate and long-term results are now excellent in most patients. As a result, IPAA has become the procedure of choice for most patients requiring surgery for ulcerative colitis and a surgical option for patients with familial polyposis.[4–8] Multiple studies have also documented that quality of life in most patients is also excellent in the long term.[9,10]

On the other hand, little is known about quality of life of patients in the early perioperative period. Assessing changes in patients' health status and quality of life during this period may be important in order to determine the benefit of different surgical techniques and perioperative care as they are introduced and adopted into practice. The Abdominal Surgery Impact Scale was developed by Urbach and colleagues to assess early outcome of patients after abdominal surgery and has been shown to be valid and sensitive to change in this cohort.[11]

Thus, the objectives of this study were to assess the impact of surgery on quality of life of patients undergoing IPAA, to assess factors which might affect quality of life, and finally, to further evaluate the reliability and internal consistency of The Abdominal Surgery Impact Scale (ASIS).

Patients and Methods

Study Population

All patients over the age of 18 who underwent IPAA for ulcerative colitis between March 2005 and October 2007 at the Mount Sinai Hospital were asked to participate in the study. Those patients who signed a consent form were then asked to complete the Abdominal Surgery Impact Scale on postoperative day 2 or 3 and again at the time of discharge. In addition, demographic information, perioperative steroid usage, and whether the patient had had a subtotal colectomy previously were collected. Information regarding surgical technique was collected including whether the procedure was performed open or laparoscopically, whether the ileo-anal anastomosis (IAA) was stapled or hand-sewn, and whether a defunctioning ileostomy was performed. Information regarding postoperative complications was collected. Patients were considered to have an anastomotic leak if they had clinical symptoms plus radiological confirmation. A small bowel obstruction was defined as inability to ingest oral intake and lack of passage of stool or flatus by day 10 as well as abdominal radiographic findings compatible with a small bowel obstruction. Postoperative stay was defined as the number of days in hospital from the time of surgery.

Abdominal Surgery Impact Scale

The ASIS is an instrument specifically designed to measure health-related quality of life after abdominal surgery.[11] The instrument has six domains including physical limitations, functional impairment, pain, visceral function, sleep, and psychological function. Each domain has three items resulting in a total of 18 items (Appendix 1). Each item is scored on a seven-point Likert scale ranging from 1 to 7. The possible total score may range from 18 to 126 with higher scores indicating improved quality of life. The ASIS was previously tested in a Canadian population undergoing abdominal surgery.[11]

Surgical Technique

All patients underwent surgery in two stages. Some patients underwent a first stage subtotal colectomy with end ileostomy followed by a proctectomy, construction of a pouch and ileal pouch-anal anastomosis (IPAA) with no diverting ileostomy. Others underwent a total proctocolectomy, pouch creation, and IPAA with a diverting ileostomy followed by a subsequent closure ileostomy. Only the hospital stay where the IPAA was constructed is considered in this study.

Statistical Analysis

All data were entered into the Mount Sinai Hospital Inflammatory Bowel Disease database. The statistical analysis was performed using Microsoft® Excel and SAS® version 9.1 software (SAS Institute Inc., Cary, NC, USA). Differences in ASIS scores over the two time-points

were examined across levels of patient and surgical characteristics (sex, steroids, anastomosis, ileostomy, anastomatic leak, laparoscopy, and bowel obstruction) using linear mixed models to account for within patient variation. Nonparametric Spearman's correlation was performed to examine the simple association between the ASIS score at two time intervals with length of stay. Each of the six ASIS domains were also assessed with length of stay in this manner. Multivariate regression analysis was performed examining the effect of ASIS scores on length of stay while controlling for gender, age, steroids, hand-sewn versus stapled anastomosis, ileostomy, and laparoscopic versus open procedures. Length of stay was highly skewed; therefore, robust linear regression using Huber's *M* estimation was used to limit the influence of outliers in length of stay during the modeling process.[12,13] Adequacy of the model was verified by normal probability plots. *P* values less than 0.05 were considered statistically significant. Internal reliability of the ASIS was measured using Cronbach's alpha coefficients. This value will increase as the correlation between items increases indicating consistency. In contrast, if items are more heterogeneous, Cronbach's alpha coefficients will be lower. All means are expressed as mean (standard deviation).

Research Ethics

This study was conducted with the approval of the Research Ethics Board at Mount Sinai Hospital.

Results

Ninety-two of a possible 100 patients agreed to participate in the study and completed the ASIS on two occasions. The average age of the participants was 36.8 (SD:10.8) years. There were 56 males and 36 females. Eighteen patients (20%) received perioperative steroid coverage. Forty-five (49%) patients had had a previous subtotal colectomy, whereas for 47 (51%) patients, this was the first procedure. All of the latter patients had a diverting ileostomy. None of the patients who previously had a subtotal colectomy were defunctioned with an ileostomy. A stapled IAA was performed in 85 (92%) patients, whereas seven patients had a hand-sewn IAA. Eleven (12%) patients had the procedure performed laparoscopically (Table 1).

Seven (7.8%) patients developed an anastomotic leak postoperatively. None of these patients required reoperation. Treatment included percutaneous drainage of abscesses, antibiotics, and bowel rest. Another seven (7.8%) patients developed a bowel obstruction postoperatively. None of these patients required reoperation. Other complications included intra-abdominal sepsis, wound infection, dehydration, and portal vein thrombosis. In total, 22 (23.9%) patients had complications. There were no postoperative deaths, and no patient required reoperation during the hospital stay. The mean length of the hospital stay was 10.8 days (SD 5.8; range 6 to 47).

Table 1 Demographic Data and Anastomotic Leaks in the Cohort Population

	Number (*N*) (%)
Overall	92 (100)
Age—mean (SD)	36.8 (10.8)
Male: female	56:46 (62.2/57.8)
Perioperative steroids	18 (18.9)
Stapled anastomosis	85 (93.3)
Ileostomy at time of IPAA	47 (51.1)
Laparoscopic-assisted IPAA	11 (12.2)
IPAA leaks	7 (7.8)
Small bowel obstruction	7 (7.8)

The first ASIS questionnaire was completed on mean day 3 postoperatively (range 1 to 8), and the second questionnaire was completed on mean day 7 (range 3 to 17). The mean score at time 1 was 56.9 (SD 18.3) and increased to 81.8 (SD 17.3) at time 2 ($p<0.001$). As shown in Table 2, the mean score in females (51.7; SD 16.8) was significantly lower than in males (60.3; SD 18.6) at time 1, but at time 2, there was no significant difference (82.6; SD 15.4 vs. 81.6; SD 18.5, respectively). In patients with ileostomies, the initial mean ASIS score was similar to the mean score of those who did not have an ileostomy (55.9; SD 15.7 vs. 58.5; SD 20.8, respectively, $p=0.905$), but the mean score at time 2 was significantly lower in this group (77.3; SD 15.7 vs. 86.8; SD 17.3, $p=0.008$). The lower ASIS scores in patients with ileostomies were secondary to lower physical limitation, functional impairment, and visceral functional subscale scores.

Length of Stay

Patients who had surgery performed laparoscopically had a significantly shorter hospital stay compared to those in whom it was performed open (8.8; SD 2.9 days vs. 11.1; SD 5.8 days, $p=0.050$), whereas the mean length of stay was not significantly different between males and females (11.5; SD 6.8 vs. 9.8; SD 2.3 days, $p=0.0920$). Mean length of stay was longer in patients who had a small bowel obstruction (16.7; SD 13.7 vs. 10.3; SD 4.1 days, $p=0.003$). Patients who had an anastomotic leak had a longer hospital stay, but the difference was not significant (12.6; SD 7.9 vs. 10.6; SD 5.4 days, $p=0.380$). As well, age of the

Table 2 Mean ASIS Scores as a Function of Time and Covariates

		Time 1 ASIS score; mean (SD)	Time 2 ASIS score; mean (SD)	*p* Value for time × covariate interaction[a]
Overall		56.93 (18.30)	81.83 (17.27)	
Sex	Male (*n*=56)	60.29 (18.60)	81.36 (18.52)	0.003
	Female (*n*=36)	51.72 (16.78)	82.56 (15.35)	
Steroids[b]	Yes (*n*=17)	56.24 (14.84)	79.18 (22.09)	0.598
	No (*n*=74)	57.37 (19.07)	82.54 (16.19)	
Anastomosis[b]	Hand-sewn (*n*=6)	61.0 (19.98)	80.00 (18.29)	0.354
	Stapled (*n*=85)	56.88 (18.26)	82.05 (17.39)	
Ileostomy[b]	Yes (*n*=47)	55.92 (15.67)	77.32 (16.93)	0.034
	No (*n*=44)	58.48 (20.83)	86.82 (16.60)	
Anastomotic leak	Yes (*n*=7)	56.14 (17.58)	78.6 (17.69)	0.665
	No (*n*=85)	57.00 (18.46)	82.09 (17.32)	
Laparoscopic vs. open IPAA	Lap (*n*=11)	60.82 (18.61)	87.55 (15.48)	0.680
	Open (*n*=81)	56.41 (18.32)	81.05 (17.45)	
Obstruction	Yes (*n*=7)	64.71 (29.29)	85.29 (23.69)	0.449
	No (*n*=85)	56.29 (17.21)	81.54 (16.79)	

[a] Significance indicates the change in ASIS scores over time varies by level of the covariate examined
[b] Total *n* does not sum to 92 due to missing data (2% or less)

patient, steroid usage, type of anastomosis, ileostomy vs. no ileostomy did not affect hospital length of stay (Table 3). ASIS score at time 1 and time 2 were not associated with length of stay.

Reliability of the ASIS

The reliability coefficient for the overall ASIS scores was 0.940. The reliability coefficients were good for five of six subscales with Cronbach's alpha ranging form 0.761 (pain) to 0.911 (functional impairment). The visceral function subscale had a lower coefficient at 0.691 (Table 4).

Table 3 Mean Length of Stay as a Function of Covariates

		Length of stay; mean (SD)	*p* Value
Overall		10.78 (5.57)	
Sex	Male (*n*=56)	11.45 (6.84)	0.092
	Female (*n*=36)	9.75 (2.32)	
Steroids	Yes (*n*=18)	11.71 (5.31)	0.450
	No (*n*=72)	10.60 (5.68)	
Anastomosis	Hand-sewn (*n*=6)	10.00 (3.10)	0.167
	Stapled (*n*=85)	10.86 (5.74)	
Ileostomy	Yes (*n*=47)	10.32 (4.02)	0.398
	No (*n*=44)	11.32 (6.92)	
Anastomotic leaks	Yes (*n*=7)	12.57 (7.87)	0.380
	No (*n*=85)	10.64 (5.38)	
Laparoscopic vs. open IPAA	Lap (*n*=11)	8.82 (2.89)	0.050
	Open (*n*=81)	11.05 (5.80)	
Bowel obstruction	Yes (*n*=7)	16.71 (13.68)	0.003
	No (*n*=85)	10.29 (4.13)	

Discussion

Over the past 15 to 20 years, there have been a number of changes made to the surgical technique and perioperative care in patients undergoing abdominal surgery aimed at decreasing pain, improving mobilization, and decreasing the time to resolution of ileus postoperatively with an expectation that both patient quality of life and satisfaction may be improved and hospital stay shortened. Some of the most noteworthy are the introduction of laparoscopy, promotion of concepts under the tutelage of "fast track surgery" and improved methods for controlling postoperative pain.

Ileal pouch–anal anastomosis is a complex operation which has undergone a number of modifications over the

Table 4 Reliability Analysis of ASIS Score and Subscale Scores

Subscale	Item	Mean	SD	Cronbach's alpha
Physical limitation		11.98	4.81	0.834
Functional impairment		7.71	3.30	0.909
Pain		11.61	4.32	0.775
Visceral function		11.43	4.28	0.675
Sleep		9.49	3.90	0.849
Psychological function		13.95	4.47	0.880
Overall score		69.60	21.73	0.940

years, so long-term outcome in most patients is good, and it has thus become the procedure of choice for most patients requiring surgery for ulcerative colitis.[14] Quality of life has been defined as the "gap between a person's expectations and achievements," and this definition appropriately describes quality of life as a personal trait that differs among people.[15] Multiple studies have shown that long-term quality of life is excellent in these patients.[9,10,16–19]

On the other hand, there have been no studies that have looked at quality of life or measured patient satisfaction using validated instruments while patients are still in the hospital despite considerable changes in surgical technique. These modifications include stapling rather than hand-sewing the ileo-anal anastomosis, differences in pouch construction, as well as omission of an ileostomy in some or all patients. In addition, the IPAA procedure is being performed laparoscopically in selected patients in some centers. Laparoscopy has been adopted by surgeons because it is less invasive and thus may lead to less postoperative pain, earlier return of gastrointestinal function, as well as improved cosmesis and body image. Although many studies have demonstrated a modest decrease in hospital stay, the advantage of a laparoscopic approach with regard to quality of life in the short term has not been evident[20]. Similarly, it is unknown whether other aspects of the surgical technique might affect patient recovery or quality of life in the early postoperative course, and it is for this reason that we undertook this study. We hypothesized that quality of life would improve over time following surgery and that those having a laparoscopic pouch procedure would have improved quality of life, while those who developed complications would have a worsened quality of life.

In this study, mean ASIS scores improved from 56.9 to 81.8 over the two time periods demonstrating that as patients recover from surgery, their scores improved. However, while the mean scores improved, the mean score still was only 81.8 out of a possible 126 at discharge which is again in keeping with what would be expected given that the average time of discharge was 10 days following surgery. The ASIS questionnaires were not administered beyond discharge since this instrument was specifically developed for assessing quality of life in the immediate postoperative period. However, one would expect that quality of life would continue to improve as has been shown by others. Muir and colleagues assessed preoperative and long-term postoperative quality of life using the Short-Form 36 instrument. They were able to demonstrate improvement in quality of life at 1 month follow-up.[10]

This study did not demonstrate that patients who had laparoscopic IPAA had better mean ASIS scores. In retrospect, the time 2 administration of the ASIS instrument should have been at a fixed date rather than at discharge, as we may have been able to detect differences which were not present at discharge since patients in the laparoscopic group were discharged on average 3 days earlier than those in the open group. This may be one reason that a difference was not detected. However, there was also no significant difference in the mean scores between the open and laparoscopic groups at time 1 (60.8 vs., 56.4), and one might predict that if there were a difference in quality of life, it would have been greater in the earlier postoperative time period. A second possible reason for there being no difference detected is that there were relatively few patients who had surgery performed laparoscopically. However, the difference between the two groups was minimal and likely would not have been significant even with more patients included. A previous study by Dunker et al. compared quality of life in 16 patients who had a laparoscopic-assisted IPAA to 19 patients who had an open IPAA.[21] They noted no difference in overall quality of life using the Short Form 36 Health Survey and the Gastrointestinal Quality of Life Index, although they did detect a difference in the cosmetic result using the Body Image Questionnaire.[21] The COST trial used the self-reported Symptoms Distress Scale and the Quality of Life Index as an assessment of global quality of life. Although the COST trial demonstrated a decrease in length of stay and postoperative analgesic requirements in patients who underwent laparoscopic colectomies, it also failed to detect differences in health-related quality of life between patients undergoing laparoscopic or open colectomy for cancer.[20] Although others have argued that the quality of life instruments used in the COST trial were unresponsive to changes in quality of life,[22] our results also did not demonstrate a significant difference in laparoscopic vs. open groups.

In this study, there was a significant difference between mean ASIS scores at discharge between the cohort with ileostomies compared to those without (55.9 vs. 77.3). The lower mean ASIS score in the ileostomy group was attributable to lower scores in the physical limitation, functional impairment, and visceral function subscales scores. The functional impairment includes questions regarding appearance, self care, leisure activities, and daily activities. It is not surprising that the ileostomy group had lower scores. Muir et al. noted that the greatest improvement in quality of life occurred after closure of the ileostomy.[10] Similarly, Camilleri-Brennan et al. evaluated 19 patients who have IPAA and compared them to age- and sex-matched patients who had had a panproctocolectomy and permanent ileostomy using the Short-Form 36 version 2 questionnaire, the Inflammatory Bowel Disease Questionnaire and specific body image questions.[23] They

demonstrated that although the overall mean quality of life scores were similar in the two groups, patients with permanent ileostomies had poorer body image scores.[23] Another possible reason for the difference in the mean scores in the present study may be due to the fact that it is our policy to perform an ileostomy if we do a colectomy and pouch procedure as a one-stage procedure, whereas if a patient has had a subtotal colectomy and ileostomy previously, then a proctectomy and pouch procedure is performed without a covering ileostomy. Thus, in this study, all patients who had an ileostomy had a colectomy and pouch procedure performed at surgery, whereas all patients in the "no ileostomy" group had only a proctectomy and pouch procedure. Thus, the differences in the mean ASIS scores may have been due, in part, to the extent of the operation rather than due to the ileostomy per se. Furthermore, patients in the "ileostomy group" may have had poorer scores preoperatively than those in the "no ileostomy" group, since this was their first operation for ulcerative colitis. However, this is only a speculation, since the ASIS was not administered preoperatively. Subsequent studies would benefit from preoperative administration of the ASIS.

The mean ASIS score at time 1 was also significantly higher in males than females, but by time 2, there was no significant difference in the mean scores. There is no obvious reason for the difference in the initial mean scores. Previous studies have not shown differences in quality of life between males and females in long-term quality of life studies.[3,16,24]

In this study, 8% of patients developed an anastomotic leak, and another 8% had a small bowel obstruction while in the hospital. Surprisingly in these two subgroups, there was no significant difference in the mean ASIS scores at either time 1 or 2. Both groups had longer hospital stays, and the mean time when the second ASIS questionnaires were completed was 6.4 (6–8) and 9.8 (6–15) days, respectively, compared to mean day 7 for the entire cohort. Thus, again if the ASIS questionnaires had been administered at a fixed time postoperatively, it might have shown differences in the scores, whereas by the time of discharged, the groups had recovered equally so that the mean scores were similar.

This study also showed that the ASIS instrument is responsive to changes in quality of life postoperatively. This confirms the findings of Urbach and colleagues.[11] However, while it was responsive to change over time we were not able to detect significant differences in outcome according to differences in surgical technique or presence of complications. We were also able to confirm that it is feasible to self-administer the ASIS to patients in the early postoperative period. Finally, the reliability of the ASIS and its subscales is high with scores ranging from 0.69 to 0.91.

Appendix 1

Abdominal Surgery Impact Scale (ASIS)

I **cannot** climb a flight of stairs	Strongly agree	Agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Disagree	Strongly disagree
I am **not** able to move easily	Strongly agree	Agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Disagree	Strongly disagree
I am **not** able to stand comfortably for five minutes	Strongly agree	Agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Disagree	Strongly disagree
It is difficult for me to get dressed	Strongly agree	Agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Disagree	Strongly disagree
I am unable to care for myself	Strongly agree	Agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Disagree	Strongly disagree
I feel dependent on others to care for me	Strongly agree	Agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Disagree	Strongly disagree
I am afraid to move because it might cause pain	Strongly agree	Agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Disagree	Strongly disagree
I have severe pain in and around my abdomen	Strongly agree	Agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Disagree	Strongly disagree
My incision(s) is/are causing me pain	Strongly agree	Agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Disagree	Strongly disagree

I am **not** able to move my bowels normally	Strongly agree	Agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Disagree	Strongly disagree
I am uncomfortable because I am thirsty	Strongly agree	Agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Disagree	Strongly disagree
I do **not** have a good appetite	Strongly agree	Agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Disagree	Strongly disagree
I wake up feeling that sleep has not refreshed me	Strongly agree	Agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Disagree	Strongly disagree
I have trouble falling asleep	Strongly agree	Agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Disagree	Strongly disagree
I wake up a lot in the night	Strongly agree	Agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Disagree	Strongly disagree
I have difficulty concentrating on what I am doing (conversation, watching TV, or reading)	Strongly agree	Agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Disagree	Strongly disagree
I feel helpless	Strongly agree	Agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Disagree	Strongly disagree
I feel anxious	Strongly agree	Agree	Somewhat agree	Neither agree nor disagree	Somewhat disagree	Disagree	Strongly disagree

This questionnaire contains a number of statements that describe ways in which your abdominal surgery might have affected you. Please circle the most appropriate number to indicate the degree to which you agree or disagree with each statement. If you are unsure about how to answer a statement, please give the best answer you can. When answering each question, please think about how you have been feeling **over the past day** (24 hours).

References

1. Parks AG, Nicholls RJ. Proctocolectomy without ileostomy for ulcerative colitis. BMJ 1978;2(6130):85–88.
2. Fazio VW, Ziv Y, Church JM, Oakley JR, Lavery IC, Milsom JW, Schroeder TK. Ileal pouch–anal anastomoses complications and function in 1005 patients. Ann Surg 1995;222(2):120–127. doi:10.1097/00000658-199508000-00003.
3. Meagher AP, Farouk R, Dozois RR, Kelly KA, Pemberton JH. J ileal pouch–anal anastomosis for chronic ulcerative colitis: complications and long-term outcome in 1310 patients. Br J Surg 1998;85(6):800–803. doi:10.1046/j.1365-2168.1998.00689.x.
4. McMullen K, Hicks T, Ray J, Gathright JB, Timmcke AE. Complications associated with ileal pouch–anal anastomosis. World J Surg 1991;15:763–766. doi:10.1007/BF01665312.
5. Oresland T, Fasth S, Nordgren S, Hulten L. The clinical and functional outcome after restorative proctocolectomy. A prospective study in 100 patients. Int J Colorectal Dis 1989;4(1):50–56.
6. Pemberton JH, Kelly KA, Beart RW Jr, Dozois RR, Wolff BG, Ilstrup DM. Ileal pouch–anal anastomosis for chronic ulcerative colitis. Long-term results. Ann Surg 1987;206(4):504–513. doi:10.1097/00000658-198710000-00011.
7. Poppen B, Svenberg T, Bark T, Sjogren B, Rubio C, Drakenberg B, Slezak P. Colectomy–proctomucosectomy with S-pouch: operative procedures, complications, and functional outcome in 69 consecutive patients. Dis Colon Rectum 1992;35:40–47. doi:10.1007/BF02053337.
8. Skarsgard ED, Atkinson KG, Bell GA, Pezim ME, Seal AM, Sharp FR. Function and quality of life results after ileal pouch surgery for chronic ulcerative colitis and familial polyposis. Am J Surg 1989;157:467–471. doi:10.1016/0002-9610(89)90636-3.
9. Delaney CP, Fazio VW, Remzi FH, Hammel J, Church JM, Hull TL, Senagore AJ, Strong SA, Lavery IC. Prospective, age-related analysis of surgical results, functional outcome, and quality of life after ileal pouch–anal anastomosis. Ann Surg 2003;238(2):221–228.
10. Muir AJ, Edwards LJ, Sanders LL, Bollinger RR, Koruda MJ, Bachwich DR, Provenzale D. A prospective evaluation of health-related quality of life after ileal pouch anal anastomosis for ulcerative colitis. Am J Gastroenterol 2001;96(5):1480–1485. doi:10.1111/j.1572-0241.2001.03801.x.
11. Urbach DR, Harnish JL, McIlroy JH, Streiner DL. A measure of quality of life after abdominal surgery. Qual Life Res 2006;15(6):1053–1061. doi:10.1007/s11136-006-0047-3.
12. Huber PJ. Robust regression: asymptotics, conjectures and Monte Carlo. Ann Stat 1973;1(5):1799–1821.
13. Lee AH, Gracey M, Wang K, Yau KK. A robustified modeling approach to analyze pediatric length of stay. Ann Epidemiol 2005;15(9):673–677. doi:10.1016/j.annepidem.2004.10.001.
14. Becker JM. Surgical therapy for ulcerative colitis and Crohn's disease. Gastroenterol Clin North Am 1999;28(2):371–90. viii–ix doi:10.1016/S0889-8553(05)70061-3.
15. Calman KC. Quality of life in cancer patients—a hypothesis. J Med Ethics. 1984;10(3):124–127. doi:10.1136/jme.10.3.124.
16. Berndtsson I, Lindholm E, Oresland T, Borjesson L. Long-term outcome after ileal pouch–anal anastomosis: function and health-related quality of life. Dis Colon Rectum 2007;50(10):1545–1552. doi:10.1007/s10350-007-0278-6.
17. Berndtsson I, Oresland T. Quality of life before and after proctocolectomy and IPAA in patients with ulcerative proctocolitis—a prospective study. Colorectal Dis. 2003;5(2):173–179. doi:10.1046/j.1463-1318.2003.00455.x.

18. Thirlby RC, Sobrino MA, Randall JB. The long-term benefit of surgery on health-related quality of life in patients with inflammatory bowel disease. Arch Surg. 2001;136(5):521–527. doi:10.1001/archsurg.136.5.521.
19. Tiainen J, Matikainen M. Health-related quality of life after ileal J-pouch–anal anastomosis for ulcerative colitis: long-term results. Scand J Gastroenterol. 1999;34(6):601–605. doi:10.1080/003655299750026065.
20. Weeks JC, Nelson H, Gelber S, Sargent D, Schroeder G. Short-term quality-of-life outcomes following laparoscopic-assisted colectomy vs open colectomy for colon cancer: a randomized trial. JAMA 2002;287(3):321–328. doi:10.1001/jama.287.3.321.
21. Dunker MS, Bemelman WA, Slors JF, van Duijvendijk P, Gouma DJ. Functional outcome, quality of life, body image, and cosmesis in patients after laparoscopic-assisted and conventional restorative proctocolectomy: a comparative study. Dis Colon Rectum 2001;44(12):1800–18007. doi:10.1007/BF02234458.
22. Urbach DR. Laparoscopic-assisted surgery for colon cancer. JAMA 2002;287(15):1938. author reply 1939 doi:10.1001/jama.287.15.1938.
23. Camilleri-Brennan J, Munro A, Steele RJ. Does an ileoanal pouch offer a better quality of life than a permanent ileostomy for patients with ulcerative colitis? J Gastrointest Surg 2003;7(6):814–819. doi:10.1016/S1091-255X(03)00103-3.
24. Farouk R, Pemberton JH, Wolff BG, Dozois RR, Browning S, Larson D. Functional outcomes after ileal pouch-anal anastomosis for chronic ulcerative colitis. Ann Surg 2000;231(6):919–926. doi:10.1097/00000658-200006000-00017.

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ORIGINAL ARTICLE

Hepatectomy for Hepatocellular Carcinoma in Elderly Patients Aged 75 Years or More

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Abstract
Background The aim of this study was to clarify the characteristics of elderly hepatocellular carcinoma (HCC) patients aged 75 years or more who underwent hepatectomy and to clarify whether elderly patients with HCC benefit from hepatectomy.
Methods Between January 1990 and December 2006, 570 patients underwent curative hepatectomy for HCC. Elderly patients were defined as those aged 75 years or more. Clinicopathological data and outcomes after hepatectomy for 64 elderly and 502 younger patients were prospectively collected and compared.
Results The proportion of elderly patients with chronic viral infection was less than that of younger patients ($p<0.001$). Cirrhotic patients in the elderly group were less than those in the younger group ($p=0.03$). The elderly patients had better liver function than did the younger patients ($p=0.007$) but had more advanced HCC with microscopic vascular invasion than did the younger patients ($p=0.04$). There was no operative mortality in the elderly patients and there was no significant difference in postoperative complication rates and long-term survival after hepatectomy between the two groups.
Conclusions Hepatectomy for elderly patients with resectable HCC is safe and feasible. Selected elderly patients with HCC might benefit from hepatectomy.

Keywords Hepatocellular carcinoma · Hepatectomy · Elderly

Introduction

The average life expectancy at birth has been increasing in many countries. Japan had the highest life expectancy worldwide in 2006. The average life expectancy in Japan is the longest in the world, life expectancy at birth for males being 79 years and that for females being 86 years.[1] The number of patients with hepatocellular carcinoma (HCC) has been increasing,[2] and elderly HCC patients have been getting older.[3] With the increase in average lifetime, the age at which a person is considered elderly is rising. Clarification of the optimal treatment strategy for extremely elderly patients with HCC has thus become an urgent necessity. With advances in surgical treatment for HCC, hepatectomy for elderly HCC patients has become safer. There have been many reports on hepatectomies for elderly HCC patients.[4–11] However, most studies were for patients aged 70 years or more. There have been few reports on the safety and feasibility of hepatectomy for HCC patients aged 75 years or more and whether HCC patients aged 75 years or more benefit from hepatectomy. The aim of this study was to identify the characteristics of elderly HCC patients aged 75 years or more who underwent hepatectomy in comparison with those of younger HCC patients and to clarify whether HCC patients aged 75 years or more benefit from hepatectomy.

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Methods

Patients' data were collected prospectively from 1986 in our program. Between January 1990 and December 2006, 570 consecutive HCC patients underwent curative hepatectomy in Hiroshima University Hospital. Curative hepatectomy was defined as the removal of all recognizable tumors. Data for four patients whose outcomes during the follow-up period were uncertain were excluded from the analysis. Data for the remaining 566 HCC patients were included in the analysis.

The patients included 429 men (76%) and 137 women (24%). The mean age at operation was 63.5 years (range, 23 to 86 years). In this study, elderly patients were defined as those aged 75 years or more. Sixty-four patients were in the elderly group and 502 patients were younger than 75 years of age (younger group). The mean age of patients in the elderly group was 77.5±2.4 years (range, 75 to 86 years) and that of the younger patients was 61.7±8.7 years (range, 23 to 74 years).

Only elderly patients whose general condition fulfilled the American Society of Anesthesiologists' Physical Status Score class I or class II were considered for hepatectomy.[12] The indication and procedure for hepatectomy were the same as those described previously.[13,14] Briefly, Child–Pugh class C was regarded as contraindication for hepatectomy. The selection of type of hepatectomy was made on the basis of liver function and tumor extent. Liver function was assessed by Child–Pugh classification and the indocyanine green retention rate at 15 min (ICGR15). In patients without ascites and with a normal bilirubin level, ICGR15 became the main determinant of resectability. For example, right hemihepatectomy could be tolerated if ICGR15 was in the normal range. One third of the liver parenchyma could be resected for patients with ICGR15 of 10% to 19%, segmentectomy was possible with ICGR15 of 20% to 29%, and limited resection was possible with ICGR15 of 30% or more.[15] Hepatectomy was indicated when it was judged by preoperative imaging studies that all tumors could be resected with sufficient hepatic functional reserve. However, when the HCC tumors were hypovascular, suggesting that the tumors were well-differentiated HCC, and were 2 cm or less in size and the number of tumors was three or less, percutaneous ablation therapies were preferable despite hepatectomy also being feasible, depending on the tumor location in the liver, irrespective of the patient's age.[16] There was no difference between the indication for hepatectomy for younger patients and that for hepatectomy for elderly patients throughout the period of the present study. Resections of two segments or more according to Couinaud's segmentation were defined as major hepatectomy. For patients undergoing multiple resections, the most important procedure was considered to be the main type of hepatectomy. There is a tendency to select limited resection in cases of severe cirrhosis or tumors located on the surface of the liver.

Clinicopathological findings were recorded according to the criteria of the Liver Cancer Study Group in Japan.[17] Liver cirrhosis was confirmed by histological examination of a resected specimen. A modification of the Clavien classification was used to grade the severity of postoperative complications.[18] Grade I complications were defined as deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. This grade also includes wound infections opened at the bedside. Grade II complications were defined as those requiring pharmacological treatments with drugs. Blood transfusions and total parenteral nutrition are also included. Grade III complications were defined as those requiring surgical, endoscopic, or radiological intervention. Grade IV complications were life-threatening complications requiring intermediate care/intensive care unit management. Grade V complications were those that resulted in death of a patient. Operative mortality was defined as death within 30 days after surgery. In-hospital mortality was defined as death occurring within the period of hospitalization.

Follow-up evaluation after the operation consisted of clinical physical examinations, blood chemistry tests, and measurements of levels of tumor markers, including alpha-fetoprotein and des-gamma-carboxy prothrombin, every month for 2 years. After 2 years, the patients were assessed every 3 months. Patients were examined by abdominal ultrasonography every 3 months and by computed tomography every 6 months during the follow-up periods. Our follow-up protocol included evaluation by hepatologists of not only cancer recurrence but also progress of chronic hepatitis or liver cirrhosis. When recurrence was indicated by any of these examinations, patients underwent hepatic angiography (Fig. 1). The patients were regularly followed up until June 30, 2007 and every patient was followed up for at least 6 months.

Statistical analyses were performed using the unpaired Student's *t* test and the chi-square test with Fisher's exact

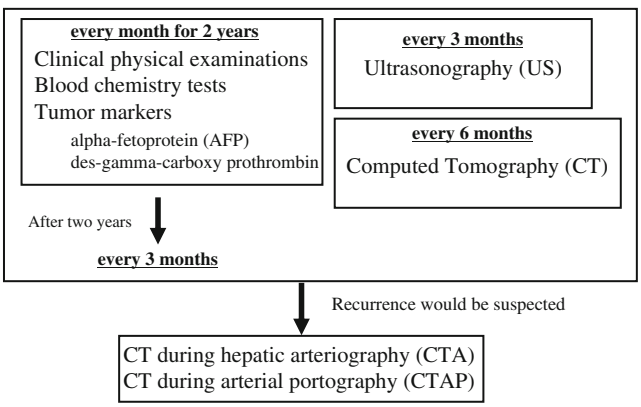

Figure 1 Follow-up evaluation after hepatectomy for hepatocellular carcinoma patients by surgeons and/or hepatologists.

test. Survival and disease-free survival rates were calculated using the Kaplan–Meier method and compared using the log-rank test. Disease-free survival was calculated by considering any death or recurrence as an event. A p value of less than 0.05 was considered to be statistically significant. Statistical analysis was carried out using the software of StatView for Windows (Version 5.0; SAS Institute, Cary, NC, USA).

Results

The mean follow-up period for all survivors was 4.4± 3.4 years (range, 0.5 to 17.0 years). Operative mortality and in-hospital mortality rates in all patients were 0.4% (n=2) and 0.7% (n=4), respectively. Characteristics of patients in the two groups are shown in Table 1. One (2%) of the 64 patients in the elderly group had positive hepatitis B surface antigen (HBsAg), whereas 119 (24%) of the 502 patients in the younger group had positive HBsAg (p<0.001). The numbers of patients without either hepatitis B virus (HBV) or hepatitis C virus (HCV) infections in the elderly group and the younger group were 17 (27%) and 51 (10%), respectively (p<0.001). The incidence of cirrhosis in the elderly group was 31%, whereas that in the younger group was 52% (p=0.03). Preoperative laboratory tests showed that the elderly group had better liver function than did the younger group as assessed by prothrombin time (PT) (p=0.007), aspartate aminotransferase (AST) (p=0.02), and alanine aminotransferase (ALT) (p<0.001).

Tumor characteristics and intra- or postoperative results in both groups are shown in Table 2. Tumors in the elderly group tended to be larger than those in the younger group (p=0.057). The incidence of microscopic vascular invasion in the elderly group was significantly higher than that in the younger group (p=0.04). Major hepatectomies were performed more frequently in the elderly group than in the younger group (p=0.008). Blood loss during the operation, perioperative blood transfusion rate, operative mortality rate, in-hospital mortality rate, and postoperative complication rate were not significantly different between the two groups. The incidences of complications that occurred after hepatectomy according to grade were comparable. The 14 complications that occurred in the elderly group were categorized as grade I in seven patients, grade II in four patients, grade III in one patient, and grade IV in two patients.

Overall survival rates after hepatectomy in the elderly group at 3, 5, and 10 years were 77%, 58%, and 32%, respectively, whereas those in the younger group were 81%, 64%, and 33%, respectively (Fig. 2). Disease-free survival rates in the elderly group at 3, 5, and 10 years were 43%, 30%, and 0%, respectively, whereas those in the younger group were 46%, 28%, and 14%, respectively (Fig. 3). There were no significant differences between the two groups in overall survival rates and disease-free survival rates.

The patterns of cancer recurrence and the details of treatments for the recurrences in both groups are shown in Table 3. Thirty-three (49%) of the patients in the elderly group and 304 (61%) of the patients in younger group had HCC recurrences after hepatectomy. The patterns of

Table 1 Backgrounds in Both Groups

Characteristics	Group		p value
	Younger (n=502)	Elderly (n=64)	
Age at operation (years)	61.7±8.7	77.5±2.4	<0.001
Sex: male (%)	381 (76)	48 (75)	N.S.
HBsAg: positive (%)	119 (24)	1 (2)	<0.001
Anti-HCVAb: positive (%)	330 (66)	45 (70)	N.S.
Non-B and non-C (%)[a]	51 (10)	17 (27)	<0.001
Liver cirrhosis (%)	261 (52)	20 (31)	0.03
Child–Pugh grade A (%)	427 (85)	59 (92)	N.S.
Platelet count (/μL)	13.7±13.5	13.7±6.1	N.S.
Prothrombin time (%)	85±20	93±19	0.007
Total bilirubin (mg/dL)	0.8±0.3	0.8±0.3	N.S.
Aspartate aminotransferase (IU/L)	50±28	41±18	0.02
Alanine aminotransferase (IU/L)	52±33	39±22	<0.001
Serum albumin (g/dL)	3.8±0.5	3.7±0.5	N.S.
ICG-R15 (%)	17.7±9.6	18.7±10.8	N.S.
Serum AFP (ng/mL) >400 (%)	94 (19)	15 (23)	N.S.

Data are expressed as the means±standard deviations or as the number of patients (percentage of total patients)
HBsAg hepatitis B surface antigen, *Anti-HCVAb* anti-HCV antibody, *AFP* alpha-fetoprotein, *ICGR15* indocyanine green retention rate at 15 min, *N.S.* not significant
[a] Patients negative for HBsAg and anti-HCVAb

Table 2 Tumor Characteristics and Intra- or Postoperative Results in Both Groups

Tumor characteristics and results	Group		*p* value
	Younger (*n*=502)	Elderly (*n*=64)	
Mean tumor size (cm)[a]	3.3±2.2	3.9±2.3	0.057
Number of tumors: multiple (%)	155 (31)	12 (19)	N.S.
Tumor stage: I, II/III, IV	370/132	48/16	N.S.
Tumor differentiation: mod. or por. (%)	398 (85)	54 (89)	N.S.
Capsule formation: positive (%)	403 (81)	54 (84)	N.S.
Microscopic vascular invasion: positive (%)	145 (29)	27 (42)	0.04
Operative procedure: major hepatectomy (%)	79 (15)	19 (30)	0.008
Blood loss (mL)[a]	430±438	356±381	N.S.
Blood transfusion: yes (%)	27 (5)	5 (8)	N.S.
Operative mortality: yes (%)	2 (0.4)	0 (0)	N.S.
Hospital mortality: yes (%)	5 (1)	1 (2)	N.S.
Postoperative complications[b]: yes (%)	97 (19)	14 (22)	N.S.
Grade I	35 (7)	7 (11)	N.S.
Grade II	36 (7)	4 (6)	
Grade III	16 (3)	1 (2)	
Grade IV	8 (2)	2 (3)	
Grade V	2 (0.3)	0 (0)	

N.S. not significant, *mod.* moderately differentiated, *por.* poorly differentiated
[a] Values are presented as the means±standard deviations
[b] Postoperative complication was defined as any event satisfying the criteria advocated by Dindo et al.[17]

recurrence, the proportions of patients who could receive treatment for recurrence, and the modalities of treatments used were not different in the two groups.

The causes of death in both groups are shown in Table 4. There was no significant difference in the distribution of causes of death between the two groups. Deaths unrelated to cirrhosis or HCC in the elderly group included death from cardiovascular disease in five patients and death from malignant diseases other than HCC in two patients.

Discussion

The present study showed a difference in etiology of HCC in elderly patients and that in younger patients. The positive rate for HBsAg was significantly lower in the elderly group. The proportion of patients negative for HBsAg and anti-HCV antibody was clearly larger in the elderly group. These findings agree with the results of previous studies.[19–21] HBV-related chronic liver disease results from a vertical transmission during the perinatal period or a horizontal

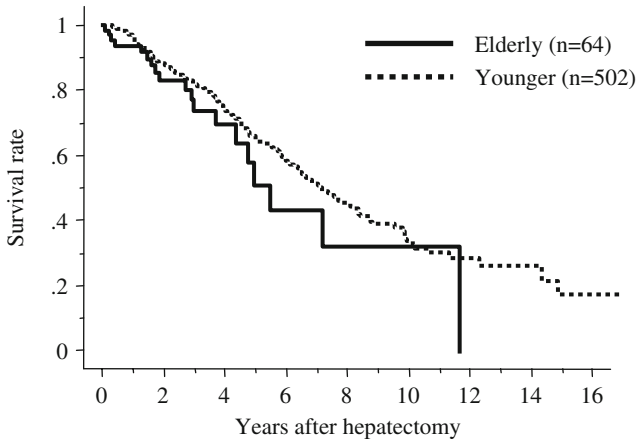

Figure 2 Survival rates after hepatectomy in elderly patients and younger patients. Data for the elderly patients (*n*=64) are shown by a *thick line* and data for the younger patients (*n*=502) are shown by a *dotted line*. There was no significant difference between the two groups in survival rate.

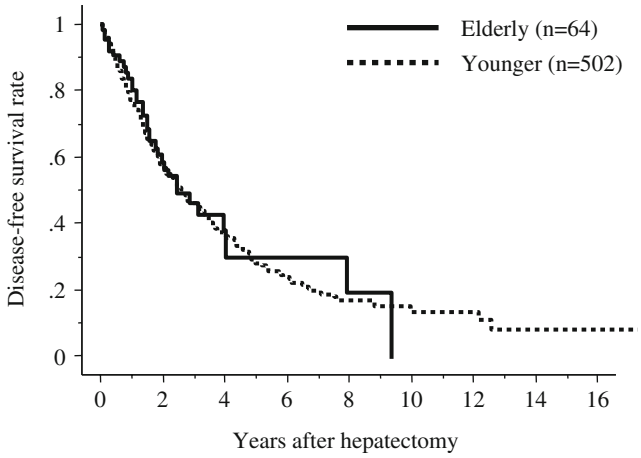

Figure 3 Disease-free survival rates after hepatectomy in elderly patients and younger patients. Data for the elderly patients (*n*=64) are shown by a *thick line* and data for the younger patients (*n*=502) are shown by a *dotted line*. There was no significant difference between the two groups in disease-free survival rate.

Table 3 Cancer Recurrence After Hepatectomy and Treatments for Recurrent HCC

		Younger (n=502)	Elderly (n=64)	p value
Cancer recurrence[a]: yes		304 (61)	33 (49)	N.S
Pattern of recurrence[b]	Remnant liver	256 (84)	25 (76)	N.S.
	Distant organ	12 (4)	4 (12)	
	Remnant liver+distant organ	36 (12)	4 (12)	
Treatments for recurrence[b]: yes		257 (85)	25 (76)	N.S.
Main treatment for recurrence[b]	Repeat hepatectomy	77 (30)	4 (16)	N.S.
	Liver transplantation	9 (4)	0	
	PAT	85 (33)	12 (48)	
	TACE	72 (28)	9 (36)	
	Others	14 (5)	0	

N.S. not significant, *PAT* percutaneous ablation therapy, *TACE* transarterial chemoembolization
[a] Data are expressed as the number of patients (percentage of total patients)
[b] Data are expressed as the number of patients (percentage of patients who had a recurrence)

transmission during early childhood in most patients.[22] Hepatitis B vaccination was started in 1986 in Japan. Although the numbers of HBV-infected newborns and infants have decreased dramatically since then, no adult population has yet benefited from hepatitis B vaccination. Most HBV-related HCCs develop in patients in their early fifties. This might be the reason why there are few elderly HCC patients with HBV infection. Factors other than hepatitis virus infection such as alcohol or genetic disturbance may contribute to the development of HCC in some elderly patients.

Although there was no difference in the distribution of Child–Pugh grades between the two groups, elderly patients showed higher values of prothrombin activity, indicating that liver function was better preserved. Elderly patients also showed lower levels of AST and ALT, indicating that inflammation of the liver was less active. Furthermore, HCC was less frequently associated with cirrhosis in the elderly patients than in the younger patients. Several studies have shown that elderly patients with HCC had good liver function and that only a small percentage of elderly patients with HCC had liver cirrhosis.[19,23] It is possible that a large proportion of patients with cirrhosis and HCC die before reaching the age of 70 years that those who survive have well-preserved hepatic function.[20] Although indications for hepatectomy in the elderly patients were similar to those in the younger patients in our program according not only to tumor stage but also to hepatic functional reserve, there might have been a bias for selecting patients with good liver function when elderly patients were referred to our surgical department.

HCC tumors in the elderly group tended to be larger than those in the younger group. Moreover, microscopic vascular invasion occurred more frequently in the elderly group than in the younger group. Approximately 30% of the patients in the elderly group in the present study had neither HBV nor HCV infection, and these patients had not received regular examination as high-risk patients for HCC. Therefore, HCC could not be detected in some elderly patients at an early stage.

Elderly HCC patients who underwent hepatectomy had a comorbid illness more often than did younger patients and were considered to be a high-risk group for hepatectomy.[4,24] However, recent studies have shown the safety and feasibility of hepatectomy for HCC patients older than 70 years of age.[8–10] The present study showed the same good results even for patients aged 75 years or more. There was no operative death and few serious postoperative complications even in patients who underwent major hepatectomy. The incidence of deaths unrelated to cirrhosis or HCC during the follow-up periods was equal to that in the younger group. These results might indicate that preoperative evaluations for the elderly with comorbid illness and patient selection were adequate in our program. Therefore, selected elderly patients have no disadvantage for receiving even major hepatectomy with regard to tolerance to hepatectomy.

The present study for the elderly (75 years of age or more) revealed that the overall 5-year survival rate and 5-year disease-free survival rate were 58% and 30%,

Table 4 Causes of Death in Both Groups

	Group	
	Younger (n=235)	Elderly (n=26)
Cancer death (%)	148 (63)	16 (62)
Liver failure or rupture of EV (%)	42 (18)	3 (12)
Death unrelated to liver cirrhosis or HCC (%)	39 (17)	7 (27)
Unknown causes (%)	4 (2)	0
Operative mortality (%)	2 (1)	0

EV esophageal varices, *HCC* hepatocellular carcinoma

respectively, similar to the results of recent studies for elderly HCC patients (70 years of age or more). The prognosis of elderly HCC patients after hepatectomy was equal to that of younger HCC patients despite the fact that the elderly patients had more advanced HCC than did the younger patients and required major hepatectomy more frequently than did the younger patients. These disadvantages of the elderly group for prognosis after hepatectomy might be diminished by the better hepatic function of this group. In Japan, 75-year-old males and females have average life expectancies of 11.3 years and 15.0 years, respectively.[25] Selected elderly patients aged 75 years or more might benefit from hepatectomy by avoiding early death from HCC.

Recently, radiofrequency ablation (RFA) has been developed as a new alternative therapy for early-stage HCCs. Not only younger patients but also elderly patients with early-stage HCC might benefit from this modality, which is less invasive than hepatectomy. Our policy for the treatment of early-stage HCC has been that, when the HCC tumors were 2 cm or less in size and the number of tumors was three or less, percutaneous ablation therapies were indicative despite hepatectomy also being feasible, depending on the tumor location in the liver, irrespective of the patient's age. However, not only long-term outcomes of RFA for elderly patients with HCCs but also the safety and feasibility of RFA for the elderly remain unclear and should be confirmed by a prospective study.

Conclusion

HCC patients aged 75 years or more who underwent hepatectomy had better liver function but had more advanced tumors than did the younger HCC patients. However, hepatectomy for HCC patients with preserved liver function was feasible and safe, and the prognosis after hepatectomy for the elderly patients was comparable to that for the younger patients. Selected elderly patients with HCC might benefit from hepatectomy.

Conflict of interest None.

References

1. McCurry J. Japan moves to guard against future health-spending rises. Lancet 2006;367:1385–1386. doi:10.1016/S0140-6736(06)68596-6.
2. El-Serag HB. Hepatocellular carcinoma: recent trends in the United States. Gastroenterology 2004;127:S27–S34. doi:10.1053/j.gastro.2004.09.013.
3. Kiyosawa K, Umemura T, Ichijo T, Matsumoto A, Yoshizawa K, Gad A, Tanaka E. Hepatocellular carcinoma: recent trends in Japan. Gastroenterology 2004;127:S17–S26. doi:10.1053/j.gastro.2004.09.012.
4. Nagasue N, Chang YC, Takemoto Y, Taniura H, Kohno H, Nakamura T. Liver resection in the aged (seventy years or older) with hepatocellular carcinoma. Surgery 1993;113:148–154.
5. Nomura F, Ohnishi K, Honda M, Satomura Y, Nakai T, Okuda K. Clinical features of hepatocellular carcinoma in the elderly: a study of 91 patients older than 70 years. Br J Cancer 1994;70:690–693.
6. Takenaka K, Shimada M, Higashi H, Adachi E, Nishizaki T, Yanaga K, Matsumata T, Ikeda T, Sugimachi K. Liver resection for hepatocellular carcinoma in the elderly. Arch Surg 1994;129:846–850.
7. Lui WY, Chau GY, Wu CW, King KL. Surgical resection of hepatocellular carcinoma in elderly cirrhotic patients. Hepatogastroenterology 1999;46:640–645.
8. Hanazaki K, Kajikawa S, Shimozawa N, Shimada K, Hiraguri M, Koide N, Adachi W, Amano J. Hepatic resection for hepatocellular carcinoma in the elderly. J Am Coll Surg 2001;192:38–46. doi:10.1016/S1072-7515(00)00778-X.
9. Yeh CN, Lee WC, Jeng LB, Chen MF. Hepatic resection for hepatocellular carcinoma in elderly patients. Hepatogastroenterology 2004;51:219–223.
10. Ferrero A, Vigano L, Polastri R, Ribero D, Lo Tesoriere R, Muratore A, Capussotti L. Hepatectomy as treatment of choice for hepatocellular carcinoma in elderly cirrhotic patients. World J Surg 2005;29:1101–1105. doi:10.1007/s00268-005-7768-2.
11. Wu CC, Chen JT, Ho WL, Yeh DC, Tang JS, Liu TJ, P'Eng FK. Liver resection for hepatocellular carcinoma in octogenarians. Surgery 1999;125:332–338.
12. Dripps RD, Lamont A, Eckenhoff JE. The role of anesthesia in surgical mortality. JAMA 1961;178:261–266.
13. Itamoto T, Nakahara H, Tashiro H, Ohdan H, Hino H, Ochi M, Asahara T. Indications of partial hepatectomy for transplantable hepatocellular carcinoma with compensated cirrhosis. Am J Surg 2005;189:167–172. doi:10.1016/j.amjsurg.2004.11.001.
14. Nakahara H, Itamoto T, Katayama K, Ohdan H, Hino H, Ochi M, Tashiro H, Asahara T. Indication of hepatectomy for cirrhotic patients with hepatocellular carcinoma classified as Child–Pugh class B. World J Surg 2005;29:734–738. doi:10.1007/s00268-005-7750-z.
15. Makuuchi M, Kosuge T, Takayama T, Yamazaki S, Kakazu T, Miyagawa S, Kawasaki S. Surgery for small liver cancers. Semin Surg Oncol 1993;9:298–304. doi:10.1002/ssu.2980090404.
16. Itamoto T, Katayama K, Fukuda S, Fukuda T, Yano M, Nakahara H, Okamoto Y, Sugino K, Marubayashi S, Asahara T. Percutaneous microwave coagulation therapy for primary or recurrent hepatocellular carcinoma: long-term results. Hepatogastroenterology 2001;48:1401–1405.
17. Liver Cancer Study Group of Japan. General rules for the clinical and pathological study of primary liver cancer. Tokyo: Kanehara, 2003.
18. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–213. doi:10.1097/01.sla.0000133083.54934.ae.
19. Tsukioka G, Kakizaki S, Sohara N, Sato K, Takagi H, Arai H, Abe T, Toyoda M, Katakai K, Kojima A, Yamazaki Y, Otsuka T, Matsuzaki Y, Makita F, Kanda D, Horiuchi K, Hamada T, Kaneko M, Suzuki H, Mori M. Hepatocellular carcinoma in extremely elderly patients: an analysis of clinical characteristics, prognosis and patient survival. World J Gastroenterol 2006;12:48–53.
20. Namieno T, Kawata A, Sato N, Kondo Y, Uchino J. Age-related, different clinicopathologic features of hepatocellular carcinoma patients. Ann Surg 1995;221:308–314. doi:10.1097/00000658-199503000-00014.
21. Dohmen K, Shigematsu H, Irie K, Ishibashi H. Comparison of the clinical characteristics among hepatocellular carcinoma of hepatitis B, hepatitis C and non-B non-C patients. Hepatogastroenterology 2003;50:2022–2027.

22. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. J Viral Hepat 2004;11:97–107. doi:10.1046/j.1365-2893.2003.00487.x.
23. Nakamuta M, Morizono S, Kohjima M, Kotoh K, Enjoji M. Baseline characterization of patients aged 70 years and above with hepatocellular carcinoma. World J Gastroenterol 2005;11:7512–7514.
24. Ezaki T, Yukaya H, Ogawa Y. Evaluation of hepatic resection for hepatocellular carcinoma in the elderly. Br J Surg 1987;74:471–473. doi:10.1002/bjs.1800740614.
25. Ministry of Health. Labour and Welfare. Abridged life tables for Japan 2006. http://www.mhlw.go.jp/english/database/db-hw/lifetb06/index.html (2006).

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ORIGINAL ARTICLE

Feasibility and Effectiveness of a New Algorithm in Preventing Hepatic Artery Thrombosis after Liver Transplantation

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Abstract
Introduction The incidence of hepatic artery thrombosis (HAT) after liver transplantation (LTx) is up to 9% in adult recipients.
Material and Methods To minimize HAT, we developed an algorithm that we have routinely applied since 2001. The algorithm is a cascade of potentially necessary procedures to improve hepatic artery blood flow before proceeding with LTx when arterial blood flow is impaired. Incidence, outcome, and possible therapeutic approaches of HAT were analyzed in prospectively non-controlled collected data during a 5-year period. There were 335 LTx in 299 adults (199 male, 100 female) with a median age of 49.7 years.
Results HAT was defined as early and late HAT (diagnosis within or after 30 days following LTx). After a mean follow-up of 17 months, nine HAT were documented (2.7%; five early and four late HAT). Treatment consisted of thrombolysis (n=1), surgical thrombectomy (n=4), and re-transplantation (n=4). Five HAT patients died during follow-up.
Discussion Complex arterial reconstruction was associated with HAT compared to branch-patch anastomoses (P=0.0193). Median arterial intraoperative blood flow was no risk factor for HAT. One-year patient survival after HAT was 31%. Once HAT occurs, complication rates are high and long-term results are devastating.
Conclusion Therefore, we have implemented the presented algorithm, which showed an acceptable HAT rate.

Keywords Arterial complication · Algorithm · Liver transplantation · Hepatic artery thrombosis

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Introduction

Liver transplantation (LTx) is considered to be the treatment of choice for patients with end-stage liver disease, acute irreversible liver failure, and hepatic malignancies in selected cases.[1,2] Improvements in surgical techniques, anesthetic protocols, medical management, and the introduction of new immunosuppressive regimens have increased patient survival after LTx, resulting in 1-year survival rates of more than 80%.[3,4] A number of studies have reported that vascular complications are a major source of morbidity and mortality.[5–7] The most common vascular complication after liver transplantation is hepatic artery thrombosis (HAT), which can lead to allograft loss and patient death. The incidence of HAT following liver transplantation varies widely, with a reported frequency of 2.5–9% in adult recipients and 9–15% in the pediatric population.[6–12] Significantly more patients die when HAT

develops in the early post-transplant period, and up to 50% of affected patients die without re-transplantation.[8] Early diagnosis and prompt revascularization, or re-transplantation has been considered to be the only chance to rescue patients with HAT.[6,13] However, re-transplantation is limited by both organ availability and the patient's condition. Urgent revascularization with thrombectomy or a combination of thrombectomy and revision of the anastomosis has been successful in some patients with early detected HAT.[14,15] HAT is most commonly diagnosed within 1 month after LTx. Therefore, the occurrence of HAT is generally divided into early (<30 days post-transplant) and late (>30 days post-transplant).[16] Previous studies showed that routine measurement of blood flow during LTx can be helpful, as flow determinations can alert the surgeon to an unrecognized intraoperative HAT or to an abnormally low flow, which can prompt immediate corrective measures.[17] Different authors described an association between intraoperative low hepatic artery blood flow (<400 mL/min) and an increased incidence of HAT.[18,19]

From 1996 to 2001, an incidence of HAT of 6.8% was observed at our institution. After reviewing the literature for HAT, all liver transplant surgeons designed and have strictly followed the algorithm since 2001 to minimize its incidence and to guarantee surgical standardization (Fig. 1). The aim of this prospective study was to assess feasibility and effectiveness of the presented algorithm in reducing HAT rate and to define the treatment modalities, risk factors, morbidity, mortality, and outcome of patients with HAT after LTx at our transplantation center during a 5-year period.

Materials and Methods

Patients and Organs

Between December 2001 and December 2006, 335 consecutive full size liver transplantations were performed in 299 adult patients (age >18 years) at our institution. We included 299 primary grafts and 36 re-transplants in this study. There were 199 male and 100 female patients with a median age of 49.7 years. Indications for liver transplantation and re-transplantation are summarized in Tables 1 and 2. Degree of cirrhosis was categorized as mild (A), moderate (B), or severe (C) according to Child–Pugh's classification. During our study period, livers were allocated by the Child–Pugh classification and not by the model of end-stage liver disease score system, which was first introduced in January 2007 in the Eurotransplant community. Almost 50% of all patients presented with Child–Pugh class C cirrhosis. Donor demographics, preoperative, and intraoperative details were compared between patients with and without HAT. Donor organs were either recovered by surgeons from our transplant center or were forwarded from other institutions according to the guidelines of the "Deutsche Stiftung für Organtransplantation (DSO)." Allografts were either preserved with histidine tryptophan ketoglutarat solution (HTK, Bretschneider solution, Dr. Franz Koehler Chemie GmbH Alsbach-Haenlein, Germany) or with University of Wisconsin solution (Du Pont Pharma GmbH, Germany). At the end of the back table procedure, the graft were flushed via the hepatic artery with 1 L of cold HTK solution with an arterial pressure of 150 mmHg (Fig. 2).

Technique

All grafts were transplanted using a modified piggy-back technique first described by Belghiti et al.[20] with a side-to-side cavocaval anastomosis. Reconstruction of the portal vein was performed with an end-to-end veno-venous anastomosis. Reperfusion of the graft was generally performed following completion of the caval and portal venous anastomoses.

At our department, the arterial anastomosis is routinely fashioned with a running 7-0 polypropylene (Prolene suture; Ethicon Inc., Johnson & Johnson Co., Somerville, NJ) as a gastroduodenal branch-patch using the bifurcation between the gastroduodenal and the proper hepatic artery in both the donor and the recipient (Fig. 3a). Accessory right hepatic arteries from the superior mesenteric artery were anastomosed end-to-end to the gastroduodenal artery of the donor during the back table preparation. Afterwards, arterial anastomosis was performed end-to-end from the common hepatic artery of the donor to the bifurcation between the gastroduodenal and the proper hepatic artery of the recipient (Fig. 3b). Large left accessory arteries were preserved in continuity with the left gastric artery, and the arterial anastomosis was performed end-to-end between the bifurcation of the common hepatic artery and the left gastric artery of the donor and the bifurcation of the gastroduodenal and the proper hepatic artery of the recipient. If the left accessory artery could not be maintained on the left gastric artery during organ recovery, it was anastomosed end-to-end on the gastroduodenal artery of the donor, and the arterial anastomosis was done end-to-end between the common hepatic artery of the donor to the bifurcation between the gastroduodenal and the proper hepatic artery of the recipient. After sufficient reperfusion, intraoperative electromagnetic blood flow measurements of both the hepatic artery and the portal vein were recorded prior to the biliary anastomosis using a flowmeter (CardioMed Flowmeter CM 1005, Medi-Stim A/S, Oslo, Norway). To define our arterial flow rate cut-off value of 150 mL/min, we investigated all arterial flows measured during LTx from 1996

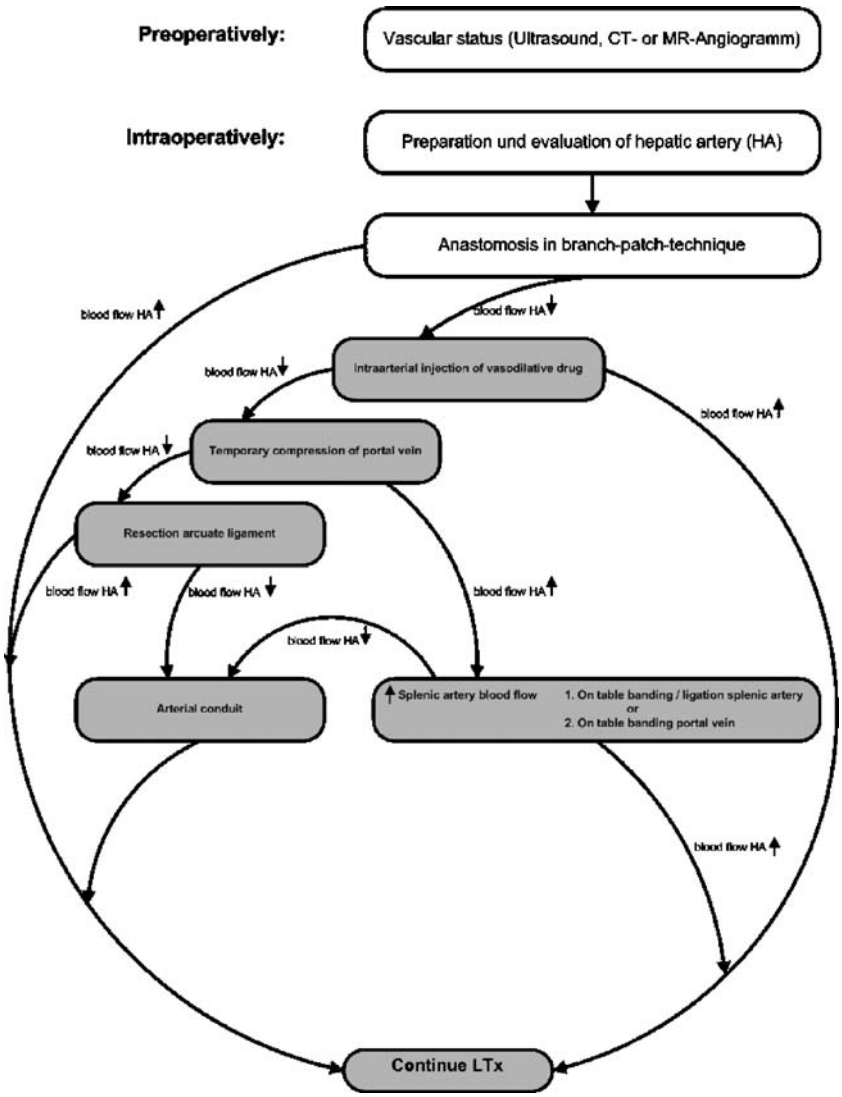

Figure 1 Heidelberger algorithm to decrease HAT rate.

to 2001 and found that only 5% had a flow greater than 400 mL/min (no incidence of HAT), 49% had an arterial flow between 200 and 400 mL/min (three cases of HAT), and 38% had an arterial flow between 150 and 200 mL/min (five cases of HAT). The remaining 8% had an arterial flow of less than 150 mL/min and showed a significant increased incidence of HAT (nine cases of HAT).

In case of an arterial flow of less than 150 mL/min, we proceeded according to the presented algorithm (Tables 1 and 2). Biliary reconstruction was performed last with an end-to-end choledocho-choledochostomy, or where indicated with a Roux en-Y choledocho-jejunostomy.

Postoperative Treatment and Monitoring

Postoperatively, patients were transferred to the intensive care unit and maintained on ventilation support until normothermic and hemodynamically stable. If the post-transplant hemoglobin levels were between 6 and 8 g/dL, the patients without cardiac problems were not administered red blood cell units. In elderly recipients or patients with coronary artery disease, the post-transplant hemoglobin level was kept at around 10 g/dL. The immunosuppressive protocol consists of steroids and cyclosporine or the combination of steroids and tacrolimus. During hospitalization, complete laboratory tests and cyclosporine level measurements were performed daily. Vascular patency was checked on a daily basis by duplex ultrasound during the first 5 days after LTx by a radiologist of our interdisciplinary team on the intensive care unit or after unexpected increase of liver enzymes or increase of international normalized ratio.[21] If indicated, assessment of the arterial tree was performed either by angiography, angio-computed tomography (angio-CT), or magnetic resonance (MR) imaging. HAT was defined as the complete disruption of arterial blood flow to the allograft.

Table 1 Primary Diagnoses and Child–Pugh Classification of 299 Liver Transplant Patients

Indications of first LTx	No. of cases	Percent	Child		
			A	B	C
Alcoholic cirrhosis	72	24.0	4	24	44
Hepatocellular carcinoma	58	19.5	26	24	8
Hepatitis C cirrhosis	51	17.5	8	14	29
Metabolic disorders	23	7.5	7	4	12
Primary sclerosing cirrhosis	18	6.0	6	4	8
Acute liver failure	17	5.5	0	0	17
Hepatitis B cirrhosis	16	5.5	2	5	9
Cryptogenic cirrhosis	14	4.5	2	4	8
Autoimmune cirrhosis	10	3.5	0	2	8
Primary/secondary biliary cirrhosis	5	1.5	0	4	1
Cancer	4	1.5	3	1	0
Budd Chiari	3	1.0	0	0	3
Others	8	2.5	6	0	2
Total	299	100	64	86	149
			21.4%	28.7%	49.9%

Follow-up

All patients were followed up at our center routinely at 1, 3, 6, and 12 months and then every 6 months after LTx, which included blood tests and duplex ultrasound of the transplanted organ. In between, patients were monitored by local hepatologists or experienced general practitioners. When arterial thrombosis was suspected, patients were transferred to our center for further diagnostic workup.

Statistical Analysis

Statistical analysis was performed using SAS software (Release 9.1, SAS Institute, Inc., Cary, NC). Non-parametric analyses were performed using the chi-square/χ^2-test, Wilcoxon test, or Fisher exact test as appropriate; parametric analyses were performed using t test. Survival curves were generated using the Kaplan–Meier method. Results were reported as the median ± range, and significance levels were set at $p<0.05$.

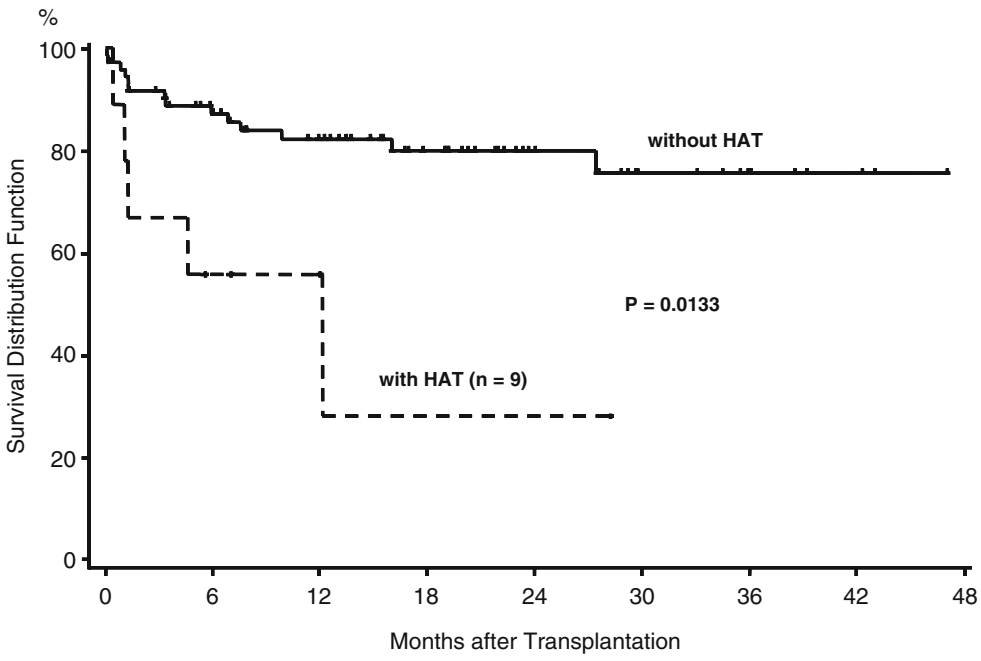

Figure 2 The patient survival rates at 1 and 3 years after liver transplantation. HAT was associated with a significant negative impact on patient survival after LTx ($p=0.0133$).

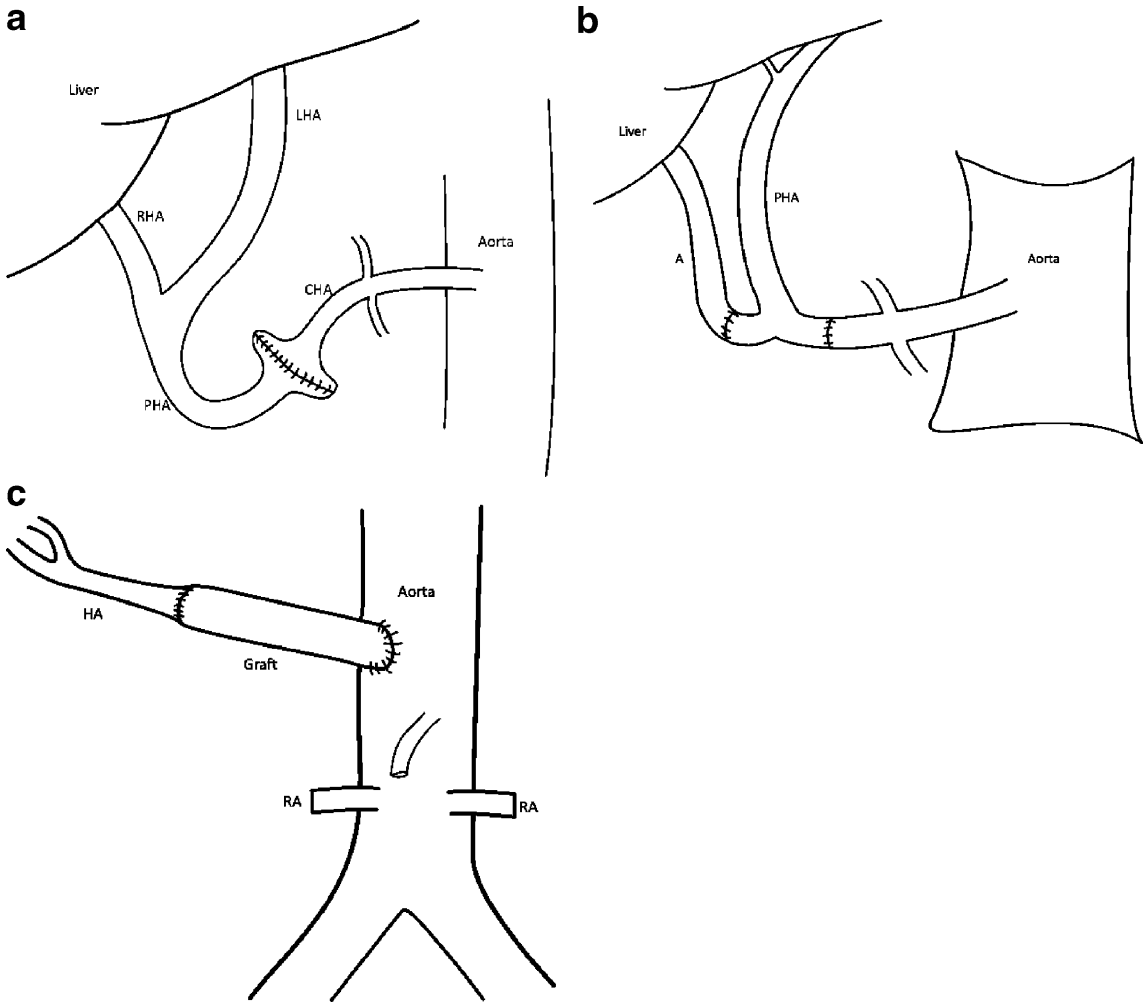

Figure 3 **a** The so-called branch-patch technique uses a splayed anastomosis between the bifurcation of the gastroduodenal and proper hepatic arteries in both the donor and the recipient. *HA* hepatic artery, *RHA* right hepatic artery, *LHA* left hepatic artery, *CHA* common hepatic artery, *PHA* proper hepatic artery. **b** For large accessory right hepatic arteries, our current method is to perform an end-to-end anastomosis using the recipient gastroduodenal artery stump following a branch-patch anastomosis using the bifurcation between the gastroduodenal and the proper hepatic artery. *PHA* proper hepatic artery, *A* accessory artery. **c** Arterial conduits that use donor iliac arteries represent a reliable technique for graft revascularization in LTx for specific indications. *HA* hepatic artery, *RA* renal artery.

Results

The most common indication for liver transplantation was alcoholic cirrhosis (24.1%), followed by hepatocellular carcinoma (19.4%), and hepatitis C virus-related cirrhosis (17.0%). Metabolic disorders included Wilson's disease (nine patients), hemochromatosis (four patients), and alpha-1 antitrypsin deficiency (three patients). Diagnoses and Child–Pugh classifications of the whole patient cohort are depicted in Tables 1 and 2. In nine of the 335 liver transplantations, HAT (2.7%) occurred during the study period (Table 3). The interval between liver transplantation and the detection of HAT ranged from 2 to 318 days (mean, 66.6 days). Interestingly, all HATs occurred after primary transplantation (9/299; 3%) and none after re-transplantation. Demographics and intraoperative parameters of all patients with and without HAT are listed in Table 4. Beside the arterial reconstruction technique ($p=0.0193$) and number of anastomosis ($p=0.0022$), there were no significant differences between the groups with and without HAT (Table 4).

Intraoperatively, we stepwise intervened to improve arterial flow in case of insufficient flow rates (<150 mL/min) according to the presented algorithm. We first performed intra-arterial injection of a vasodilatative drug (Verapamil 5 mg in 20 cc saline) in the recipient hepatic artery ($n=26$). Generally, an increase of at least 50% of the first determined value was accepted, but a minimal flow of 150 mL/min was strictly needed to continue LTx. If arterial flow remained low, further steps in the cascade of our algorithm were undertaken. If arterial flow increased by at least 50% after clamping the portal vein for 30–60 s, thus

Table 2 Primary Diagnoses and Child–Pugh Classification of 36 Patients Needing Re-transplantation Due to Organ Failure

Primary diagnoses of 1st LTx	No. of cases	Percent	Child		
			A	B	C
Hepatitis C cirrhosis	9	25.7	0	1	8
Hepatocellular carcinoma	7	20	1	3	3
Alcoholic cirrhosis	5	14.3	0	1	4
Primary/secondary biliary cirrhosis	4	11.4	0	1	3
Metabolic disorders	2	5.7	0	1	1
Cryptogenic cirrhosis	3	8.6	0	1	2
Autoimmune cirrhosis	2	5.7	0	1	1
Others	3	8.6	0	1	2
Total	36	100	1	10	24

defining the hepatic artery buffer response, we ligated the splenic artery to decrease splanchnic circulation (n=5).[22] The hepatic arterial buffer response is an intrinsic regulatory mechanism of the hepatic artery that compensates for reductions in portal venous blood flow by hepatic vasodilatation. In small grafts that are accompanied by an excessive portal inflow (>250 mL/min/100 g graft weight), perioperative ligation of the splenic artery may improve arterial flow.[23] Experimental data have shown that the immunological function of the spleen is preserved after ligating the splenic artery.[24] If the flow still remained below 150 mL/min, we resected the arcuate ligament (n=13). If the inflow remained inadequate, we perform an arterial conduit to the aorta (Fig. 3c; n=5).

Regarding the technique of arterial anastomosis, the gastroduodenal branch-patch method has been the technique of choice and was used in 92.2% of cases. In 4.0%, an additional arterial anastomosis was carried out due to accessory hepatic arteries. Vascular conduits from the iliac artery or aorta and other reconstructive techniques, e.g., supraceliac anastomosis, were rarely necessary. The type of arterial reconstruction (complex arterial reconstruction techniques versus gastroduodenal branch patch) was found to be significantly associated with the complication rate (p=0.0193; Table 4). In all five patients with splenic artery ligation, no splenic infarction, pancreatitis, post-stenotic aneurysm, or other related complications were observed. During the follow-up period, no incidence of graft edema due to impaired venous outflow or the occurrence of silent HAT were observed in our study population. Arterial stenoses, a well-known precursor of HAT, occurred in six patients. The clinical symptoms of liver artery stenoses

Table 3 Demographics of Patients with HAT and of all 299 Patients

HAT	Age	Sex	Primary diagnosis	Child	1st/ReTx	Early HAT[a]	Late HAT[a]
n=9							
1	25	m	Wilson's Disease	C 14	1st	2	
2	56	m	Hepatocellular carcinoma	A 6	1st	16	
3	43	m	Hepatitis B	C 12	1st	9	
4	51	m	Hepatitis C	B 8	1st	8	
5	39	w	Acute liver failure	C 11	1st	20	
6	62	m	Hepatitis C	C 12	1st		318
7	59	m	Hepatitis C	B 9	1st		53
8	47	m	Alpha-1 antitrypsin deficiency	C 12	1st		138
9	51	m	Alcohol	B 8	1st		35
		m=8					
		w=1					
Median range	48.1 (25–62)					11 (2–20)	136 (35–138)
n=299							
Median	49.7	m=199	See Tables 1 and 2	A=64	1st=299		
Range	(18–68)	f=100		B=86	ReTx=36		
				C=149			

Eight of nine patients developed HAT following the first liver transplantation and only one after re-transplantation
1st first transplantation, *ReTx* Re-transplantation, *HAT* hepatic artery thrombosis
[a] Days to diagnosis

Table 4 Differences in Demographics and Intraoperative Variables Analyzed Between the HAT and Non-HAT Groups

	HAT	Range	Non-HAT	Range	*p* value
Age	51	25–62	51	18–68	0.6623
Sex, m/f	8:1	89%:11%	191:99	66:34%	0.2806
Red blood cell units	3.4	0–20	3.0	0–33	0.3491
Fresh frozen plasma (units)	17	0–70	12	0–64	0.8228
Platelets (units)	1.1	0–4	1.2	0–6	0.5175
Blood loss (mL)	1,935	250–8,000	1,670	200–20,000	0.4023
Duration of surgical procedure (h)	05:18	03:15–09:25	05:18	02:20–11:40	0.3309
Cold ischemia time (h)	09:22	05:10–16:00	09:05	01:00–17:00	0.3997
Median portal vein flow (mL/min)	1,750	1,400–2,000	1,410	400–3,300	0.2176
Median arterial flow rate (mL/min)	274.5	80–350	321	35–1,300	0.9261
Number of arterial reconstruction	4	44%	18	6%	0.0022
Branch patch technique	6	67%	273	92.2%	0.0193

Values are given as median with range

appeared immediately after transplantation and developed in all six cases within the first 6 months. Two stenoses were successfully managed by balloon dilatation, and two patients were under observation without abnormalities in liver function. Stenoses with concomitant thrombosis were treated by re-transplantation due to acute primary non-function of the liver (patient 6 and 8). In patients with HAT, treatment consisted of surgical revision of the arterial anastomosis (n=4) and local lysis (n=1) in the early HAT group. In the late HAT group, re-transplantation was required in all four patients.

Early HAT

Early HAT occurred in five (1.5%) patients with a median age of 42.8 (25–56) years. HAT was diagnosed on the median postoperative day 11 (range, 2–20 days). Two of the patients underwent transplantation for viral cirrhosis, one for hepatocellular carcinoma, one Wilson's disease, and one for fulminant liver failure of unknown origin. The technique of the anastomosis, hepatic arterial flow during surgery, the site of HAT, and the management are summarized in Table 5. Three patients with early HAT had branch-patch anastomosis. One patient had an arterial interposition, and one had a supraceliac aortic anastomosis. The last-mentioned patient's anastomosis was performed in a young patient presented with acute decompensated Wilson's disease. A possible reversible acute pancreatitis was observed leading to extreme difficulties in preparing the celiac trunc arteries. Therefore, an interposition jump graft was placed from the supraceliac aorta utilizing the donor's common iliac artery to maintain hepatic arterial inflow.

The median intraoperative arterial flow rate in patients with early HAT was 246 mL/min (range, 80–340 mL/min).

Table 5 Type of Arterial Anastomosis, Hepatic Arterial Flow During Surgery, the Site of HAT, and its Management in Early and Late HAT After Liver Transplantation

Patient number	Technique of anastomosis				HA flow (mL/min)			Site of HAT	Management	Death
	b-p	a	i	o	>400	200–400	<200			
Early HAT, n=5										
1			1			1		Right HA	S	Yes
2	1					1		Anastomosis	S	yes
3				1			1	Left HA	S	No
4	1					1		Anastomosis	S	Yes
5	1					1		Anastomosis	L	No
Late HAT, n=4										
6	1						1	Anastomosis	ReTx	Yes
7	1					1		Right HA	ReTx	No
8		1				1		Anastomosis	ReTx	Yes
9	1					1		Donor HA	ReTx	No

HAT hepatic artery thrombosis, *S* surgery, *L* lysis, *Re-Tx* Re-transplantation, *b-p* branch-patch, *a* accessory anastomosis, *i* interposition, *o* other techniques, *HA* flow, hepatic artery flow

The mean portal vein flow rate was 1,420 ml/min (range, 1,250–1,630 mL/min). In one patient, HAT occurred in the left hepatic artery, in one in the right hepatic artery, in two patients at the anastomosic site, and in one at the proximal hepatic artery of the recipient. Four patients with early thrombosis were treated by surgical revascularization (thrombectomy with a Fogarty-catheter and refashioning of the arterial anastomosis). Successful catheter-directed thrombolysis therapy with urokinase (100,000 units/h) was performed in one patient with systemic therapeutic anti-coagulation with heparin. Three of the five patients died during the follow-up due to acute right heart failure (day 12), fulminant pancreatitis (day 39), and aspergillosis and subsequent multi-organ failure (day 138). The fifth patient is in a good general condition but is listed for re-transplantation due to intrahepatic cholangitic abscesses. It should be mentioned that in the Eurotransplant liver allocation program, it is only possible to be listed as "high urgent" for the first 14 days after transplantation in the event of primary non-function of the graft. This accounts for the high mortality rate in the early HAT group, as the accessibility to donor livers is limited and surgical intervention is the only option for treatment.

Late HAT

Late HAT occurred in four (1.2%) patients with a median age of 54.7 years (range, 47–62); median HAT was diagnosed on postoperative day 136 (range, 35–318). Two patients underwent transplantation for viral cirrhosis, one for alcoholic cirrhosis, and one for alpha-1 antitrypsin deficiency. Three patients had branch-patch anastomoses and one had an additional accessory anastomosis (Table 5). The mean intraoperative arterial flow rate during surgery was 288 mL/min (range, 180–351 mL/min). The median portal vein flow rate was 1,490 ml/min (range, 1,400–1,850 mL/min). Three patients had a clotted main hepatic artery and one an isolated thrombosis of the right hepatic artery. All patients subsequently presented with sepsis due to biliary complications and/or graft dysfunction. All four patients underwent re-transplantation after 39 days, 6 months, 10 months, and 20 months, respectively. Two of four patients died due to fulminant pancreatitis of unknown origin (day 33) and multi-organ failure (day 369).

Survival

The mean follow-up was 18 months (4–33 months). Five of nine patients (55.5%) with HAT died during long-term follow-up (Fig. 2). Three of five (60%) died in the early HAT group and two of four (50%) in the late HAT group. HAT was associated with a significant negative impact on patient survival after LTx (p=0.0133) with a 1-year patient survival rate of only 31%. Overall long-term survival rates after LTx were recently published by our group showing 1- and 3-year patient survival rates of 79% and 74%, respectively.[23]

Discussion

Various risk factors, both surgical and non-surgical, have been implicated in the development of HAT in liver transplant recipients.[25–27] It has been shown that imbalance of the procoagulative and anticoagulative factors synthesized by the liver favors a hypercoagulable state in the first few days following liver transplantation.[28] Other nonsurgical factors for HAT include among others AB0-incompatibility,[29] cigarette smoking,[30] and cytomegalovirus infection.[31] Other studies showed that an increased operation time, prolonged cold, and warm ischemia times are risk factors for early HAT.[32–34] Also compression of the celiac artery by the median arcuate ligament, which in turn decreases blood flow in the celiac artery and across the arterial anastomosis, has been suggested as a risk factor for HAT.[35] We reported four unexplainable non-anastomotic HAT events, which were likely due to donor or surgical factors. Important factors that may cause these HAT events include arterial allograft rejection.[36,37]

Due to our own experience with HAT, we introduced an algorithm to minimize its incidence and its unfavorable outcome following liver transplantation in 2001. Preoperative imaging with MR-angiography or CT-angiography, and duplex sonography of all hepatic vessels are the standard of reference and can reveal altered vascular anatomy and flow dynamics.[38] A general principle of liver transplant surgery has been to reconstruct all donor accessory hepatic arteries while attempting to keep the number of arterial anastomoses low. However, only about 10% of accessory left hepatic arteries have to be reconstructed.[39] Anatomical variants of the donor or recipient's hepatic arteries are important findings. Proposito et al.[40] and Meroin et al.[41] noted that variant hepatic artery anatomy in a liver transplant recipient had little impact on post-transplantation hepatic artery complications as long as the native artery had an appropriate size and flow. Normal anatomy is found in only 51–76% of patients. The most common variants are accessory left or right hepatic arteries, which occur in 5–18% and 11–21% respectively, a combination of both in up to 4% or a hepatic artery arising directly from the aorta in up to 6%.[38] Particular considerations for reconstructed arteries include the avoidance of twisting and kinking caused by excessive length and angled attachments. While vessel diameter should be maximized, excessively small hepatic arteries (diameter, <1 mm) can usually be ligated if there is sufficient back flow in arterial

vessels at the time when the hepatic artery is flushed on the back table.[42]

Quinones-Baldrich et al.[43] first described the gastroduodenal branch-patch technique using the bifurcation between the gastroduodenal and the proper hepatic artery in both the donor and the recipient. This technique is associated with a significant reduction in thrombosis and stenosis compared with the classical end-to-end anastomosis.[39,43,44] Therefore, this technique is preferred in our institution and was performed in more than 90% of all LTx. We confirm that this technique is associated with a significant reduction (p=0.0193) in thrombosis compared with other arterial anastomoses. Complex hepatic artery reconstruction was defined as any revascularization requiring additional anastomosis or the use of a donor iliac artery interposition graft (aortic conduit). The number of accessory arterial anastomoses in our series was 14 (4.0%). Donor iliac artery interposition grafts was used in seven patients (2.2%).

There were no cases of splenic infarction, pancreatitis, or other related complications reported in the associated literature of this technique,[45,46] though one case of splenic infarction was reported following paediatric liver transplantation and ligation of the splenic artery.[47] In small grafts that are accompanied by an excessive portal inflow (>250 mL/min/100 g graft weight), perioperative ligation of the splenic artery may improve arterial flow.[23] Experimental data have shown that the immunological function of the spleen is preserved after the ligature of the splenic artery.[24]

Drazan et al.[48] attributed inadequate blood flow in the recipient hepatic artery as the cause of post-transplantation HAT in nine of 11 patients. In our center, a low arterial flow limit of 150 mL/min was defined. After correcting arterial vasospasm and patients' hemodynamic factors, Abbasoglu et al.[18] reported that patients with hepatic arterial flows less than 400 mL/min were more than five times as likely to develop hepatic artery stenoses and thromboses and recommended to revising the hepatic artery reconstruction if a flow <200 mL/min was obtained. Lin et al. reported that the risk of HAT was increased by a factor of six if the intraoperative hepatic artery flow rate was less than 200 mL/min during the first 2 months postoperatively.[19] It should be noted that more than 80% of all 300 LTx at our institution had an intraoperative flow of less than 400 mL/min and even 20% with a flow less than 200 mL/min without developing a HAT.

Inflow problems caused by the arcuate ligament are treated by dissection of the ligament. With significant arcuate compression, these techniques result in a doubling of the arterial flow rate.[35] To detect a compressive arcuate ligament preoperatively, it is recommended to perform a CT or arteriography in both inspiratory and exspiratory phases. Goldstein et al.[49] improved 22 patients with technical difficulties or inadequate blood flow using donor iliac arteries to construct aortohepatic or iliohepatic conduits placed ante- or retropancreatically. Intraoperative hemodynamics and postoperative liver function of patients with a vascular conduit are similar to those patients with the classical reconstructions.[50,51] There were two cases of arterial thrombosis in the conduit group and in the standard group. Two major infections were encountered: both pancreatic abscesses and both in conduits placed retropancreatically. Thus, the antepancreatic approach is our preferred technique performing aortohepatic conduits.[49]

Although a high hematocrit and hemoglobin level is associated with an increased risk of HAT, it was not a significant factor in our series. According to the guidelines of the American Society of Anesthesiologists, perioperative blood transfusion to a patient without any organ dysfunction is indicated if the hemoglobin level is lower than 6 g/dL.[52] This critical value is based on experiences with low hemoglobin levels during operations on Jehovah's Witness'. Organ dysfunction will develop at a hemoglobin level lower than 5 g/dL. Experimental investigations about hemodilution showed that a hemoglobin level of 6 g/dL provides a sufficient oxygen supply to the liver. Tisone et al.[53] reported an increased incidence of HAT if the hematocrit was higher than 44%.[54]

In our study cohort, no coronary artery events or low hemoglobin associated renal dysfunction were observed in the post-transplant period.

Limitations

There are limitations of our study. The results of the application of this algorithm were not compared with a control group. We designed this algorithm based on the knowledge of our long-lasting experience with liver transplantation and literature pertaining to arterial inflow. Nevertheless, we believe that this algorithm can be helpful in the management of impaired arterial flow during LTx.

Conclusion

Due to its effectiveness, we adhere to the presented algorithm in the presence of an insufficient arterial blood supply to the graft resulting in lower rates of early and late HAT. Prevention of HAT is of vital importance due to unsatisfactory therapeutical options and its unfavourable outcome with poor graft and patient survival. Therefore, careful pre- and intraoperative monitoring and management is mandatory. Due to many possible factors that may negatively influence the outcome, it is crucial to plan LTx individually.

References

1. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–699. doi:10.1056/NEJM199603143341104.
2. Bismuth H, Chiche L, Adam R, Castaing D, Diamond T, Dennison A. Liver resection versus transplantation for hepatocellular carcinoma in cirrhotic patients. Ann Surg 1993;218:145–151. doi:10.1097/00000658-199308000-00005.
3. SRTR analysis. 2007. http://www.ustransplant.org. Accessed May 1998.
4. Eurotransplant statistics. http://www.eurotransplant.nl
5. Sanchez-Bueno F, Robles R, Acosta F, Ramirez P, Lujan J, Munitiz V, Rios A, Parrilla P. Hepatic artery complications in a series of 300 orthotopic liver transplants. Transplant Proc 2000;32:2669–2670. doi:10.1016/S0041-1345(00)01835-2.
6. Settmacher U, Stange B, Haase R, Heise M, Steinmüller T, Bechstein WO, Neuhaus P. Arterial complications after liver transplantation. Transpl Int 2000;13:372–378.
7. Langnas AN, Marujo W, Stratta RJ, Wood RP, Shaw BW Jr. Vascular complications after orthotopic liver transplantation. Am J Surg 1991;161:76–82. doi:10.1016/0002-9610(91)90364-J.
8. Tzakis AG, Gordon RD, Shaw BW Jr, Iwatsuki S, Starzl TE. Clinical presentation of hepatic artery thrombosis after liver transplantation in the cyclosporine era. Transplantation 1985;40:667–671. doi:10.1097/00007890-198512000-00019.
9. Mazzaferro V, Esquivel CO, Makowka L, Belle S, Kahn D, Koneru B, Scantlebury VP, Stieber AC, Todo S, Tzakis AG, et al. Hepatic artery thrombosis after pediatric liver transplantation: A medical or surgical event? Transplantation 1989;47:971–977. doi:10.1097/00007890-198906000-00011.
10. Mazzaferro V, Esquivel CO, Makowka L, Kahn D, Belle S, Kahn D, Scantelbury VP, Ferla G, Koneru B, Scotti-Foglieni CL, et al. Factors responsible for hepatic artery thrombosis after pediatric liver transplantation. Transplant Proc 1989;21:2466–2467.
11. Stevens LH, Emond JC, Piper JB, Heffron TG, Thistlethwaite JR Jr, Whitington PF, Broelsch CE. Hepatic artery thrombosis in infants. A comparison of whole livers, reduced-size grafts, and grafts from living-related donors. Transplantation 1992;53:396–399. doi:10.1097/00007890-199202010-00025.
12. Oh CK, Pelletier SJ, Sawyer RG, Dacus AR, McCullough CS, Pruett TL, Sanfey HA. Uni- and multi-variate analysis of risk factors for early and late hepatic artery thrombosis after liver transplantation. Transplantation 2001;71(6):767–772.
13. Langnas AN, Marujo W, Stratta RJ, Wood RP, Li SJ, Shaw BW. Hepatic allograft rescue following arterial thrombosis. Role of urgent revascularization. Transplantation 1991;51(1):86–90. doi:10.1097/00007890-199101000-00013.
14. Pinna AD, Smith CV, Furukawa H, Starzl TE, Fung JJ. Urgent revascularization of liver allografts after early hepatic artery thrombosis. Transplantation 1996;62(11):1584–1587. doi:10.1097/00007890-199612150-00010.
15. Sakamoto Y, Harihara Y, Nakatsuka T, Kawarasaki H, Takayama T, Kubota K, Kimura W, Kita Y, Tanaka H, Ito M, Hashizume K, Makuuchi M. Rescue of liver grafts from hepatic artery occlusion in living-related liver transplantation. Br J Surg 1999;86(7):886–889. doi:10.1046/j.1365-2168.1999.01166.x.
16. Bhattacharjya S, Gunson BK, Mirza DF, Mayer DA, Buckels JA, McMaster P, Neuberger JM. Delayed hepatic artery thrombosis in adult orthotopic liver transplantation—a 12-year experience. Transplantation 2001;71(11):1592–1596. doi:10.1097/00007890-200106150-00018.
17. Yanaga K, Shimada M, Makowka L, Esquivel CO, Tzakis AG, Starzl TE. Significance of blood flow measurement in clinical liver transplantation. Transplant Proc 1989;21:2330–2331.
18. Abbasoglu O, Levy MF, Testa G, Obiekwe S, Brkic BS, Jennings LW, Goldstein RM, Husberg BS, Gonwa TA, Klintmalm GB. Does intraoperative hepatic artery flow predict arterial complications after liver transplantation? Transplantation 1998;66:598–601. doi:10.1097/00007890-199809150-00008.
19. Lin M, Crawford M, Fisher J, Hitos K, Verran D. Hepatic artery thrombosis and intraoperative hepatic artery flow rates in adult orthotopic liver transplantation. ANZ J Surg 2002;72(11):798–800. doi:10.1046/j.1445-2197.2002.02552.x.
20. Belghiti J, Panis Y, Sauvanet A, Gayet B, Fekete F. A new technique of side to side caval anastomosis during orthotopic hepatic transplantation without inferior vena caval occlusion. Surg Gynecol Obstet 1992;175(3):270–272.
21. Mehrabi A, Schemmer P, Schmidt J, Sauer P, Friess H, Kraus T, Martin E, Büchler MW, Uhl W. Heidelberg's first experiences in establishing a living-donation liver transplantation programme. Nephrol Dial Transplant 2004;19(Suppl 4):1–5. doi:10.1093/ndt/gfg390.
22. Golling M, Jahnke C, Fonouni H, Ahmadi R, Urbaschek R, Breitkreutz R, Schemmer P, Kraus TW, Gebhard MM, Büchler MW, Mehrabi A. Distinct effects of surgical denervation on hepatic perfusion, bowel ischemia, and oxidative stress in brain dead and living donor porcine models. Liver Transpl 2007;13(4):607–617. doi:10.1002/lt.21069.
23. Troisi R, Cammu G, Militerno G, De Baerdemaeker L, Decruyenaere J, Hoste E, Smeets P, Colle I, Van Vlierberghe H, Petrovic M, Voet D, Mortier E, Hesse UJ, de Hemptinne B. Modulation of portal graft inflow: a necessity in adult living-donor liver transplantation? Ann Surg 2003;237:429–436. doi:10.1097/00000658-200303000-00019.
24. Schwalke MA, Crowley JP, Spencer P, Metzger J, Kawan M, Burchard KW. Splenic artery ligation for splenic salvage: clinical experience and immune function. J Trauma 1991;31:385–388. doi:10.1097/00005373-199103000-00013.
25. Schemmer P, Nickkholgh A, Hinz U, Gerling T, Mehrabi A, Sauer P, Encke J, Friess H, Weitz J, Büchler MW, Schmidt J. Extended donor criteria have no negative impact on early outcome after liver transplantation: a single-center multivariate analysis. Transplant Proc 2007;39(2):529–534. doi:10.1016/j.transproceed.2006.12.002.
26. Vivarelli M, Cucchetti A, La Barba G, Bellusci R, De Vivo A, Nardo B, Cavallari A, Pinna AD. Ischemic arterial complications after liver transplantation in the adult: multivariate analysis of risk factors. Arch Surg 2004;139:1069–1074. doi:10.1001/archsurg.139.10.1069.
27. Neuhaus P, Neumann U. Analysis of risk factors for the development of late hepatic artery thrombosis: do CREG mismatches play a role? Liver Transpl 2000;6(4):512–514. doi:10.1053/jlts.2000.7574.
28. Velasco F, Villalba R, Fernandez M, de la Mata M, Roman J, Rubio V, Rufian S, Varo E, Pera C, Torres A. Diminished anticoagulant and fibrinolytic activity following liver transplantation. Transplantation 1992;53(6):1256–1261. doi:10.1097/00007890-199206000-00017.
29. Lo CM, Shaked A, Busuttil RW. Risk factors for liver transplantation across the ABO barrier. Transplantation 1994;58(5):543–547. doi:10.1097/00007890-199409000-00003.
30. Pungpapong S, Manzarbeitia C, Ortiz J, Reich DJ, Araya V, Rothstein KD, Munoz SJ. Cigarette smoking is associated with an increased incidence of vascular complications after liver transplantation. Liver Transpl 2002;8:582–587. doi:10.1053/jlts.2002.34150.
31. Madalosso C, de Souza NF Jr, Ilstrup DM, Wiesner RH, Krom RA. Cytomegalovirus and its association with hepatic artery thrombosis

after liver transplantation. Transplantation 1998;66(3):294–297. doi:10.1097/00007890-199808150-00003.
32. Pastacaldi S, Teixeira R, Montalto P, Rolles K, Burroughs AK. Hepatic artery thrombosis after orthotopic liver transplantation: a review of nonsurgical causes. Liver Transpl 2001;7(2):75–81. doi:10.1053/jlts.2001.22040.
33. Silva MA, Jambulingam PS, Gunson BK, Mayer D, Buckels JA, Mirza DF, Bramhall SR. Hepatic artery thrombosis following orthotopic liver transplantation: a 10-year experience from a single centre in the United Kingdom. Liver Transpl 2006;12 (1):146–151. doi:10.1002/lt.20566.
34. Stange BJ, Glanemann M, Nuessler NC, Settmacher U, Steinmüller T, Neuhaus P. Hepatic artery thrombosis after adult liver transplantation. Liver Transpl 2003;9(6):612–620. doi:10.1053/jlts.2003.50098.
35. Jurim O, Shaked A, Kiai K, Millis JM, Colquhoun SD, Busuttil RW. Celiac compression syndrome and liver transplantation. Ann Surg 1993;218:10–12. doi:10.1097/00000658-199307000-00003.
36. Bell R, Sheil AG, Thompson JF, Stephen MS, Eyers AA, Shun A, Waugh RC. Vascular complications following orthotopic liver transplantation. ANZ J Surg 1990;60(3):193–198.
37. Karatzas T, Lykaki-Karatzas E, Webb M, Nery J, Tsaroucha A, Demirbas A, Khan F, Ciancio G, Montalvo B, Reddy R, Schiff E, Miller J, Tzakis AG. Vascular complications, treatment, and outcome following orthotopic liver transplantation. Transplant Proc 1997;29(7):2853–2855. doi:10.1016/S0041-1345(97)00706-9.
38. Settmacher U, Haase R, Heise M, Bechstein WO, Neuhaus P. Variations of surgical reconstruction in liver transplantation depending on vasculature. Langenbecks Arch Surg 1999;384:378–383. doi:10.1007/s004230050217.
39. Meneu-Diaz JC, Moreno-Gonzalez E, Garcia Garcia I, Jimenez Romero C, Loinaz Segurola C, Gomez Sanz R, Proposito D, Elola-Olaso AM. Hepatic allograft arterialization by means of the gastroduodenal bifurcation (branch patch) as a prognostic factor. Transplantation 2004;77:1513–1517. doi:10.1097/01.TP.0000113805.21387.A1.
40. Proposito D, Loinaz Segurola C, Garcia Garcia I, Jimenez C, Gonzalez Pinto I, Gomez Sanz R, De La Cruz J, Moreno Gonzalez E. Assessment of risk factors in the incidence of hepatic artery thrombosis in a consecutive series of 687 liver transplantations. Ann Ital Chir 2001;72:187–205. (in Italian).
41. Merion RM, Burtch GD, Ham JM, Turcotte JG, Campbell DA. The hepatic artery in liver transplantation. Transplantation 1989;48(3):438–443.
42. Soliman T, Bodingbauer M, Langer F, Berlakovich GA, Wamser P, Rockenschaub S, Muehlbacher F, Steininger R. The role of complex hepatic artery reconstruction in orthotopic liver transplantation. Liver Transpl 2003;9:970–975. doi:10.1053/jlts.2003.50167.
43. Quinones-Baldrich WJ, Memsic L, Ramming K, Hiatt J, Busuttil RW. Branch patch for arterialization of hepatic grafts. Surg Gynecol Obstet 1986;162(5):488–490.
44. Shaw BW Jr, Iwatsuki S, Starzl TE. Alternative methods of arterialization of the hepatic graft. Surg Gynecol Obstet 1984;159:490–493.
45. Figueras J, Pares D, Aranda H, Rafecas A, Fabregat J, Torras J, Ramos E, Lama C, Llado L, Jaurrieta E. Results of using the recipient's splenic artery for arterial reconstruction in liver transplantation in 23 patients. Transplantation 1997;64:655–658. doi:10.1097/00007890-199708270-00020.
46. Ayalon A, Wiesner RH, Perkins JD, Tominaga S, Hayes DH, Krom RA. Splenic artery aneurysms in liver transplant patients. Transplantation 1988;45:386–389. doi:10.1097/00007890-198802000-00028.
47. Lehar SC, Zajko AB, Koneru B, Stevenson W, Sumkin J. Splenic infarction complicating pediatric liver transplantation. J Comput Assist Tomogr 1990;14:362–365. doi:10.1097/00004728-199005000-00007.
48. Drazan K, Shaked A, Olthoff KM, Imagawa D, Jurim O, Kiai K, Shackelton C, Busuttil R. Etiology and management of symptomatic adult hepatic artery thrombosis after orthotopic liver transplantation (OLT). Am Surg 1996;62:237–240.
49. Goldstein RM, Secrest CL, Klintmalm GB, Husberg BS. Problematic vascular reconstruction in liver transplantation. Part I. Arterial. Surgery 1990;107:540–543.
50. Del Gaudio M, Grazi GL, Ercolani G, Ravaioli M, Varotti G, Cescon M, Vetrone G, Ramacciato G, Pinna AD. Outcome of hepatic artery reconstruction in liver transplantation with an iliac arterial interposition graft. Clin Transplant 2005;19(3):399–405. doi:10.1111/j.1399-0012.2005.00363.x.
51. Muralidharan V, Imber C, Leelaudomlipi S, Gunson BK, Buckels JA, Mirza DF, Mayer AD, Bramhall SR. Arterial conduits for hepatic artery revascularisation in adult liver transplantation. Transpl Int 2004;17(4):163–168. doi:10.1111/j.1432-2277.2004.tb00423.x.
52. Practice Guidelines for blood component therapy: A report by the American Society of Anesthesiologists Task Force on Blood Component Therapy. Anesthesiology 1996;84:732–747.
53. Tisone G, Gunson BK, Buckels JA, McMaster P. Raised hematocrit–a contributing factor to hepatic artery thrombosis following liver transplantation. Transplantation 1988;46(1):162–163. doi:10.1097/00007890-198807000-00032.
54. Buckels JA, Tisone G, Gunson BK, McMaster P. Low haematocrit reduces hepatic artery thrombosis after liver transplantation. Transplant Proc 1989;21(1 Pt 2):2460–2461.

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ORIGINAL ARTICLE

Fibroinflammatory Biliary Stricture: A Rare Bile Duct Lesion Masquerading as Cholangiocarcinoma

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Abstract
Introduction Fibroinflammatory biliary stricture (FIBS) is a rare benign tumor-like process of the extrahepatic bile duct that masquerades as cholangiocarcinoma.
Methods In order to distinguish this unusual entity from cancer, we performed a systematic analysis of 11 patients with FIBS. All patients presented with jaundice; six patients had coexisting autoimmune disease. Preoperative evaluation included computed tomography scan and endoscopic retrograde cholangiopancreatography with benign brush cytology. Surgical treatment included nine bile duct resections with five concurrent liver resections and two incisional biopsies. Light microscopy demonstrated fibrous lesions admixed with chronic inflammation.
Results and discussion Immunohistochemistry demonstrated smooth muscle actin expression in all lesions except one; five tumors exhibited IgG4 positive plasma cells. The lesions were negative for cytokeratin, ALK1, CD21, S100, Ki67, and p53. Six patients received postoperative immunosuppression. At 41 month median follow-up (range 15–58 months), there was no evidence of recurrent FIBS in ten patients, while one was lost to follow-up.
Conclusion FIBS is a rare myofibroblastic lesion with an immunohistochemical profile distinct from other epithelial and stromal neoplasms of the extrahepatic bile duct. A subset of these cases appear to represent IgG4-related sclerosing cholangitis. Because preoperative cytology is not diagnostic of FIBS, surgical resection remains the mainstay of diagnosis and treatment, while immunosuppression may reduce the risk of recurrence.

Keywords Biliary stricture · Bile duct tumor · Benign · Autoimmune cholangitis

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Introduction

Fibroinflammatory biliary strictures (FIBS) are rare benign lesions of the extrahepatic bile duct that can masquerade as cholangiocarcinoma. Because histopathologic examination is currently required to distinguish between benign and malignant lesions of the bile duct, resection has become the method for diagnosis as well as treatment of extrahepatic biliary strictures. Emerging technologies like endoscopically directed forceps biopsy (Spyglass™)[1], 2-fluoro-2-deoxy-D-glucose-positron emission tomography,[2] contrast-enhanced MRI,[3] and molecular analysis of cytologic specimens[4] may soon have sufficient sensitivity and specificity to identify benign bile duct lesions nonoperatively. Clinical application of these technologies requires uniform classification of benign lesions of the bile duct as well as an understanding of their natural history, unique pathology, and response to treatment.

The term "malignant masquerade" was first used by Hadjis in 1985 to describe the clinical and radiographic similarities between benign and malignant lesions of the bile duct.[5] Although once thought to be rare, recent data suggest that benign tumors of the extrahepatic bile duct cause 8–13.4% of all biliary strictures.[6] Verbeek and Corvera reported unsuspected focal fibrotic strictures instead of cholangiocarcinoma in 11 of 82 (13.4%) and 22 of 275 (8%) patients, respectively.[6,7] Similarly, Wetter reported eight patients (8%) with benign strictures in a series of 98 cases of suspected bile duct cancer, including three cases labeled "idiopathic benign focal stenosis."[8] Published descriptions of benign bile duct tumors[6,8,9] include disparate diseases like lymphoplasmacytic sclerosing cholangitis associated with autoimmune pancreatitis,[10] idiopathic benign focal stenosis,[8] periductal fibrosis,[11] cholangitis glandularis proliferans,[12,13] and inflammatory pseudotumor.[14] Although these reports do not provide a uniform classification of the underlying bile duct pathology, the bile duct lesions consistently demonstrate an infiltrating, non-neoplastic mass associated with chronic inflammation and fibrosis.

The term "inflammatory pseudotumor" loosely describes a diverse group of fibroinflammatory diseases characterized by the growth of an inflammatory mass which displaces surrounding structures and causes organ dysfunction related to compression. These inflammatory lesions were first described in the lung but also have been reported in the spleen, liver, lymph nodes, and common bile duct.[15,16] The descriptive name arises from the discrepancy between the macroscopic appearance of the biliary lesion, suggesting a mass lesion infiltrating the bile duct, and its histological appearance of inflammation and fibrosis. Fibroinflammatory disorders are a heterogeneous group of clinical conditions of unclear etiology including retroperitoneal fibrosis, sclerosing cholangitis, sclerosing mesenteritis, and Reidel's thyroiditis. The pathogenesis of these lesions has recently been linked to autoimmune diseases like collagen vascular disease and IgG4- related sclerosing diseases.[17]

We selected patients undergoing surgery for suspected bile duct cancer at the University of Pittsburgh Medical Center and excluded those with confirmed cancer, classic intrahepatic primary sclerosing cholangitis, autoimmune pancreatitis, anastomotic strictures from prior biliary surgery, and choledocholithiasis. We chose the term FIBS to encompass the remaining group of benign biliary lesions of the extrapancreatic bile duct, and we summarized the clinical, radiographic, pathologic, and immunohistochemical features of this rare entity in 11 patients.

Materials and Methods

Study procedures were approved by the Institutional Review Board of the University of Pittsburgh. De-identified medical records were reviewed for demographics, symptoms, and coexisting medical conditions, results of radiographic and laboratory evaluations, operative findings, pathologic diagnosis, medical management, and postoperative follow-up. Potential cases of FIBS were screened by two pathologists (AK and JD) using hematoxylin and eosin-stained tissue sections. Classic intrahepatic primary sclerosing cholangitis, preexisting bile duct injury or surgery, intrapancreatic duct involvement by autoimmune pancreatitis, choledocholithiasis, or the unexpected finding of cholangiocarcinoma precluded a diagnosis of FIBS. The radiographs and endoscopic retrograde cholangiograms (ERC) of patients with confirmed FIBS were reviewed (M.E.T.) for common diagnostic features. Operative reports and frozen section results were assessed to identify findings unique to this type of bile duct lesion.

Archived pathology specimens were retrieved to perform immunohistochemical analysis. Additional formalin-fixed, paraffin-embedded 4-μm thick sections were cut from available tissue blocks and processed using the Ventana Benchmark XT automated platform (Ventana Medical Systems, Inc., Tucson, AZ, USA) with established positive and negative controls. Sections were incubated for 28 min at 37°C with a panel of primary antibodies (Table 1). Antibody binding was visualized using the Ventana iVIEW™ detection system (Ventana Medical Systems, Inc.). Because the frequency of IgG4-positive cells is not firmly established for IgG4-related biliary tract disease, we selected a minimum of ten IgG4-positive plasma cells per hpf consistent with diagnostic criteria for autoimmune pancreatitis.[18] Serum IgG levels were not measured in our series.

Table 1 Immunohistochemical Reagents and their Pathologic Significance

Antibody	Clone	Company	Diagnostic significance
Smooth muscle actin (SMA)	IA4	Dako, Carpinteria, CA, USA	Myofibroblast differentiation
CD34	IOM34	AMAC, Inc., Westbrook, ME, USA	Solitary fibrous tumor and stromal tumors
Ki67 (MIB-1)	Ki-S5	Dako, Carpinteria, CA, USA	Marker of cell proliferation
Pan-cytokeratin	Polyclonal	Dako, Carpinteria, CA, USA	Marker for epithelial differentiation
ALK 1	ALK-01	Ventana Medical Systems, Tuscon, AZ, USA	Inflammatory myofibroblastic tumor
CD21	1F8	Dako, Carpinteria, CA, USA	Dendritic cell sarcoma
S100	Polyclonal	Dako, Carpinteria, CA, USA	Neural tumors (schwannomas)
p53	DO7	Dako, Carpinteria, CA, USA	Tumor suppressor gene
IgG4	HP6025	Zymed, San Francisco, CA, USA	IgG4-positive plasma cells

Results

Clinical and Radiographic Features

Eleven patients were treated for FIBS of the extrahepatic bile duct between 1998 and 2007. The median age of the patients was 53 years (range 29–68) with seven females and four males (Table 2). All patients presented with vague abdominal pain, jaundice, light-colored stools, and dark urine. Four patients had coexisting autoimmune diseases at the time of diagnosis, while two patients were diagnosed with an autoimmune disease postoperatively. The presenting serum CEA values were all within normal limits (0.4–2.0 ng/ml), whereas Ca 19-9 was elevated (>37 U/ml) in three patients and ranged from 6 to 1,085 (median=33 U/ml).

Computed tomography (CT) was performed in all patients; radiographic features of bile duct cancer were seen in eight patients (Table 3, Fig. 1). Four patients had a definable mass associated with the extrapancreatic bile duct, while four patients had soft tissue infiltrating the porta hepatis, five had abnormal-appearing hilar lymph nodes, and two had vascular encasement or occlusion of the hepatic artery and/or portal vein. Only one patient had gallstones; however, five patients had undergone prior cholecystectomy. Among the five patients with prior cholecystectomy, no relationship was established with timing of presentation or location of hemoclips. No additional clips were noted at surgical exploration which might have indicated an anatomically challenging prior procedure nor were any clips noted to be in close proximity to the presenting stricture. The preoperative CT scans showed residual biliary ductal dilatation following stenting in eight patients. The sensitivity and specificity of these CT findings may have been compromised by prior endoscopic manipulation of the

Table 2 Clinical Presentation and Outcome of Patients with Fibroinflammatory Biliary Stricture

Patient	Age (years old)/Gender	Autoimmune Disease	CA 19-9 (U/ml)	CEA (ng/ml)	Procedure	IgG4 stain (cells/HPF)	Medical Treatment	Status
1	51 F		34.3	2.0	BDR	>10, ductocentric	Immunosuppression	Dead; Adenocarcinoma[a]
2	68 M	Ulcerative Colitis	88.9	1.3	BDR + HR	>50, diffuse	Immunosuppression	Alive; NED
3	63 M		16.1	0.79	BDR + HR	Rare	None	Alive; NED
4	49 F	Scleroderma; Raynaud's	6.1	N/A	BDR + HR	Negative	None	Dead; NED
5	48 F	Rheumatoid arthritis	39.4	<0.5	Biopsy; then BDR 10 months later	Rare	Immunosuppression	Alive; NED
6	67 M	Crohn's Disease	1085	1.7	BDR + HR	>10	Immunosuppression	Dead; NED
7	29 F		N/A	N/A	Biopsy	N/A	None	Lost to follow up
8	36 F	Reidel's sclerosing thyroiditis	26	0.5	Biopsy	Rare	Immunosuppression	Alive; NED
9	42 F		32.5	1.1	BDR + HR	Rare	None	Alive; NED
10	64 F	Temporal Arteritis	N/A	N/A	BDR	>10, ductocentric	Immunosuppression	Alive; NED
11	68 M		6.3	1.0	BDR	>10	None	Alive; NED

BDR bile duct resection, *HR* hepatic resection, *NED* no evidence of disease

[a] Died of adenocarcinoma of unknown primary metastatic to the liver 12 months after bile duct resection without evidence of recurrent bile duct stricture

Table 3 CT and ERC Findings in Patients Diagnosed with FIBS

Patient	Biliary Dilatation	Extrapancreatic BD mass	Soft tissue infiltration of porta	Hilar LAD	Hepatic Artery/ Portal Vein Involvement	Gallstones	ERC dominant stricture of bile duct	Lobar atrophy
1.	No	No	No	Yes	No	No	Yes	No
2.	Yes	No	Yes	Yes	No	No	Yes	No
3.	Yes	No	No	No	No	No	Yes	Yes
4.	Yes	Yes (1.2×1.6 cm)	Yes	No	No	No	Yes	No
5.	No	No	No	No	No	Yes	Yes	No
6.	Yes	Yes (3.8×2.9 cm)	Yes	Yes	Yes (hepatic artery encasement)	s/p cholecystectomy	Yes	No
7.	Yes	Yes (3.4×3 cm)	Yes	No	No	s/p cholecystectomy	Yes	No
8.	Yes	No	No	Yes	No	s/p cholecystectomy	Yes	No
9.	Yes	No	No	Yes	Yes (Right portal vein thrombus)	No	Yes	Yes
10.	No	No	No	No	No	s/p cholecystectomy	Yes	No
11.	Yes	Yes (13 mmx9 mm)	No	No	No	s/p cholecystectomy	Yes	No

biliary tree and biliary stenting. Endoscopic retrograde cholangiography (ERC) revealed a dominant stricture of the extrapancreatic bile duct in all patients, and endoscopic biliary stents were inserted to relieve obstructive jaundice in all patients (Fig. 2). Brush cytology was performed in ten of 11 patients, and all were negative for malignancy. Five specimens showed atypical epithelial cells, while five had reactive or degenerated epithelial cells (two with scant acute and chronic inflammation).

Operative Management and Follow-up

All patients with FIBS underwent surgical exploration with the intention of resecting bile duct cancer (Table 2). Operative findings were generally consistent with the preoperative suspicion of cholangiocarcinoma. As a result, nine patients underwent resection of the extrahepatic bile duct, including five concurrent major hepatic resections for definitive tumor clearance. Two patients were found to have unresectable involvement of the porta hepatis and underwent biopsy of the bile duct to establish a tissue diagnosis. No discrete pancreatic masses were identified. Frozen section examination was suspicious for malignancy in only one case. The remaining cases were classified intraoperatively as benign and/or inflammatory. Operative exploration of patients with FIBS demonstrated the following common features: the bile duct was firm in all cases; the infiltrative process originated in the mid common bile duct in six patients and the hilum in five. Eight patients had

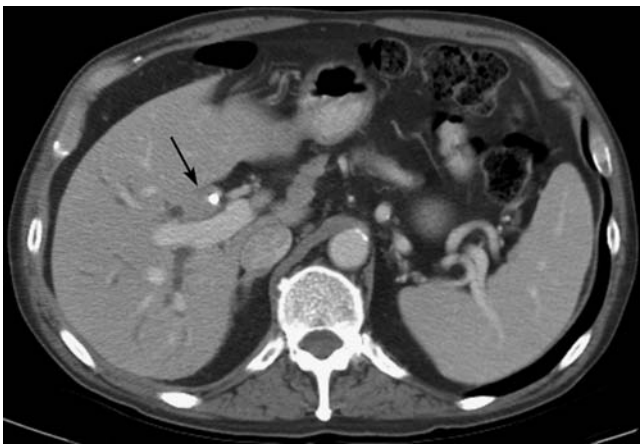

Figure 1 Representative hepatic phase CT shows compressed right portal vein and infiltrating tumor in an inflammatory myofibroblastic biliary stricture case presumed to be Klatskin's tumor preoperatively.

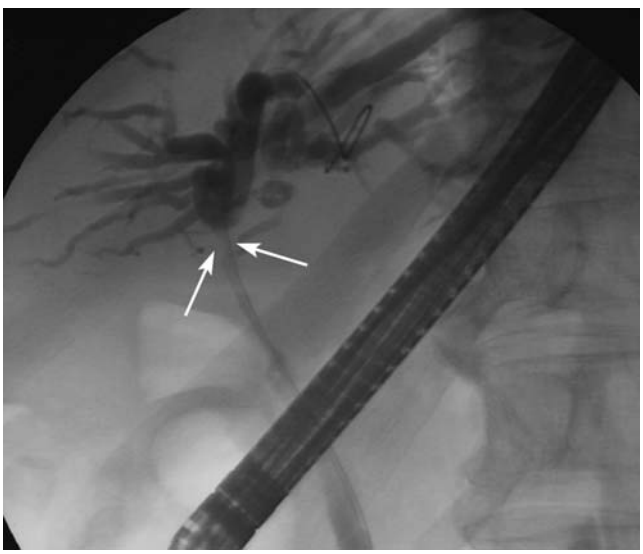

Figure 2 ERCP during stent placement shows focal hilar biliary stricture.

identifiable masses associated with the bile duct, and three were suspected of having malignant lymphadenopathy. The mass infiltrated the transverse mesocolon in one case and appeared to encase the portal vasculature in two cases.

Postoperatively, six patients received immunosuppression with azathioprine and/or tapered dose prednisone based on the final pathologic impression of an inflammatory process/autoimmune disease. After 41 month median follow-up (range 15–58 months), ten patients were free of recurrent FIBS, and one was lost to follow-up. Two patients died without evidence of malignancy. A third patient died 12 months after bile duct resection due to bilobar hepatic metastases caused by adenocarcinoma of unknown primary. Re-review of the original cases' pathologic material did not identify any evidence of malignancy in the resected bile duct. It is possible that the malignant biliary stricture was missed on the initial bile duct resection; however, the presenting clinical picture of jaundice resolved for 1 year postoperatively, and the bile duct resection specimen did contain a dominant stricture.

Pathologic and Immunohistochemical Characterization

Routine histology of the bile duct lesions exhibited varying degrees of fibrosis in all cases with a mild to marked inflammatory infiltrate (Table 4). Five lesions (45%) demonstrated a lymphocytic and plasma cell infiltrate centered around the bile duct (Fig. 3a, b). Four additional lesions (36%) showed an inflammatory cell infiltrate containing either scattered eosinophils or prominent lymphoid follicles with germinal centers. The mixed fibroinflammatory process spread beyond the porta hepatis in four cases (36%) and involved the peripancreatic fat, mesentery, liver, and colonic serosa (Fig. 3c).

To investigate the biology of these lesions, immunohistochemistry was used to probe for markers of cell proliferation, neoplastic transformation, and differentiation including Ki67, pancytokeratin, p53, smooth muscle actin, CD34, ALK1, CD21, S100, and IgG4 (Table 4). All lesions except one expressed smooth muscle actin, consistent with smooth muscle or myoepithelial (myofibroblastic) origin. Rare ki67 positivity among the stromal cells indicated a low proliferative index and did not support neoplastic transformation of a mesenchymal tumor. The focal CD34 labeling was interpreted as nonspecific antibody binding rather than evidence for a solitary fibrous tumor or stromal tumor. Conversely, none of the lesions expressed cytokeratins or p53 to indicate an epithelial-derived carcinoma like bile duct cancer. The absence of ALK1, CD21, and S100 expression excluded the remaining tumors in the differen-

Table 4 Pathological Features of Fibroinflammatory Biliary Strictures

Pt	Morphologic Features	IgG4 stain (cells/HPF)	SMA	CD34	Ki67	Pancytokeratin, ALK1, CD21, S100, p53	DELTE THIS COLUMN Pathologic Impression
1	Dense periductal fibrosis with mild LP inflammation and scattered eosinophils	>10, ductocentric	Neg	Pos (focal)	Neg	Neg	AIC/NFIP
2	Marked fibroinflammatory process with periductal and perineural LP inflammation	>50, diffuse	Pos	Pos (focal)	Neg	Neg	AIC
3	Focally marked ductocentric LP inflammation with fibrosis; polypoid granulation tissue within duct	Rare	Pos	Pos (focal)	Neg	Neg	NFIP
4	Mixed fibroinflammatory process	Negative	Pos	Pos (focal)	Low	Neg	IMT
5	Marked fibroinflammatory process involving mesentery and liver	Rare	Pos	Pos (focal)	Low	Neg	SM
6	Dense fibrosis with periductal, perivenular and perineural LP inflammation with scattered eosinophils	>10	Pos	Pos (focal)	Neg	Neg	AIC
7	Mixed fibroinflammatory process	N/A	N/A	N/A	N/A	S100 Neg	IMT
8	Fibroinflammatory process of mesentery, colonic serosa and peripancreatic fat	Rare	Pos	Pos (focal)	Low	Neg	SM/RP
9	Dense fibrosis with old (fibrotic) venous thrombi	Rare	Pos	Pos (focal)	Low	Neg	NFIP
10	Marked ductocentric LP inflammation with fibrosis	>10, ductocentric	Pos	Pos (focal)	Low	Neg	AIC/NFIP
11	Marked ductocentric LP inflammation with fibrosis	>10	Pos	N/A	N/A	ALK1, S100 Neg	???

Pt patient, *HPF* high-power field, *LP* lymphoplasmacytic, *SMA* smooth muscle actin, *NFIP* nonspecific fibroinflammatory process, *AIC* autoimmune cholangitis, *SM* sclerosing mesenteritis, *RP* retroperitoneal fibrosis, *IMT* inflammatory myofibroblastic tumor

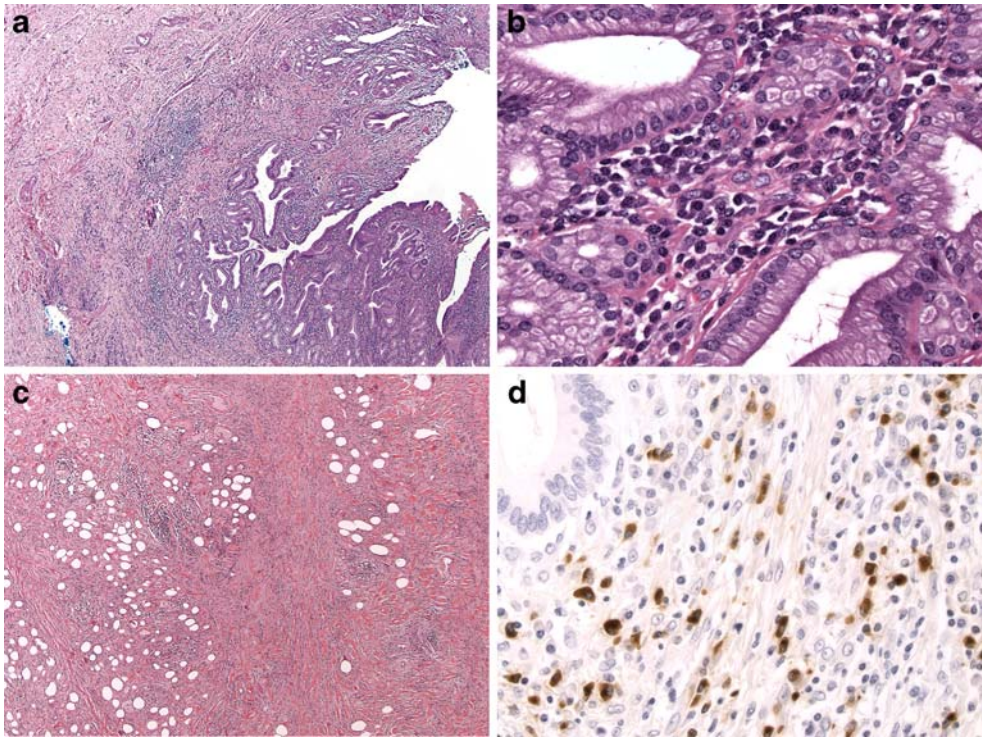

Figure 3 Pathologic findings. In five of the cases, the chronic inflammatory infiltrate was centered around the bile duct and its branches. **a** In this example, there is a moderate amount of chronic inflammation present beneath the bile duct epithelium and increased periductal fibrosis (×40); **b** At higher magnification, numerous plasma cells are present within the inflammatory infiltrate (×400). In two cases, the fibroinflammtory process was predominantly fibrotic, more diffuse, and involved periductal soft tissue and fat, as well as other organs, consistent with sclerosing mesenteritis. **c** In this example, dense fibrosis and short fibrotic bands are admixed with chronic inflammatory cells and the fibroinflammatory process infiltrates adipose tissue (the bile duct is not present in this field) (×40). **d** Representative example of an IgG4-postive case showing numerous IgG4-positive cells beneath the ductal epithelium and within the wall of the bile duct (IgG4 immunohistochemical stain), consistent with IgG4-related sclerosing cholangitis (×400).

tial diagnosis of neoplastic bile duct stricture, which includes spindle cell carcinoma, dendritic cell sarcoma, and neural tumors arising from the bile duct.

Since fibroinflammatory processes can be caused by a systemic IgG4-related sclerosing disease, we probed the available tissue blocks for evidence of IgG4-secreting plasma cells.[12,13] Five tumors had >10 IgG4-positive cells per hpf (Fig. 3d), all of which had ductocentric lymphoplasmacytic inflammation indicating IgG4-related sclerosing cholangitis (FIBS + IgG4). The remaining six cases did not contain IgG4-positive plasma cells but possessed a similar pattern of inflammation and fibrosis (FIBS-IgG4).

Discussion

This report is the first detailed characterization of extrapancreatic bile duct stricture caused by a benign lesion that we designated "fibroinflammatory biliary stricture." FIBS patients presented with signs and symptoms typical of bile duct cancer including vague abdominal pain and obstructive jaundice. The median age at the time of diagnosis was 53 years with a 2:1 female preponderance. Six of eleven patients had coexisting autoimmune diseases. Serum CEA levels were normal in all patients, while Ca19-9 exceeded 100 U/ml in only one patient (11%). ERC demonstrated a dominant stricture of the extrapancreatic bile duct in all patients, while brush cytologies were benign or inconclusive. Operative findings included a thickened bile duct with an infiltrating mass, the suspicion of malignant adenopathy, encasement or occlusion of the portal vasculature, and involvement of adjacent organs. Although these features are characteristic of cholangiocarcinoma, malignancy was not identified on any intraoperative frozen sections with the exception of one sample regarded as suspicious. The final pathologic diagnosis of FIBS required immunohistochemical analysis of resected tissue. Six patients received postoperative immunosuppression, four on the basis of IgG4-positive plasma cells suggesting a component of IgG4-related sclerosing cholangitis. After 41 months median follow-up, all patients remained free of disease. Three died of unrelated causes of which one died of bilobar hepatic metastases from adenocarcinoma of unknown primary.

We designated these diverse fibroinflammatory lesions "FIBS" on the basis of a non-neoplastic pattern of tumor

marker expression and low proliferative index. By definition, FIBS is a subset of benign bile duct tumors unrelated to autoimmune pancreatitis, primary sclerosing cholangitis, cholangiocarcinoma, prior bile duct injury or repair, and choledocholithiasis. Histologically, the FIBS lesion is composed of spindle cells, fibroblasts, and myoblasts with varying degrees of fibrosis and lymphoplasmacytic inflammatory infiltrate.[19] If a defined mass was present, it was firm and lacked a capsule. By comparison with patients having bile duct cancer, FIBS patients presented at a significantly younger age, 53 vs. 69 years old, were more likely to be female, and had a high incidence of coexisting autoimmune diseases (54%).[20] No FIBS patients had a serum CEA level >2.2 ng/ml unlike a recently published cohort of cholangiocarcinoma patients, 69% of whom had serum CEA >2.2 ng/ml.[21] Only one FIBS patient (11%) had a serum Ca 19-9 level exceeding 100 U/ml, a diagnostic threshold for cholangiocarcinoma which has 68% positive predictive value. Finally, none of the FIBS patients had positive endoscopic retrograde cholangiopancreatography (ERCP) brush cytology unlike a cohort of patients with surgically confirmed cholangiocarcinoma, 31% of whom had positive cytology specimens.[22]

Inflammatory pseudotumors were originally described in the lung but have also been reported in a variety of extrapulmonary sites including the liver, omentum, ureters, lymph nodes.[23] The varying degrees of fibrosis and inflammatory infiltration associated with FIBS is responsible for confusing nomenclature that includes inflammatory pseudotumor, inflammatory myofibroblastic tumor (IMFT), postinflammatory tumor, idiopathic benign focal stenosis, and nonspecific inflammatory process.[6,24–28] The term "inflammatory pseudotumor" has been used to describe nonneoplastic lesions of the viscera and soft tissue, and unfortunately, the same term has been applied to some true inflammatory neoplasms like dendritic cell tumors[29] and myofibroblastic tumors[30] including inflammatory fibrosarcoma.[31] Given such diverse histologies, the biological behavior of inflammatory pseudotumor is actively debated in the literature,[31,32] although the term is now most commonly used to describe a "benign nonmetastasizing proliferation of myofibroblasts with potential for recurrence and persistent local growth."[32] Long-term follow-up of 38 patients undergoing surgical resection for histopathologically similar inflammatory tumors of the retroperitoneum and mesentery demonstrated a 37% local recurrence rate as well as an 11% rate of distant metastasis. The term "inflammatory fibrosarcoma" was applied to these lesions because of their aggressive behavior.[31] Cytogenetic abnormalities discovered in inflammatory lesions of the mesentery, liver, lung, and soft tissue lesion have been cited as potential evidence of malignant behavior.[33–36] Conversely, a series of 84 extrapulmonary inflammatory tumors has been reported with a 15% rate of intra-abdominal recurrence but no distant metastases.

The malignant potential of FIBS in the extrapancreatic bile duct remains unknown due to the rarity of this disease. These lesions can masquerade as cholangiocarcinoma due to reactive epithelial hyperplasia, perineural extension, and involvement of vascular structures and adjacent organs. These features can be particularly misleading when examining intraoperative frozen sections due to the limitations of sample processing and the time constraints of immunohistochemistry. Nonetheless, the absence of cytokeratin, CD34, CD21, p53, and Ki67 expression among FIBS patients significantly reduced the likelihood of a neoplastic diagnosis. Although the development of liver metastases in one of our patients raised the possibility of missed cholangiocarcinoma, metastatic adenocarcinoma is not consistent with malignant degeneration of a benign fibrous inflammatory tumor because of published data indicating fibrosarcoma histology in such metastatic deposits.[31]

The pathological characteristics of FIBS resemble inflammatory pseudotumors and are plasma-cell predominant. Immunohistochemistry may demonstrate muscle-specific actin and smooth muscle actin expression consistent with myofibroblasts as well as positivity for anaplastic lymphoma kinase (ALK), an oncogenic tyrosine kinase.[37] Though IgG4-positive infiltrates have been identified in the IgG4-related sclerosing diseases of autoimmune sclerosing cholangitis and autoimmune pancreatitis,[38] there is little published data linking an IgG4-positive sclerosing process with fibrous inflammatory strictures/tumors of the extrahepatic bile duct.

We subclassified FIBS on the basis of the IgG4 status of the dense lymphoplasmacytic infiltrate as strictures with autoimmune cholangitis (FIBS + AC).[39,40] Although primary sclerosing cholangitis is also associated with autoimmune diseases, the clinical features of FIBS are distinct from PSC. No patient in this series exhibited either the characteristic onion-skinning appearance of PSC or biliary cirrhosis on final pathology. PSC patients show a slow progression of disease over a 5- to 10-year period compared to those with inflammatory myofibroblastic tumors who have a more aggressive natural history and a focal stricture which generally regresses following immunosuppression.[41–43,49]

Although the etiology of FIBS is unclear, recent data suggest that IgG4-related sclerosing pancreatititis and cholangitis are inflammatory disorders caused by activation of T helper 2 (Th2) cells and T regulatory cells. Real-time PCR and immunohistochemistry of human tissues demonstrate overproduction of Th2 cells and regulatory cytokines, such as interleukin-10, interferon-γ, and TGF-β, which precede IgG4 class switching and fibroplasia in autoimmune pancreatitis.[44] Additional stimuli for cytokine overproduction may include biliary tract infection. Case reports

of hepatic inflammatory tumors demonstrate parasitic fragments and bacteria, and there is speculation that Ebstein–Barr virus (EBV) or dendritic cells may be responsible for FIBS.[45,46] Recent data suggest a link between hepatic stellate cells and the formation of an inflammatory stricture. Cytokines cause hepatic stellate cells to acquire myofibroblast-like features and produce extracellular matrix during liver fibrogenesis.[47] We speculate that the myofibroblasts observed in FIBS are derived from activated stellate cells adjacent to the bile ducts which cause fibrogenesis and extracellular matrix production resulting in stricture formation. By inhibiting lymphocyte activation and cytokine production, immunosuppression may prevent the myofibroblast transformation of stellate cells and resulting fibrogenesis. Because platelet-derived growth factor mediates cytokine-induced signaling and proliferation of stellate cells, anti-PDGF therapy may offer a targeted approach to FIBS which will ameliorate the phenotype of this disease and prevent recurrence after resection.[47]

Given the potential morbidity of hepatobiliary resection for suspected bile duct cancer, FIBS should be entertained in the differential diagnosis of bile duct stricture in relatively younger patients with coexisting autoimmune diseases and normal serum tumor marker levels. Negative or atypical preoperative brush cytology has insufficient specificity to exclude cholangiocarcinoma in the presence of a biliary stent, and intraoperative findings may suggest locally advanced cancer, for which nonsurgical palliation has a dismal outcome. Until new methods of detecting cholangiocarcinoma are developed, surgical resection will remain the mainstay of diagnosis and treatment for presumed malignant biliary strictures. Recent data indicate that major postoperative complications develop in 32% of patients treated for benign biliary stricture with long-term sequelae of surgery developing in a further 36% of surgical patients.[6] The clinical suspicion of FIBS may significantly alter intraoperative decision-making if frozen sections are negative for malignancy and a conservative surgical approach is warranted to permit a short-course of postoperative corticosteroid treatment.[48,49] The importance of ancillary studies and extensive pathologic evaluation remains paramount to rule out true biliary malignancies. The combination of molecular pathology, including loss of heterozygosity analysis and gene sequencing for k-ras mutations, and endoscopically directed forceps biopsy of the bile duct lesion (Spyglass™) are promising techniques which may be applied to the preoperative diagnosis of FIBS.[1,4] The testing for elevated IgG4 in the serum of patients and increased numbers of IgG4+ cells in preoperative tissue biopsies hold the potential to render the diagnosis preoperatively in the future. Given the rare nature of this lesion, the long-term prognosis and risk of recurrence following surgical treatment for FIBS remains a subject of active scrutiny.

We acknowledge that this is a rare disorder, and current management remains surgical resection given that most cases will represent cholangiocarcinoma. Biliary brushings and tumor markers are important elements for consideration in all biliary stricture cases. Currently, we continue to address resectable lesions operatively and have found that this diagnosis should be considered with a patient with normal tumor markers, autoimmune disease, young in age, and perhaps female presents with a dominant stricture. The inflammatory elements of this stricture and its common occurrence with autoimmune disease support the logic of immunosuppression, and patients are typically followed with yearly contrast imaging (CT/MRI).

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References

1. Chen YK, Pleskow DK. SpyGlass single-operator peroral cholangiopancreatoscopy system for the diagnosis and therapy of bile-duct disorders: a clinical feasibility study (with video). Gastrointest Endosc 2007;65(6):832–841. doi:10.1016/j.gie.2007.01.025.
2. Nishiyama Y, Yamamoto Y et al. Comparison of early and delayed FDG PET for evaluation of biliary stricture. Nucl Med Commun 2007;28(12):914–919.
3. Kim JY, Lee JM et al. Contrast-enhanced MRI combined with MR cholangiopancreatography for the evaluation of patients with biliary strictures: differentiation of malignant from benign bile duct strictures. J Magn Reson Imaging 2007;26 (2):304–312.
4. Khalid A, Pal R, Sasatomi E, Swalsky P, Slivka A, Whitcomb D, Finkelstein S. Use of microsatellite marker loss of heterozygosity in accurate diagnosis of pancreaticobiliary malignancy from brush cytology samples. GUT 2004;53:1860–1865.
5. Hadjis NS, Collier NA, Blumgart LH. Malignant masquerade at the hilum of the liver. Br J Surg 1985;72(8):659–661. Aug.
6. Corvera CU, Blumgart LH, Darvishian F, Klimstra DS, DeMatteo R, Fong Y, D'Angelica M, Jarnagin WR. Clinical and pathologic features of proximal biliary strictures masquerading as hilar cholangiocarcinoma. J Am Coll Surg 2005;201(6):862–869. Epub 2005 Oct 13, Dec.
7. Verbeek PC, van Leeuwen DJ, de Wit LT, Reeders JWAJ, Smits NJ, Bosma A, Huibregtse K, van der Heyde MN. Benign fibrosing disease at the hepatic confluence mimicking Klatskin tumors. Surgery 1992;112:866–870.
8. Wetter LA, Ring EJ, Pellegrini CA, Way LW. Differential diagnosis of Sclerosing cholangiocarcinomas of the common hepatic duct (Klatskin tumors). Am J Surg 1991;161:57–63.
9. Standfield NJ, Salisbury JR, Howard ER. Benign non-traumatic inflammatory strictures of the extrahepatic biliary system. Br J Surg 1989;76:849–852.
10. Kram MT, May LD, Cooperman A et al. Lymphoplasmacytic sclerosing pancreatitis and cholangitis. Gastrointest Endosc 2002;55:588–590.
11. Hawegawa K, Kubota K, Komatsu Y et al. Mass-forming inflammatory periductal fibrosis mimicking hilar bile duct carcinoma. Hepatogastroenterology 2000;47:1230–1233.

12. Graham SM, Barwick K, Cahow CE, Baker CC. Cholangitis glandularis proliferans. A histologic variant of primary sclerosing cholangitis with distinctive clinical and pathological features. J Clin Gastroenterol 1988;10:579–583.
13. Krukowski ZH, McPhie JL et al. Proliferative cholangitis (cholangitis glandularis proliferans). Br J Surg 1983;70(3):166–171.
14. Ozeki Y, Matsubara N et al. [Inflammatory tumor of the hepatic hilus mimicking bile duct cancer–report of a case]. Nippon Geka Gakkai Zasshi 1993;94(9):1064–1067.
15. Hamdi I, Marzouk I et al. [Inflammatory pseudotumor of the spleen and radiopathologic correlation]. J Radiol 2006;87(12 Pt 1):1894–1896.
16. Locke JE, Choti MA et al. Inflammatory pseudotumor of the liver. J Hepatobiliary Pancreat Surg 2005;12(4):314–316.
17. Dehner LP. Extrapulmonary inflammatory myofibroblastic tumor: the inflammatory pseudotumor as another expression of the fibrohistiocytic complex (Abstract). Lab Invest 1986;54:15. [typically, abstracts are not cited] [a better older reference might be: Dehner LP.
18. Zhang L, Notohara K, Levy MJ, Chari ST, Smyrk TC. IgG4-positive plasma cell infiltration in the diagnosis of autoimmune pancreatitis. Mod Pathol 2006, Sept 15.
19. Palazzo JP, Chang CD. Inflammatory pseudotumor of the pancreas. Histopathology 1993;23:86–91.
20. Jepsen P, Vilstrup H et al. Incidence rates of intra- and extrahepatic cholangiocarcinomas in Denmark from 1978 through 2002. J Natl Cancer Inst 2007;99(11):895–897.
21. Qin XL, Wang ZR et al. Utility of serum CA19-9 in diagnosis of cholangiocarcinoma: in comparison with CEA. World J Gastroenterol 2004;10(3):427–432.
22. Are C, Gonen M et al. Differential diagnosis of proximal biliary obstruction. Surgery 2006;140(5):756–763.
23. Nonmura A, Minato H, Shimizu K, Kadoya M, Matsui O. Hepatic hilar inflammatory pseudotumor mimicking cholangiocarcinoma with cholangitis and phlebitis: a variant of primary sclerosing cholangitis? Pathol Res Pract 1997;193:519–525.
24. Bahadori M, Liebow AA. Plasma cell granuloma of the lung. Cancer 1973;31:191–208.
25. Gonzalez-Crussi F, deMello DE, Sotelo-Avilla C. Omental mesenteric myxoid hamartomas: infantile lesions simulating malignant tumors. Am J Surg Pathol 1983;7(6):567–578.
26. Pisciotto PT, Gray GF, Miller DR. Abdominal plasma cell pseudotumor. J Pediatr 1978;93:628–630.
27. Tang TT, Segura AD, Oechler MD et al. Inflammatory myofibrohistiocytic proliferation simulating sarcoma in children. Cancer 1990;65:1626–1634.
28. Umiker WO, Iverson L. Post inflammatory tumors of the lung: report of four cases simulating xanthoma, fibroma or plasma cell tumor. J Thorac Surg 1954;28:55–62.
29. Shek TWH, Ho FCS, Ng IOC et al. Follicular dendritic cell tumor of the liver. Evidence for an Ebstein-Barr virus related proliferation of follicular dendritic cells. Am J Surg Pathol 1996;20 (3):313–324.
30. Fukushima N, Suzuki M et al. A case of inflammatory pseudotumour of the common bile duct. Virchows Arch 1997;431(3):219–224.
31. Meis JM, Enzinger FM. Inflammatory fibrosarcoma of the mesentery and retroperitoneum. A tumor closely simulating inflammatory pseudotumor. Am J Surg Pathol 1991;15:1146–1156.
32. Coffin Cm, Watterson J, Priest JR et al. Extrapulmonary inflammatory myofibroblastic tumor (inflammatory pseudotumor). A clinicopathological and immunohistochemical study of 84 cases. Am J Surg Pathol 1995;19(8):859–872.
33. Donner L, Tompler R, White R. Progression of inflammatory myofibroblastic tumor (inflammatory pseudotumor) of soft tissue into sarcoma after several recurrences. Hum Pathol 1996; 27:1096–1098.
34. Spencer H. The pulmonary plasma cell/histiocytoma complex. Histopathology 1984;8:90316.
35. Treissman SP, Gillis DA, Lee CLY et al. Omental–mesenteric inflammatory pseudotumor. Cytogenetic demonstration of genetic changes and monclonality in one tumor. Cancer 1994;73:1433–1437.
36. Zavaglia C, Barberis M, Gelosa F. Inflammatory pseudotumor of the liver with malignant transformation. Report of two cases. Ital J Gastroenterol 1996;28(3):152–159.
37. Chiarle R, Voena C et al. The anaplastic lymphoma kinase in the pathogenesis of cancer. Nat Rev Cancer 2008;8(1):11–23.
38. Zen Y, Harada K, Sasaki M, Sato Y, Tsuneyama K, Haratake J, Kurumaya H, Katayanagi K, Masuda S, Niwa H, Morimoto H, Miwa A, Uchiyama A, Portmann BC, Nakanuma Y. IgG4-related sclerosing cholangitis with and without hepatic inflammatory pseudotumor, and sclerosing pancreatitis-associated sclerosing cholangitis: do they belong to a spectrum of sclerosing pancreatitis. Am J Surg Pathol 2004;28(9):1193–1203. Sep.
39. Hamano H, Kawa S, Uehara T, Ochi Y, Takayama M, Komatsu K, Muraki T, Umino J, Kiyosawa K, Miyagawa S. Immunoglobulin G4-related lymphoplasmacytic sclerosing cholangitis that mimics infiltrating hilar cholangiocarcinoma: part of a spectrum of autoimmune pancreatitis. Gastrointest Endosc 2005;62(1):152–157. Jul.
40. Kamisawa T, Nakajima H, Egawa N, Funata N, Tsuruta K, Okamoto A. IgG4-related sclerosing disease incorporating sclerosing pancreatitis, cholangitis, sialadenitis and retroperitoneal fibrosis with lymphadenopathy. Pancreatology 2006;6(1–2):132–137.
41. Stathopoulos G, Nourmand AD, Blackstone M, Anderson D, Baker AL. Rapidly progressive sclerosing cholangitis following surgical treatment of pancreatic pseudotumor. J Clin Gastroenterol 1995;21(2):143–148.
42. Weisner RH, Grambsch PM, Dickson ER et al. Primary sclerosing cholangitis: natural history, prognostic factors and survival analysis. Hepatology 1989;10:430–436.
43. Knox T, Kaplan M. A double-blind controlled trial of oral-pulse methotrexate therapy in the treatment of primary sclerosing cholangitis. Gastroenterology 1994;106:494–499.
44. Zen Y, Fujii T et al. Th2 and regulatory immune reactions are increased in immunoglobin G4-related sclerosing pancreatitis and cholangitis. Hepatology 2007;45(6):1538–1546.
45. Arber A, Kamel OW, Van de Rijn M et al. Frequent presence of Ebstein–Barr virus in inflammatory pseudotumor. Hum Pathol 1995;26:1093–1098.
46. Selves J, Meggetto F, Bousset P et al. Inflammatory pseudotumor of the liver. Evidence for follicular dendritic reticulum cell proliferation associated with clonal Epstein–Barr virus. Am J Surg Pathol 1996;20:747–753.
47. Borkham-Kamphorst E, Stoll D et al. Inhibitory effect of soluble PDGF-beta receptor in culture-activated hepatic stellate cells. Biochem Biophys Res Commun 2004;317(2):451–462.
48. Wakabayashi T, Kawaura Y et al. Long-term prognosis of duct-narrowing chronic pancreatitis: strategy for steroid treatment. Pancreas 2005;30(1):31–39.
49. Nishino T, Toki F et al. Long-term outcome of autoimmune pancreatitis after oral prednisolone therapy. Intern Med 2006;45 (8):497–501.

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ORIGINAL ARTICLE

A Critical Analysis of the Surgical Management of Early-Stage Gallbladder Cancer in the United States

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Abstract
Background Radical resection is recommended for selected patients with gallbladder (GB) cancer. We sought to determine whether radical resection improves survival for patients with early-stage cancer and to evaluate surgeon compliance with current treatment recommendations.
Patients and methods Patients with stage 0, I, or II GB cancer who underwent surgical resection were identified from the Surveillance, Epidemiology, and End Results (SEER) tumor registry from 1988 through 2004. Patients were classified by surgical procedure performed (simple vs. radical resection) and adjuvant treatment given (radiation therapy [RT] vs. no RT). Unadjusted and adjusted overall survival (OS) and cancer-specific survival (CSS) were compared.
Results Of the 4,631 patients who underwent surgery for early-stage GB cancer from 1988 through 2004, 4,188 (90.4%) underwent cholecystectomy alone and 443 (9.6%) underwent radical surgery including hepatic resection. The proportion of patients having radical surgery for T1b, T2, and T3 cancers was 4.5%, 5.6%, and 16.3%, respectively. For patients with T1b/T2 cancer, radical resection was associated with significant improvement in adjusted CSS ($p=0.01$) and OS ($p=0.03$). For patients with T3 cancers, we noted no improvement in CSS or OS. Survival for patients with node-positive disease (stage 2b) was universally poor and not improved by radical resection. For all patients who underwent radical resection, node negativity, female sex, age <70, low grade, and RT predicted improved CSS and OS.
Conclusions Despite a significant survival advantage for patients with T1b/T2 GB cancer who undergo radical resection, this treatment is significantly underutilized. Ensuring delivery of recommended surgical treatment is vital to improving outcomes for patients with this disease.

Keywords Gallbladder cancer · Radical cholecystectomy · Cholecystectomy · Practice guidelines

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Background

Gallbladder (GB) cancer affects about 9,000 patients in the USA each year. Of these, it is estimated that only 15.1% will survive longer than 5 years after diagnosis.[1] Current National Comprehensive Cancer Network (NCCN) guidelines recommend radical resection of the GB fossa with dissection of the regional lymph nodes as optimal treatment for patients with early-stage GB cancer (i.e., stages 1 through 2b).[2] This group of patients includes those with T tumor invasion extending into the muscularis layer (T1b) or beyond and with no evidence of metastatic disease. These guidelines are based on retrospective data that show a survival benefit in patients who undergo radical resection.[3–7] Although radical resection is typically defined as resection of the GB and at least 2 cm of GB fossa in addition to

dissection of portal lymph nodes, many authors report improved survival with much more aggressive surgeries including bile duct resection, right hepatectomy, central hepatectomy, or extended right hepatectomy.[6] The choice of procedure is typically dictated by the extent of disease at the time of resection, with the ultimate goal of achieving negative margins.

Unfortunately, debate continues regarding appropriate patient selection for radical resection of GB cancer. Most authors agree that patients with early-stage GB cancer (stage 1 or 2) gain a survival benefit from radical resection. Even in this group, however, Wright et al. recently reported that only a very small percentage (4%) of patients with T2 cancers actually undergo the recommended surgery.[8] For patients with node-positive disease, the benefit of radical resection remains unclear. Moreover, most early GB cancers are found incidentally after laparoscopic cholecystectomy, without nodal sampling, so the decision to proceed with radical resection is typically made on the basis of T-stage alone.

Given the rarity of this disease and the inability to randomize patients to potentially less effective treatments (cholecystectomy alone), randomized prospective trials to directly compare cholecystectomy alone and radical resection are impossible. Similarly, most retrospective studies typically have few highly selected patients, spanning long periods of time with comparisons to historical controls. In our study, we used the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database to determine whether patients who underwent radical resection for early-stage GB cancer had any improvement in their overall survival (OS) and cancer-specific survival (CSS), as compared with those who underwent cholecystectomy alone. Our primary aims were (1) to determine the benefit of radical resection over cholecystectomy alone for patients with early-stage GB cancer and (2) to assess compliance with current NCCN recommendations for radical resection.

Methods

This study was given exempt status by the University of Minnesota Institutional Review Board Human Subjects Committee (Protocol #0707E13102). Data on the incidence of GB cancer, survival, treatment modalities, and staging were obtained from the SEER database. The SEER database collects population-based data on incident cancers from 17 registries composed of nine states (Connecticut, Hawaii, Iowa, New Mexico, Utah, Alaska, Kentucky, Louisiana, and New Jersey), six metropolitan areas (San Francisco, Detroit, Seattle, Atlanta, San Jose, Los Angeles), greater California, and rural Georgia. These areas represent about 26% of the US population; data span 1973 through 2004, all de-identified and publically available.

Case Definitions

We restricted our analyses to GB cancer diagnosed in or after 1988 and included patients 16 through 102 years old upon diagnosis. We selected codes to define radical resection as removal of the GB and hepatic resection with or without lymph node dissection. We defined cholecystectomy alone by codes corresponding to removal of the GB with or without dissection of lymph nodes. Excluded from our analysis were patients coded as not receiving surgery and patients who underwent debulking, excisional biopsy, exploratory surgery, cryosurgery, cautery, laser surgery, and nonspecified surgery. Also excluded were patient's classified as having sarcoma or lymphoma, metastatic disease, disease of unknown stage, and any T4 cancers. Thus, our analysis was limited to T1, T2, or T3 cancers. Our final cohort consisted of patients diagnosed with stage 1–2B GB adenocarcinoma (T1b–T3, node positive or negative) who underwent surgical resection (simple or radical cholecystectomy) between 1988 and 2004.

Analyses

For our univariate comparison of patient characteristics and tumor-related features by extent of resection (cholecystectomy alone vs. radical resection), we used the Student *t* test and chi-square test. To test for trends, we used the Cochran–Armitage test. When two or more subcategories of an independent variable were present, we used the most clinically relevant or the most frequent subgroup as a reference category. For each T stage, we calculated rates and trends by type of surgery and by presence or absence of RT. We measured CSS by censoring for noncancer-related deaths and for persons alive at follow-up. To measure 5 years OS and CSS, we used Kaplan–Meier methods and log-rank tests. To predict OS and CSS, we constructed multivariate Cox proportional hazard regression models, while controlling for patient age, race, sex, tumor grade, tumor stage, presence of absence of RT, and cancer registry. Nonsignificant predictors were dropped from the models if parameter estimates remained stable within 10%. p values ≤ 0.05 were considered statistically significant. All statistical analyses were performed using SAS 9.1 software (SAS Institute Inc., Cary, NC, USA).

Results

We identified 4,631 patients who underwent surgery for early-stage GB cancer from 1988 through 2004. Mean age at diagnosis was 71. Women comprised 72.5% of the total cohort. A total of 443 (9.6%) patients underwent radical

resection; 4,188 (90.4%) underwent cholecystectomy alone. The proportion of patients who underwent radical resection for T1b, T2, and T3 cancers was 4.5%, 5.6%, and 16.3%, respectively. Individuals with T3 primary tumors were significantly more likely to receive radical surgery than those with T1b or T2 tumors (both $p=0.0001$). Overall, only 11.3% of potentially operable patients underwent radical resection. Patients <70 years old, nonwhite patients, and individuals with high grade tumors were more likely to undergo radical resection. Sex was not significantly associated with radical resection. Our bivariate analysis showed that patients with unknown stage, unknown lymph node (LN) status, or unknown grade were significantly less likely to undergo radical resection than those with known pathologic diagnosis (all p values <0.05). Table 1 summarizes these findings.

Our initial analysis was performed without considering LN status, in order to replicate typical surgical decision making in which the decision to proceed with radical resection is made following laparoscopic cholecystectomy without nodal evaluation. We therefore initially classified patients by T stage only. Figure 1a–d shows unadjusted survival analysis comparing radical resection to cholecystectomy alone for patients with T1b/T2 cancers. For patients with tumor stage T1b/T2 cancer (node positive or negative), radical resection was associated with a significant improvement in CSS and OS (Fig. 1a). This benefit was also confirmed following multivariate analysis adjusting for patient age, race, sex, tumor grade, tumor stage, presence of absence of RT, and cancer registry (Table 2).

To evaluate the effect of LN metastases on survival, we further stratified patients into node-positive and node-negative groups. As expected, radical resection was associated with a significantly improved CSS and OS survival for T1b/T2 node-negative cancer (Fig. 1b). In unadjusted analysis, for patients with T1b/T2 node-positive cancer, the benefit of radical resection was also associated with a statistically significant improvement in CSS and OS (Fig. 1c); however, this benefit was not statistically significant following multivariate analysis. Patients whose LN's were not evaluated gained no benefit from radical resection (Fig. 1d). Table 2 shows the adjusted hazard ratios and 95% confidence intervals for patients with T1b/T2 cancer by type of surgery (radical resection vs. cholecystectomy alone).

For patients with T3 cancer, when we considered T stage only, CSS and OS did not differ by type of surgery. CSS and OS for stage 2B patients with node-positive cancer was

Table 1 Patient Characteristics

	Total	Cholecystectomy alone	Radical resection	p value[a]
n (%)	4,631	4,188 (90.4)	443 (9.6)	
Age				
Mean	71.0	71.3	68.5	<0.0001
SD	12.9	12.9	12.5	
Range	16–102	16–102	28–95	
Sex				
Male	1,275 (27.5)	1,144 (27.3)	131 (29.6)	
Female	3,356 (72.5)	3,044 (72.7)	312 (70.4)	0.3123
Race				
White	3,711 (80.1)	3,374 (80.6)	337 (76.1)	
Black	364 (7.9)	319 (7.6)	45 (10.2)	0.0404
Other	556 (12.0)	495 (11.8)	61(13.8)	0.1529
Stage				
0	61 (1.3)	58 (1.4)	3 (0.7)	
IA	217 (4.7)	192 (4.6)	25 (5.6)	0.1301
IB	201 (4.3)	177 (4.2)	24 (5.4)	0.1141
IIA	250 (5.4)	173 (4.1)	77(17.4)	<0.0001
IIB	715 (15.4)	596 (14.2)	119 (26.9)	0.0157
Unknown	3,187 (68.8)	2,992 (71.4)	195 (44.0)	<0.0001
Tumor grade				
Low	2,301 (49.7)	2,093 (50.0)	208 (47.0)	
High	1,504 (32.5)	1,322 (31.6)	182 (41.1)	0.0023
Unknown	826 (17.8)	773 (18.5)	53 (12.0)	0.0194
Radiation				
None	3,742 (80.8)	3,426 (81.8)	316 (71.3)	
Beam RT	791 (17.1)	671 (16.0)	120 (27.1)	<0.0001

[a] p values represent comparison of proportions of the variable of interest between radical and cholecystectomy group with respect to reference level

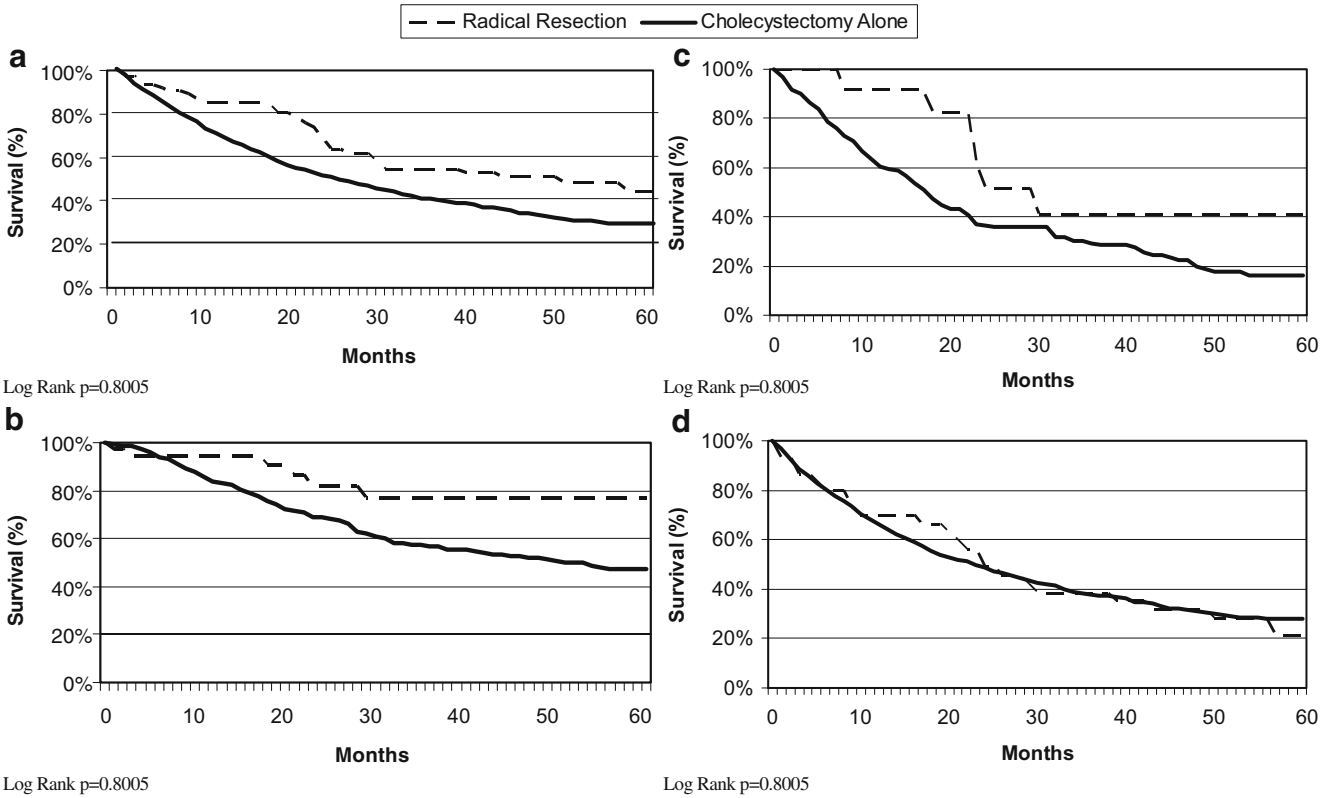


Figure 1 **a** Overall survival in patients with T1b and T2 tumors by type of surgery performed. *chole* cholecystectomy alone, *rad* radical resection. **b** Overall survival in patients with T1b and T2 node negative tumors by type of surgery performed. *chole* cholecystectomy alone, *rad* radical resection. **c** Overall survival in patients with T1b and T2 node positive tumors by type of surgery performed. *chole* cholecystectomy alone, *rad* radical resection. **d** Overall survival in patients with T1b and T2 node unexamined tumors by type of surgery performed. *chole* cholecystectomy alone, *rad* radical resection.

universally poor and was not improved by radical resection (Table 2).

Overall, 28.6% of patients who underwent cholecystectomy alone had at least one LN examined pathologically, compared with 56% of patients who underwent radical resection. LN involvement was most common with T3 cancer (63.7%); however, a significant proportion of patients with T1b/T2 cancer also had LN metastases (T1b, 24.4% and T2, 44.9%).

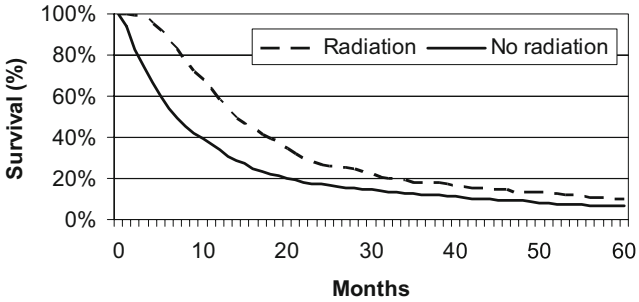
Table 2 Hazard Ratios Comparing Overall Survival Following Radical Resection Compared to Cholecystectomy Alone

Stage	Hazard ratio	95% Confidence interval	*p* value
All T1bT2	0.681	0.485–0.956	0.0265
Node-negative T1b–T2	0.432	0.189–0.986	0.0461
Node-positive T1b–T2	0.439	0.186–1.036	0.0602
All stage 2B	1.114	0.891–1.394	0.3437

[a] Reference group = cholecystectomy alone

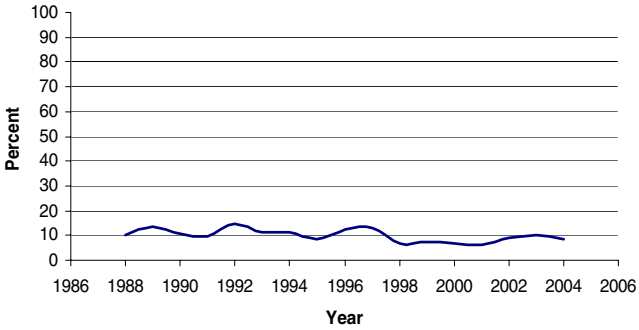
After surgery, 17.1% of patients received RT. RT was more likely for patients who underwent radical resection (27%) than for those who underwent cholecystectomy alone (16%; $p<0.0001$). Similarly, RT was more likely for patients with T3 cancer (23.1%) than for those with T1b/T2 cancer (17.6%; $p<0.0001$). For patients with T3 cancer, RT was associated with improved median OS and CSS independent of the type of surgery performed (both $p<0.0001$). Unadjusted overall survival curves are shown in Fig. 2. RT was less likely for patients with T3 cancer whose LNs were not evaluated (18.9%) than for those with known positive or negative LNs (30.7%; $p<0.0001$).

For all patients who underwent radical resection, node negativity, female sex, age <70, low grade, lower T stage, and RT were associated with improved CSS and OS (Table 3). Given the low rate of radical resection observed for early-stage GB cancer, we also evaluated the trend in radical resection rates since 1988. Figure 3 shows the rates of radical resection for early-stage cancers during our study time period. No significant change was identified.



Log rank p<0.0001

Figure 2 Overall survival in patients with T3 tumors by receipt of radiation.



GB=gallbladder

Figure 3 Trends in radical resection rates for GB cancer 1988–2004. *GB* gallbladder.

Discussion

This study provides population-based validation that radical resection improves survival for patients with early-stage GB cancer, as compared with cholecystectomy alone. Additionally, it highlights the wide gap between surgical guidelines and actual practice trends in this country: A very small proportion of patients actually received the nationally recommended treatment. We identified a subset of patients (those with T1b and T2 cancer) who seemed to derive the most benefit from radical resection (Fig. 1a–d). Unfortunately, only 5% of patients in that subset actually underwent the recommended treatment. In addition, only 56% of patients who underwent radical resection actually had LNs evaluated, even though LN evaluation is an integral part of recommended therapy. Thus, about 98% of patients received inadequate surgical care, a finding that raises concern regarding both surgical technique and pathologic evaluation for patients with GB cancer in the USA. Clearly, current practice is not in keeping with established NCCN guidelines.

We initially classified individuals by T stage alone, in an attempt to accurately reflect the typical clinical scenario of a patient being considered for radical resection after simple cholecystectomy. As expected, most patients with early-stage cancer who underwent cholecystectomy alone did not have LNs evaluated (71.4%). When evaluated solely on T stage, radical resection was associated with improved CSS and OS for patients with T1b/T2 cancer. This finding validates the current typical practice in which the decision to proceed with radical resection is made on T-stage information alone. It is also consistent with previous retrospective reports of improved survival after radical resection for early-stage tumors.[7,9]

In our study, patients with T3 cancer did not have an improvement in survival after radical resection. Even when considering only pathologically node-negative patients, radical resection did not seem to improve CSS or OS for those with T3 cancer. In retrospective review, others have reported that lymphadenectomy alone is an independent predictor of improved survival.[4] It is not clear whether this finding represents a benefit that is due to the surgical procedure alone, or if it is more reflective of patient selection and of improved delivery of care in general. In our study, we found a significant proportion of patients did not have LN evaluated at the time of radical surgery. We also noted that those who do not have LN evaluated are also less likely to receive adjuvant radiation, a therapy which has been shown to be beneficial in this group of patients.

Several other authors have reported a significant benefit to radical resection in patients with T3 cancer.[6,10,11] Those reports were all retrospective reviews and likely included a highly selected patient population. Particularly for those patients with stage 2B cancer (T3, node-positive), the benefit of radical resection is unclear.[5] In our study population, over 60% of patients with T3 cancer had positive LNs identified. For this group of patients, patient selection and a multidisciplinary approach (including RT and chemotherapy) likely play a significant role in improving outcomes.

Finally, we evaluated the role of RT for patients with GB cancer. For those with T1b/T2 cancer, RT did not appear to be associated with a significant improvement in survival

Table 3 Factors Associated with Improved Overall Survival After Radical Resection

	Hazard ratio[a]	Confidence interval	*p* value
Node negativity	0.665	0.483–0.915	0.0123
Female sex	0.686	0.541–0.870	0.0019
Age <70	0.666	0.529–0.839	0.0005
Low grade	0.618	0.487–0.784	<.0001
Receipt of radiation	0.737	0.570–0.951	0.0192

[a] Reference groups: node positive, male sex, age >70, high grade, no radiation

over radical resection alone. For those with T3 cancer, however, RT was associated with a significant improvement in both CSS and OS (Fig. 2): both for patients who underwent cholecystectomy alone and for those who underwent radical resection. These observations are consistent with previously reported data and suggest that RT may be important in the adjuvant treatment of localized GB cancer.[12,13] A total of 31.4% of our patients who underwent radical resection for T3 cancer received RT. As mentioned in our results, patients who did not have their LNs evaluated were less likely to receive RT than those who did, regardless of the type of surgery performed ($p<0.0001$).

Several limitations of the SEER database affect our results. Most notably, we are unable to determine margin status after resection. Particularly for patients with more advanced cancer (T3), this lack of information may lead to bias, making radical resection seem less beneficial than it truly is when negative margins are achieved. In addition, we have no record of adjuvant chemotherapy given. Our inability to identify a survival benefit for patients with T3 cancer who underwent radical resection may be related to our inability to determine which patients received appropriate adjuvant therapy. As noted previously, multiple authors have reported significantly improved survival rates for selected patients with T3 cancer,[6,10,11] a finding we were not able to validate in our study. Other limitations include the retrospective nature of the SEER database and the lack of information regarding patient performance status. Appropriate patient selection (which may be vital to optimizing outcomes) is also impossible to verify through the use of a database like this. Finally, despite large numbers of patients with early-stage GB cancer, so few of them received radical surgery that our power was somewhat limited for analysis.

Our aims in this study were to validate current NCCN guidelines recommending radical resection for early-stage GB cancer as well as to determine current practice trends in the USA. Clearly, radical resection for localized disease does provide a survival benefit over cholecystectomy alone. It is surprising and disappointing that such a small fraction of patients seem to receive appropriate therapy. In addition, this trend has not improved over time, despite widely recognized guidelines (Fig. 3). These findings suggest a significant lack of delivery of care, the reason for which remains unknown. Multiple retrospective reviews and now population-based studies have shown consistently improved CSS and OS for patients who underwent radical resection for GB cancer and the surgical mortality rate at most high-volume institutions is <2% for hepatic resection.

Our study validates the current NCCN guidelines recommending radical resection for early-stage GB cancer, including the necessity for appropriate LN evaluation. At the same time, we found that only a small fraction of patients actually received the recommended therapy. Only with a significant improvement in the quality and delivery of care in this country will we ever improve outcomes for patients with GB cancer.

References

1. Surveillance Epidemiology, End Results (SEER) Program. (http://www.seer.cancer.gov) Limited-Use Data (1973–2004), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2007, based on the November 2006 submission.
2. Benson AB, 3rd, Bekaii-Saab T, Ben-Josef E, et al. Hepatobiliary cancers. Clinical practice guidelines in oncology. J Natl Compr Netw 2006; 4(8):728-50.
3. Fong Y, Malhotra S. Gallbladder cancer: recent advances and current guidelines for surgical therapy. Adv Surg 2001;35:1–20.
4. Shih SP, Schulick RD, Cameron JL, et al. Gallbladder cancer: the role of laparoscopy and radical resection. Ann Surg 2007;245 (6):893–901. doi:10.1097/SLA.0b013e31806beec2.
5. Foster JM, Hoshi H, Gibbs JF, et al. Gallbladder cancer: defining the indications for primary radical resection and radical re-resection. Ann Surg Oncol 2007;14(2):833–840. doi:10.1245/s10434-006-9097-6.
6. Reddy SK, Marroquin CE, Kuo PC, et al. Extended hepatic resection for gallbladder cancer. Am J Surg 2007;194(3):355–361. doi:10.1016/j.amjsurg.2007.02.013.
7. Chan SY, Poon RT, Lo CM, et al. Management of carcinoma of the gallbladder: a single-institution experience in 16 years. J Surg Oncol 2008;97(2):156–164. doi:10.1002/jso.20885.
8. Wright BE, Lee CC, Iddings DM, et al. Management of T2 gallbladder cancer: are practice patterns consistent with national recommendations? Am J Surg 2007;194(6):820–825. discussion 825–6. doi:10.1016/j.amjsurg.2007.08.032.
9. Wise PE, Shi YY, Washington MK, et al. Radical resection improves survival for patients with pT2 gallbladder carcinoma. Am Surg. 2001;67(11):1041–1047.
10. Chijiiwa K, Kai M, Nagano M, et al. Outcome of radical surgery for stage IV gallbladder carcinoma. J Hepatobiliary Pancreat Surg 2007;14(4):345–350. doi:10.1007/s00534-006-1186-1.
11. Kai M, Chijiiwa K, Ohuchida J, et al. A curative resection improves the postoperative survival rate even in patients with advanced gallbladder carcinoma. J Gastrointest Surg 2007;11 (8):1025–1032. doi:10.1007/s11605-007-0181-4.
12. Mojica P, Smith D, Ellenhorn J. Adjuvant radiation therapy is associated with improved survival for gallbladder carcinoma with regional metastatic disease. J Surg Oncol 2007;96(1):8–13. doi:10.1002/jso.20831.
13. Kresl JJ, Schild SE, Henning GT, et al. Adjuvant external beam radiation therapy with concurrent chemotherapy in the management of gallbladder carcinoma. Int J Radiat Oncol Biol Phys 2002;52 (1):167–175. doi:10.1016/S0360-3016(01)01764-3.

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ORIGINAL ARTICLE

Management of ERCP-Related Perforations: Outcomes of Single Institution in Korea

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Abstract
Introduction The aim of this study was to analyze clinicoradiologic findings and treatment outcomes of patients with endoscopic retrograde cholangiopancreatography (ERCP)-related perforations. Between May 2003 and November 2007, 2,247 ERCP procedures with or without sphincterotomy were performed at Ajou University Medical Center, Suwon, Korea, and 20 perforations (0.89%) were identified.
Discussion We retrospectively reviewed medical and surgical records of each patient. Of 18 patients, 11 patients (61.1%) underwent nonsurgical management, and seven patients (38.9%) received surgical management. There were no significant differences in age, gender, and laboratory findings between two groups ($P>0.05$). The hospital stay was significantly longer in the operative group than that of the conservative group ($P<0.05$, respectively). The most common cause of perforation was sphincterotomy ($n=8$) in the conservative group whereas scope itself ($n=6$) in operative group, showing a significant difference between the two groups ($P<0.05$). The retroperitoneal air was most common findings in eight patients (72.7%) of the conservative group, while six (85.7%) patients of the operative group presented with intraperitoneal air, displaying a significant difference in location of air between the two groups ($P<0.05$). Most of sphincterotomy-related perforations were managed nonsurgically. However, the scope-related perforations were usually large and required immediate surgery. Moreover, the delayed operation resulted in a longer hospital stay and high morbidity. Therefore, the selective early surgical intervention is suggested when scope-related perforations are discovered.

Keywords ERCP-related perforation · Nonsurgical management · Surgery

Abbreviations
ERCP Endoscopic retrograde cholangiopancreatography

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Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) with diagnostic and therapeutic intervention is commonly used for management of patients who are suspected of common bile duct stones and obstructive jaundice caused by other lesions. However, the rate of complications, such as pancreatitis, bleeding, cholangitis, and perforation, has been reported to range from 4% to 30%.[1] Furthermore, the rate of mortality after ERCP is 1.0% to 1.5%,[2,3] and the most serious complication after ERCP is perforation: Although ERCP-related perforations are rare with an incidence of 0.35% to 2.1%, it presents high mortality rate up to 25%.[3–5]

For the management of ERCP-related perforations, some authors recommend primary surgical operation[6–8] whereas others promote conservative managemrnt.[2,9,10] Recently, Fatima et al.[11] reported that most perforations (70%)

secondary to periampullary endoscopic interventions can be managed nonoperatively.

Until now, some authors classified ERCP-related perforations according to the site and mechanisms of injury and suggested management guidelines acoordingly.[4,12,13] However, according to this guideline, the classification of perforations has not exactly been defined, and the management of ERCP-related perforation still remains controversial. The aim of this study was to investigate clinicoradiologic findings and treatment outcomes in patients with ERCP-related perforation and to suggest useful treatment modalities for the perforations.

Patients and Method

Between May 2003 and November 2007, 2,247 ERCP procedures with or without sphincterotomy were performed at the Ajou University Medical Center, Suwon, South Korea. Twenty patients (0.89%) who were diagnosed with retro-/intraperitoneal perforations were enrolled in the present study. Among 20 patients, we selected 18 patients excluding two patients who underwent ERCP to diagnose and manage bile leakage after cholecystectomy. Nine patients were male and nine patients were female, whose age ranged from 50 to 77 years. We also divided patients into two groups, depending on whether they underwent surgery or not. We collected consecutive identification of patients who underwent surgical management for ERCP-related perforations. Moreover, we were able to obtain identification of patients, who underwent nonsurgical management, from the ERCP database of the department of gastroenterology. Retrospectively, we reviewed medical and surgical records of each patient and analyzed characteristics of patients, indication for ERCP, findings during ERCP, imaging findings, methods of diagnosis, time to surgery, surgical procedure, and postoperative outcome. Patients with preoperative hyperbilirubinemia [serum bilirubin higher than twice the normal value and/or dilated common bile duct (>8 mm)] underwent endoscopic retrograde cholangiopancreatography. Two gastroenterologists performed the ERCP procedures.

Patients were conservatively managed when the following parameters were present; no peritoneal irritation signs, minimal leak during ERCP, and absence of sepsis or retroperitoneal fluid collections. These patients underwent initial conservative management, which included nasogastric and/or nasobiliary drainage, intravenous fluids, antibiotics, and close monitoring with cooperations of surgical and medical departments. The simple abdomen and chest X-ray was checked immediately after ERCP and daily follow-up until symptoms improved. Abdominal computed tomography (CT) was performed in patients with aggravated abdominal pain during conservative management. The nasogastric tube was removed when patients started to show clear improvement. Diet was resumed usually 1 to 2 days later. Patients were discharged when they were completely asymptomatic and tolerated food intake.

Surgery was performed in patients who presented abdominal irritation sign, intraperitoneal fluid collection on abdominal CT, distinct perforation with retained common bile stones, and deteriorated condition during conservative management. Data were analyzed using the SPSS software package (version 13.0; SPSS, Chicago, IL, USA). Age, hospital stay, and laboratory data were compared between two groups using the Mann–Whitney U test. The mechanism and diagnosis of perforation and site of air in the two groups were compared using a chi-square test or Fisher's exact test where appropriate. To analyze correlations between time to surgery and other factors, a Spearman's correlation was used. P value <0.05 was considered statistically significant.

Results

Of 18 patients, 11 patients (61.1%) underwent conservative management, and seven patients (38.9%) were treated by surgery for perforation after ERCP. The mean follow-up period was 22.9±14.8 months. The demographic and laboratory data for each group are compared in Table 1.

Table 1 Characteristics of Patients

	Conservative group (n=11)	Operative group (n=7)	P value
Age (years)	67.9±8.6	68.7±4.8	>0.05
Gender (M/F)	6/5	3/4	
Hospital stay (days)	13.0±9.8	33.0±23.2	0.032
Diverticulum (%)	5 (45.5)	2 (28.6)	>0.05
Laboratory findings (post-ERCP)			
Total bilirubin (pre.) (IU/dl)	2.1±2.6	3.6±3.6	>0.05
Amylase (IU/dl)	85.6±126.2	431.6±480.2	>0.05
White blood cell count	9,703.6±4,896.4	9,648.5±4,935.9	>0.05
Complications (%)		5 (71.4)	
Mortality (%)		1 (14.3)	

There were no significant differences in age, gender, and laboratory findings between two groups ($P>0.05$). The hospital stay was significantly longer in the operative group than the conservative group ($P<0.05$). The diverticulum was present in five patients of the conservative group and in two patients of the operative group; however, the difference was not significant ($P>0.05$). The diagnosis and indications for ERCP are described in Table 2.

Mechanism and Diagnosis of Perforation

The most common cause of perforation was sphincterotomy in the conservative group ($n=8$), whereas scope itself in the operative group ($n=6$). In the conservative group, there were two scope-related perforations: One had diverticulum and the other had perforation of duodenum. These two patients recovered well without surgery. There was statistically significant difference in the mechanism of perforation between the two groups ($P<0.05$; Table 3).

In the conservative group, the site of perforation included periampullary ($n=7$), posteriomedial duodenum ($n=2$), and diverticulum ($n=2$), and the two diverticulum occupied a periampullary duodenum. In the operative group, the site of perforation was periampullary ($n=1$), lateral duodenum ($n=3$), diverticulum ($n=1$), and jejunum ($n=2$), and the diverticulum occupied a lateral site of 1st duodenum. The difference in the site of perforation was statistically significant between two groups ($P<0.05$; data not shown).

In the conservative group, the perforation of most patients ($n=10$) was identified at the time of ERCP: It was confirmed by findings such as dye leakage and pneumoperitoneum on fluoroscopy. In the operative group, four perforations were detected at the time of ERCP. In remaining three patients, we suspected perforation because of intraperitoneal air on the postprocedural X-ray. An upper gastrointestinal study was not used in all patients. The retroperitoneal air was the most common findings in the conservative group, eight patients (72.7%). On the other hand, six patients (85.7%) of the operative group presented intraperitoneal air, displaying significant difference in the location of air between two groups ($P<0.05$; Table 3).

Table 2 Diagnosis and Indications for ERCP

	Number of patient (%)
Ampullary cancer	2 (11.1)
CBD and GB stone	9 (50)
CBD stone	2 (11.1)
Acute cholangitis	1 (5.6)
Distal CBD cancer	3 (16.7)
Stomach cancer	1 (5.6)

CBD common bile duct, *GB* gallbladder

Nonsurgical Management

Of 13 patients who were initially managed conservatively, ten patients were managed on purpose, whereas three patients were not, but because of delayed diagnosis. Eleven of the 13 patients were successfully managed without operation; however, two patients finally underwent surgery. Of the 11 patients, five patients (45.4%) had abdominal pain, characterized as mild to moderate, and two patients had a fever above 38.0°C. No patients had any evidence of irritation sign or a suspicion of pertitonitis. Six patients had nasogastric tube, and two patients had aggressive endoscopic drainage with a stent ($n=1$) and nasobiliary tubes ($n=1$).

Interestingly, three patients with intraperitoneal air were well managed without surgery. First patient was a 76-year-old man who was suspected of common bile duct stones (Fig. 1 A-a–A-c). ERCP was successfully performed with removal of stones. Second patient was a 75-year-old women diagnosed with acute cholangitis. She received metallic stent because of common bile duct cancer. She had mild abdominal pain and fever above 38.0°C during 4 days. Third patient was a 59-year-old man who was managed by biliary stent because of advanced gastric cancer (Fig. 1 B-a–B-d). In all patients, we checked abdominal CT and found intraperitoneal free air, ranging from small to large. However, they did not have peritoneal irritation sign, although they had mild abdominal pain. Moreover, the volume of free air was not increasing on follow up X-ray. We recommended conservative management with close observation. Finally, the three patients recovered well and were discharged on the 9th, 17th, and 22nd hospital day, respectively.

Four patients underwent laparoscopic cholecystectomy for gallbladder stone and cholecystitis, and one patients diagnosed with ampullary cancer underwent palliative hepaticojejunostomy due to aortocaval nodal metastasis. The mean follow-up period was 21.1±15.0 months: No patient had any complications during the period.

Surgical Management

Of seven patients, four patients had duodenal perforations (three intraperitoneal and one retroperitoneal perforations), one had perforation in the ampulla, and two patients with Billoth II anatomy had jejunal perforations. Five patients were operated on early within 12 h after ERCP, whereas two patients (nos. 1 and 5) had their surgery 12 h later (Table 4).

In no. 3 patient who underwent early operation, the perforation was suspected by intraperitoneal air on the postprocedural abdominal X-ray. Surgery was done as soon as possible; within 9 h after ERCP. There was no bile collection at laparotomy; however, a 1.5-cm perforation was found in the retroperitoneal second portion of the

Table 3 Comparisons of Mechanism and Diagnosis of Perforation

	Conservative group (n=11)	Operative group (n=7)	P value
Mechanism of perforation (%)			0.020
Sphincterotomy-related	8 (72.7)	1 (14.3)	
Scope-related	2 (18.2)	6 (85.7)	
Guidewire-related	1 (9.1)		
Diagnosis (%)			>0.05
During ERCP	10 (90.9)	4 (57.1)	
After ERCP	1 (9.1)	3 (42.9)	
Site of air (%)			0.019
Retroperitoneal air	8 (72.7)	1 (14.3)	
Intraperitoneal air	3 (27.3)	6 (85.7)	

duodenum after duodenotomy. The patients were admitted to intensive care unit for 9 days and then discharged on the 31st postoperative day. The remaining four patients were operated immediately after ERCP; there were significant correlations between time to surgery and hospital stay (r=0.828, P<0.05) and between time to surgery and complications (r=0.886, P<0.05; Fig. 2). Therefore, we suggest an early surgery if the scope-related perforations develop.

Surgical procedures included primary repair with omentopexy and drainage (n=6), common bile duct exploration and T-tube placement (n=3), duodenotomy (n=3), choledochoduodenostomy (n=1), and cholecystectomy (n=5). None of the patients underwent exploratory laparotomy with drain placement only. None of the seven patients managed by surgery required reoperation for duodenal leakage, although there was one duodenal leakage.

At laparotomy, bile-tinged fluid collections were found in five patients, but not in two patients. Strangely, one patient (no. 4) without intraperitoneal air had bile collection. On the other hand, two patients (nos. 2 and 3) with

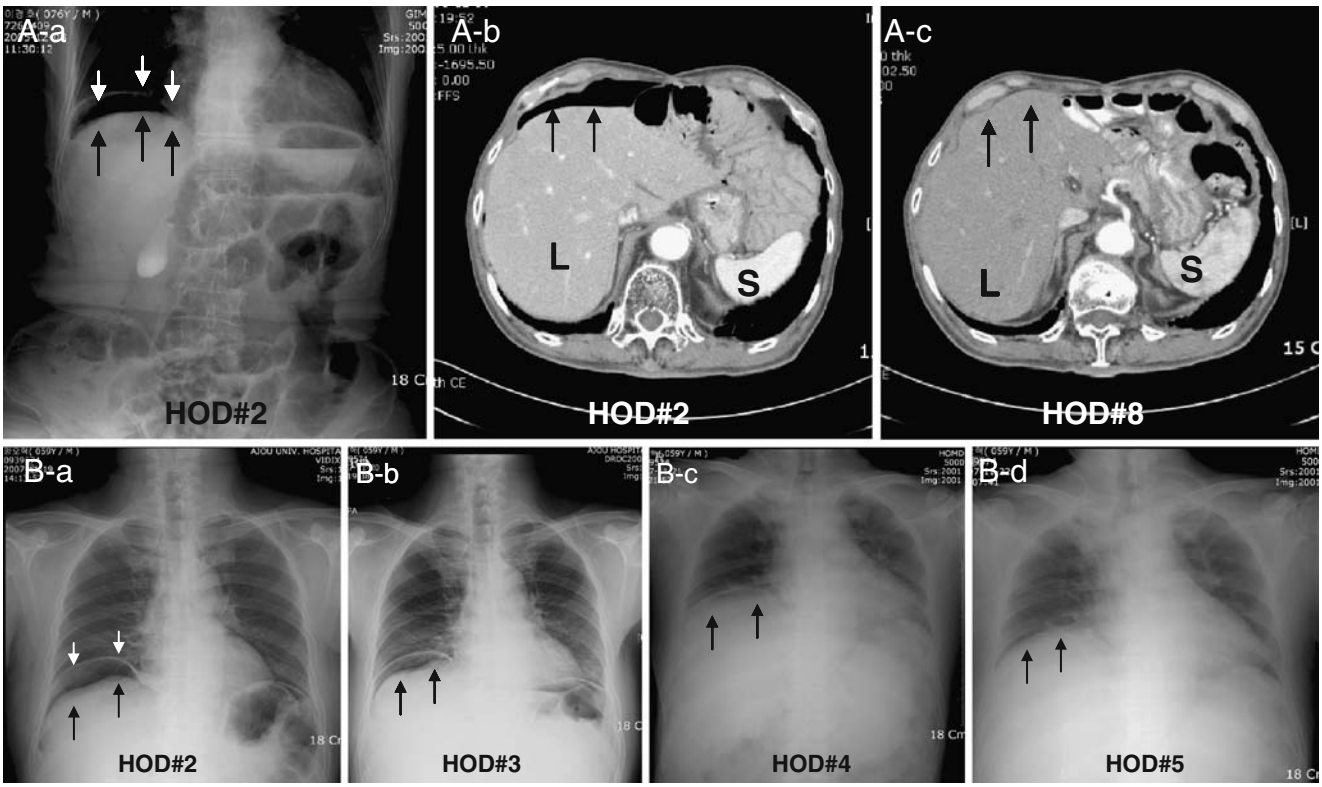

Figure 1 Radiological findings of intraperitoneal air after ERCP in conservative group (*A-a–A-c* 76-year-old man; *B-a–B-d* 59-year-old man). *A-a*, *A-b* There was a large intraperitoneal air 1 day after ERCP on X-ray of simple abdomen and abdominal CT (*HOD#2*; *arrow*). *A-c* Follow-up on the 6th day after perforation: intraperitoneal air disappear (*HOD#8*). *B-a* Chest X-ray showed intraperitoneal air in the right subdiaphragm (*arrow*). *B-b–B-d* Air was decreasing as days go by and disappeared after 4 days. *HOD* day of hospital, *L* liver, *S* spleen.

Table 4 Characteristics of Patients Operated for ERCP-Related Perforations

No.	Gender/ age	Time to surgery (h)	Surgical findings	Surgical management	Complications	Hospital stay
1	M/63	20	Jejunum (3 cm) fluid collection (+)	Primary repair	GI bleeding, pleural effusion	52
2	F/70	4	Duodenum (2nd, lateral wall, 2.5 cm), fluid collection (−)	Duodenotomy, primary repair, and CC	None	10
3	F/77	9	Duodenum (2nd, posteriomedial wall, 1.5 cm), fluid collection (−)	Duodenotomy, primary repair, and CC	Wound infection, pleural effusion	31
4	M/69	6	Not found, fluid collection (+)	Duodenotomy, CC, and CBDE	Hyperbilirubinemia	18
5	F/66	30	Duodenum (1st, lateral wall, 3 cm), fluid collection (+)	Primary repair, CC, and CBDE	Duodenal leakage, wound infection, bleeding	41 mortality
6	M/72	5	Jejunum (1.5 cm), fluid collection (+)	Primary repair, CC, CBDE, and CD	None	8
7	M/64	5	Duodenum (3rd, lateral wall, 1.0 cm), fluid collection (+)	Primary repair	Wound seroma, intra-abdominal fluid collection	21

CC cholecystectomy, *CBDE* common bile duct exploration and T-tube placement, *CD* choledochoduodenostomy

intraperitoneal air had no bile collections, suggesting that the site of perforation might have been sealed up.

The development of septic peritonitis with large intra-abdominal fluid collections led to a delayed surgical procedure in two patients (nos. 1 and 5) in whom conservative management failed. At laparotomy in the patient no. 5, about 3-cm perforation was found in the lateral first portion of the duodenum and subhepatic bile collection. Two patients required intensive care unit admission with prolonged hospital stay. The patient no. 1 recovered well and was discharged on the 52nd postoperative day. However, he died 7 months later due to ampullary cancer with multiple metastasis. The patient no. 5 died on 41st postoperative days due to sepsis and multiple organ failure secondary to the duodenal leakage. The patient no. 7 was readmitted, however, not related with previous operation. Other patients had no complications during the follow-up: The mean follow-up period was 26.0±15.2 months.

Discussion

As a serious complication after ERCP, perforations have been reported in some series to occur in 0.35% to 2.1% of patients.[3–5] ERCP-related perforations are diagnosed more frequently by experienced endoscopists, because of either contrast extravasations or appearance of retro-/intraperitoneal air during the procedure. In the present study, ERCP-related perforations occurred in 0.89% of patients. Of 18

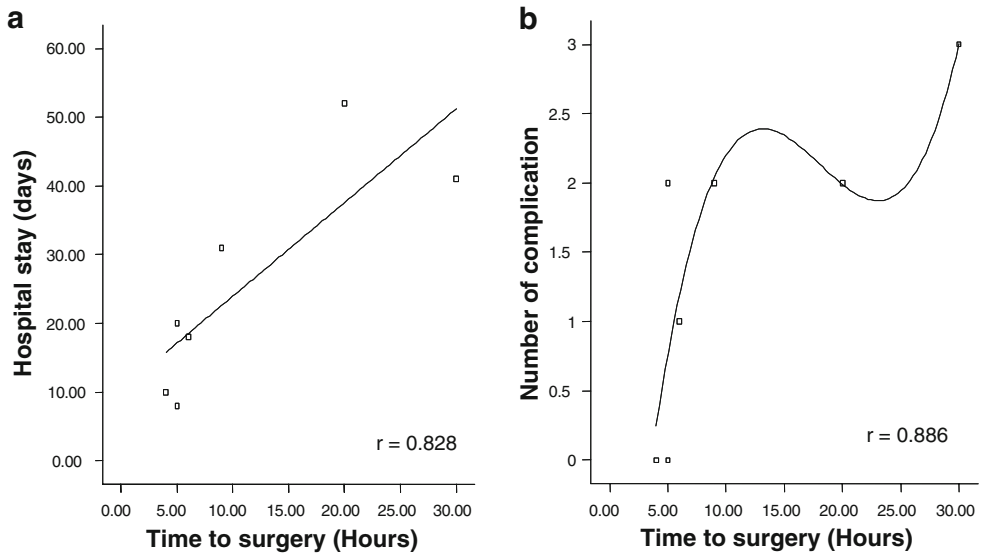

Figure 2 Correlations between time to operation and other factors. **a** There was a significant correlation between time to surgery and hospital stay (r=0.828, P=0.042). **b** There was a significant correlation between time to surgery and complications (r=0.886, P=0.019). r = correlation coefficient.

patients, 14 patients (77.7%) were suspected at the time of ERCP (ten patients in the conservative group and four in the operative group), showing a frequency similar to other reports.[2,13,14]

Some authors[4,12,13] have introduced classifications of ERCP-related perforations based on anatomical location and mechanisms of injury, thereby suggesting management guidelines. In our study, ERCP-related perforations were classified by the leading cause to scope-related, sphincterotomy-related, and guidewire-related perforation. Enns et al.[4] reported that sphincterotomy- and guidewire-related perforations rarely require surgery, whereas esophageal, gastric, and duodenal perforations caused by scope itself usually require surgery. Moreover, Stapfer et al.[13] suggested that the clinical and radiological features of ERCP-related periduodenal perforations can be used to stratify patients into selective management. In our opinions, these two reports show similar mechanism of injury, although classifications of ERCP-related perforation are different.

The incidence of sphincterotomy-related or peri-Vaterian (type II) perforations ranges between 15.0% and 55.0%,[4,11–13] and most cases are managed by nonsurgical treatment. In the present study, sphincterotomy-related perforations included nine cases, and eight cases were treated conservatively. As expected, the conservative treatment was more commonly used in sphincterotomy in our data. Seven of nine patients with sphincterotomy-related perforation showed retroperitoneal air and were treated by conservative management. One of eight patients with scope-related perforation showed retroperitoneal air and was well managed conservatively: It was a small perforation on the diverticulum at the periampullary duodenum. The retroperitoneal air alone could probably be due to compressed air to maintain patency of a lumen; it is a sealed perforation, therefore, does not require surgical intervention.[15] Howard et al.[12] reported that early diagnosed periampullary perforation responds to aggressive endoscopic drainage and medical treatment; however, postsphincterotomy perforations diagnosed late (particularly duodenal) require surgical drainage, which carries a high morbidity and mortality rate.

There are some reports that scope-related perforations presented in gastric, esophageal, and lateral wall of duodenum and jejunum tend to be large and remote from the ampulla and require immediate surgery.[4,13] In our operative group, six patients were caused by scope itself with intraperitoneal air and one patient by sphincterotomy with retroperitoneal air: One patient with sphincterotomy-related perforation underwent surgery because of retained stones. However, Kayhan et al.[16] reported that therapeutic ERCP may be repeated and has a high success rate in patients who retained stone. Therefore, we suggest that surgery may not be necessary for retained stone.

Early operation usually allows a primary repair and results in good outcomes. However, a high incidence of morbidity and mortality has been reported to be associated with failed nonsurgical management.[6,13,17] However, using other modalities, recent studies[18] show a promise for allowing endoscopic closure. In the present study, seven patients with ERCP-related perforations underwent surgery: Four patients had early surgery and three patients had delayed surgery. There were significant correlations between time to surgery and hospital stay and between time to surgery and complications, respectively. Therefore, we suggest an early surgery if scope-related perforations develop.

Surprisingly, three patients who had intraperitoneal air underwent nonsurgical management, regardless of mechanism of injury. There are well-known guides by which we decided conservative treatment. Does patient have abdominal irritation sign? Is free air increasing or decreasing on consecutive X-ray, and does symptoms aggravate during close observation? Traditionally, duodenal perforations have been managed surgically[19]; however, in the past decade, management of limited esophageal, colonic, and even duodenal perforations has evolved toward a more selective approach.[7,20,21]

The surgical procedure was selected, based on mechanism and degree of injury. Some authors performed pyloric exclusion and gastrojejunostomy in any patients with duodenal perforation and failed conservative management,[13] whereas duodenal diversion was used more frequently in patients with peri-Vaterian perforations and those operated on late.[8] In the present study, only one patient underwent duodenal diversion. In most patients who underwent early operation, the primary closure without duodenal diversion is enough. When the site of perforation could not be found with or without fluid collections, we performed transduodenal approach (duodenotomy): Strangely, one patient (no. 4) without intraperitoneal air had fluid collections, whereas two patients (nos. 2 and 3) with intraperitoneal air had no fluid collections, suggesting that the site of perforation might have been sealed up. Recently, Sarli et al.[22] reported that a transduodenal operative repair is a useful method for periampullary perforation.

Conclusion

Most of sphincterotomy-related perforations are managed nonsurgically. However, scope-related perforation is usually large and requires immediate surgery. Moreover, the delayed operation results in a longer hospital stay and high morbidity. Therefore, the selective early surgical intervention is suggested when scope-related perforations are discovered.

References

1. Freeman ML. Adverse outcomes of ERCP. Gastrointest Endosc 2002;56:S273–282. doi:10.1016/S0016-5107(02)70025-4.
2. Dunham F, Bourgeois N, Gelin M, Jeanmart J, Toussaint J, Cremer M. Retroperitoneal perforations following endoscopic sphincterotomy; clinical course and management. Endoscopy 1982;14:92–96.
3. Cotton PB, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, Liguory C, Nickl N. Endoscopic sphincterotomy complications and their management: An attempt at consensus. Gastrointest Endosc 1991;37:383–393.
4. Enns R, Eloubeidi MA, Mergener K, Jowell PS, Branch MS, Pappas TM, Baillie J. ERCP-related perforations: Risk factors and management. Endoscopy 2002;34:293–298. doi:10.1055/s-2002-23650.
5. Freeman ML, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, Moore JP, Fennerty MB, Ryan ME, Shaw MJ, Lande JD, Pheley AM. Complications of endoscopic biliary sphincterotomy. N Engl J Med 1996;335:909–918. doi:10.1056/NEJM199609263351301.
6. Sarr MG, Fishman EK, Milligan FD, Siegelman SS, Cameron JL. Pancreatitis or duodenal perforation after peri-Vaterian therapeutic endoscopic procedures: Diagnosis, differentiation, and management. Surgery 1986;100:461–466.
7. Booth FV, Doerr RJ, Khalafi RS, Luchette FA, Flint LM Jr. Surgical management of complications of endoscopic sphincterotomy with precut papillotomy. Am J Surg 1990;159:132–135. discussion 135–6. doi:10.1016/S0002-9610(05)80618-X.
8. Preetha M, Chung YF, Chan WH, Ong HS, Chow PK, Wong WK, Ooi LL, Soo KC. Surgical management of endoscopic retrograde cholangiopancreatography-related perforations. ANZ J Surg 2003;73:1011–1014. doi:10.1046/j.1445-2197.2003.t01-15-.x.
9. Safrany L. Duodenoscopic sphincterotomy and gallstone removal. Gastroenterology 1977;72:338–343.
10. Byrne P, Leung JW, Cotton PB. Retroperitoneal perforation during duodenoscopic sphincterotomy. Radiology 1984;150:383–384.
11. Fatima J, Baron TH, Topazian MD, Houghton SG, Iqbal CW, Ott BJ, Farley DR, Farnell MB, Sarr MG. Pancreaticobiliary and duodenal perforations after periampullary endoscopic procedures: Diagnosis and management. Arch Surg 2007;142:448–454. discussion 454–5. doi:10.1001/archsurg.142.5.448.
12. Howard TJ, Tan T, Lehman GA, Sherman S, Madura JA, Fogel E, Swack ML, Kopecky KK. Classification and management of perforations complicating endoscopic sphincterotomy. Surgery 1999;126:658–663. discussion 664–5.
13. Stapfer M, Selby RR, Stain SC, Katkhouda N, Parekh D, Jabbour N, Garry D. Management of duodenal perforation after endoscopic retrograde cholangiopancreatography and sphincterotomy. Ann Surg 2000;232:191–198. doi:10.1097/00000658-200008000-00007.
14. Bell RC, Van Stiegmann G, Goff J, Reveille M, Norton L, Pearlman NW. Decision for surgical management of perforation following endoscopic sphincterotomy. Am Surg 1991;57:237–240.
15. Genzlinger JL, McPhee MS, Fisher JK, Jacob KM, Helzberg JH. Significance of retroperitoneal air after endoscopic retrograde cholangiopancreatography with sphincterotomy. Am J Gastroenterol 1999;94:1267–1270. doi:10.1111/j.1572-0241.1999.00996.x.
16. Kayhan B, Akdogan M, Sahin B. ERCP subsequent to retroperitoneal perforation caused by endoscopic sphincterotomy. Gastrointest Endosc 2004;60:833–835. doi:10.1016/S0016-5107(04)02171-6.
17. Scarlett PY, Falk GL. The management of perforation of the duodenum following endoscopic sphincterotomy: A proposal for selective therapy. Aust N Z J Surg 1994;64:843–846. doi:10.1111/j.1445-2197.1994.tb04561.x.
18. Mutignani M, Iacopini F, Dokas S, Larghi A, Familiari P, Tringali A, Costamagna G. Successful endoscopic closure of a lateral duodenal perforation at ERCP with fibrin glue. Gastrointest Endosc 2006;63:725–727. doi:10.1016/j.gie.2005.11.028.
19. Cameron JL, Kieffer RF, Hendrix TR, Mehigan DG, Baker RR. Selective nonoperative management of contained intrathoracic esophageal disruptions. Ann Thorac Surg 1979;27:404–408.
20. Berne TV, Donovan AJ. Nonoperative treatment of perforated duodenal ulcer. Arch Surg 1989;124:830–832.
21. Cobb LM, Vinocur CD, Wagner CW, Weintraub WH. Intestinal perforation due to blunt trauma in children in an era of increased nonoperative treatment. J Trauma 1986;26:461–463. doi:10.1097/00005373-198605000-00009.
22. Sarli L, Porrini C, Costi R, Regina G, Violi V, Ferro M, Roncoroni L. Operative treatment of periampullary retroperitoneal perforation complicating endoscopic sphincterotomy. Surgery 2007;142:26–32. doi:10.1016/j.surg.2007.02.002.

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ORIGINAL ARTICLE

Prediction of Anastomotic Leakage After Pancreatic Head Resections by Dynamic Magnetic Resonance Imaging (dMRI)

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Abstract
Purpose The texture of the pancreatic tissue is a main risk factor for leakage after pancreaticojejunostomy and can be differentiated using dynamic contrast enhanced magnetic resonance imaging (dMRI). In order to identify risk factors and to assess the role of pancreatic dMRI, a cohort of patients was retrospectively reviewed.
Patients and methods One hundred seven consecutive patients were identified in the departmental database and examined by means of a standardized dMRI protocol using a 1.5-T MRI system. Signal intensity (SI) measurements (aorta, body of the pancreas, muscle tissue) were performed in the axial T1-weighted sequences before and after 25 and 60 s after i.v. application of gadolinium–diethylenetriaminepentaacetic acid. For all patients with a standardized contrast medium curve in the aorta (n=72), a muscle-normalized signal intensity curve (SIC) with SI_{ratio} was calculated. SI_{ratio}s were classified in two groups: rapid increase ($SI_{ratio} \geq 1.1$, early arterial value > portal-venous value, "soft" pancreas) and delayed increase (SI_{ratio} <1.1, "firm" or "hard" pancreas). All patients received pancreatic head resection with a duct-to-mucosa pancreaticojejunostomy. The dMRI data was correlated with prospectively acquired clinical data.
Results Leakage of the pancreaticojejunostomy occurred more frequently (12/37 vs. two of 35, 32% vs. 6%, p=0.006) in patients with a rapid increase and an $SI_{ratio} \geq 1.1$ ("soft" pancreas, n=37) compared to those with delayed perfusion (SI_{ratio} <1.1, "hard" pancreas, n=35). The more severe type B and C anastomotic leakages occurred only in the group of patients with $SI_{ratio} \geq 1.1$. Patients with a rapid increase had significantly better preoperative American Society of Anesthesiologists staging, lower carbohydrate antigen 19-9 values, and smaller tumor sizes. Most of them had not only benign tumors but also longer postoperative hospital stay, in comparison to patients with delayed perfusion (SI_{ratio} <1.1). Multivariate analysis revealed SI_{ratio} of ≥1.1 to be the only preoperative parameter predicting leakage significantly with an odds ratio of 7.9.

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Conclusion dMRI with SI_{ratio} calculation provided reliable information for the prediction of pancreatic texture. Patients with a $SI_{ratio} \geq 1.1$ had a 7.9-fold increased risk of anastomotic leakage and a prolonged hospital stay. SIC with measurements of SI_{ratio} in dMRI could therefore define patients at risk for anastomotic leakage.

Keywords Pancreatic surgery · Anastomotic leakage · Dynamic magnetic resonance imaging

Introduction

The mortality of pancreatic head resection, with or without pylorus preservation, has significantly declined over the past decades and lies below 5% in experienced centers.[1,2] The morbidity of this procedure is, however, high with 30[1–3] to 60%.[4,5] The pancreatic anastomosis is the "Achilles' heel" in pancreatic surgery.[6,7] Leakage of the pancreaticointestinal anastomosis is the main trigger for other morbidities after this procedure. Clinically, a leakage may present as a pancreatic–cutaneous fistula, intraabdominal abscess, delayed gastric emptying, intestinal atony, or it can result in sepsis and hemorrhage leading to a significant mortality.[1,7,8] The two common reasons for leakage of pancreatic anastomosis are a "soft" pancreatic texture and a small pancreatic duct size.[9–12] Chronic pancreatitis leads to fibrotic, "hard" pancreatic tissue. Anastomotic leakage is therefore observed less frequently after resections due to chronic pancreatitis, compared with resections due to cancer.[13] The reported incidence of leakage lies between 0 and 30% and may represent a marked underestimation due to selection bias as well as publication bias.[7] Since duct size is an objective parameter the surgeon can easily identify an anastomosis being at risk for leakage during the operation and can spontaneously change the operation procedure; for instance one can decide to switch to another anastomosis technique.

The degree of "softness" of the pancreatic tissue and its role in estimation of an anastomosis being at risk remains to be a problem. Reliable preoperative diagnostic tools or risk scores for prediction of a soft texture are currently not available. The normal exocrine fluid output of the "soft" pancreatic tissue, as compared to that of the fibrotic ("hard") tissue in patients with chronic pancreatitis, has been described as another risk factor for leakage.[7,14] It is therefore not proven that "soft" correlates with "normal" healthy pancreatic tissue. In magnetic resonance imaging (MRI), Sittek and his coauthors could observe various patterns of pancreatic perfusion depending on various pancreatic textures.[15]

The aim of this study was to evaluate the role of dynamic magnetic resonance imaging (dMRI) in prediction of soft pancreatic texture and leakage of the pancreatic anastomosis. Additionally, it was attempted to identify other risk factors for leakage of the pancreatic anastomosis.

Materials and Methods

Between 2002 and 2007, a total of 217 patients underwent a pancreatic resection (Kausch–Whipple resection or pylorus-preserving pancreaticoduodenectomy) due to a pancreatic head tumor in the Department of Surgery. All patients were identified in the prospective departmental pancreatic database.[1,16–18] During this 5-year period, a total number of 107 consecutive patients with a sonographically suspected tumor of the pancreas head were evaluated by dMRI prior to resection. All patients with a dMRI in our institution were included in the present analysis. The data of the latter patients examined comprised demographics; pathology report; tumor, node, metastasis stage; and International Union Against Cancer classification, preoperative presenting symptoms, preoperative procedures (e.g., biliary stent), lab work (including tumor marker carbohydrate antigen (CA) 19-9), the American Society of Anesthesiologists (ASA) score, details of the surgical therapy (including blood loss and blood transfusions), the hospital course (including complications), and the postoperative survival.

Follow-up was performed through personal contact with the patient or patient's primary physician and was terminated on June 1 2008 or at patient's death. All deaths occurring within 30 days after surgery or throughout the hospital stay were classified as surgical mortality. In all patients, drains were placed at the pancreaticojejunostomy and at the hepaticojejunostomy site.

An anastomotic leakage was defined according to the International Study Group on Pancreatic Fistula (ISGPF) definition.[19] A grade A leakage is a so-called "biochemical, transient fistula" and has no clinical impact. A grade A leakage requires little change in management or deviation from the normal clinical pathway. A grade B leakage requires a change in the patient management or an adjustment in the clinical pathway. It usually leads to a delay in discharge, to readmission, or to discharge of the patient with drains in situ. A grade C leakage leads to a major change in the clinical management or a deviation from the normal clinical pathway. A deteriorating clinical status with a grade C leakage together with sepsis and an organ dysfunction may require reexploration in an attempt to repair the site of leakage with wide peripancreatic drainage, or a conversion to alternative pancreaticoenteric anastomosis, or a complete pancreatectomy.

Surgical Technique of Pancreatic Anastomosis

Within 1 to 10 days (median 3 days) after the dMRI, all patients underwent a pancreatic head resection (Kausch–

Whipple or pylorus-preserving procedure) with reconstruction as duct-to-mucosa pancreaticojejunostomy. The two-layer pancreatointestinal anastomosis was standardized as follows: After mobilization of the pancreatic remnant, the inner suture layer was placed on the pancreatic duct. Usually eight stitches were required (resorbable monofilament 5-0 sutures), the posterior wall was sutured from inside to outside, the anterior wall from outside to inside. The mesenteric surface of jejunum was approximated to the pancreas stump. The posterior wall of the outer suture layer was sewn in a running manner after placing a knot on the cranial edge of the pancreas (resorbable monofilament 4-0 sutures). A small incision corresponding to the localization and diameter of the pancreatic duct was made on the antimesenteric surface of the jejunum and the inner layer (duct to mucosa) was completed by stitching the previously placed sutures and tying them gently. The anastomosis was completed by a running suture of the outer anterior wall with the previously placed suture (serosal surface of the pancreatic remnant to seromuscular layer of jejunum; Fig. 1). Two soft drains were placed in every patient: one at the pancreatic anastomosis and one close to the hepaticojejunostomy.

Dynamic MRI

All patients underwent a MRI examination of the pancreas using the same 1.5-T system (Magnetom Vision, Siemens Medical Solutions, Erlangen, Germany). The sequence protocol is described in Table 1 in detail. All patients underwent standard sequences for the description of the morphology followed by a native T1-weighted fat saturated sequence centered on the body of the pancreas with a slice thickness of 5 mm without a gap. The sequence was repeated after intravenous administration of 0.1 mmol/kg bodyweight gadolinium–diethylenetriaminepentaacetic acid (Gd-DTPA; Magnevist®, Bayer Schering, Berlin, Germany) via an automatized injection with a flow rate of 2 ml/s using a 21-G i.v. line in a cubital vein, followed by a saline flush with 40 ml isotonic saline solution. The T1-weighted fat saturated sequence was repeated approximately 25 and 60 s after application of contrast medium in the axial plane, after 2 min in a coronal plane, and after 2.5 min for the termination of the examination in an axial plane without fat saturation. In order to compare pancreas-healthy individuals with the resected patients, the MRI data of 15 age- and gender-correlated patients without an apparent pancreatic or liver disease were evaluated within 12 months after the dMRI examination following the above mentioned protocol.

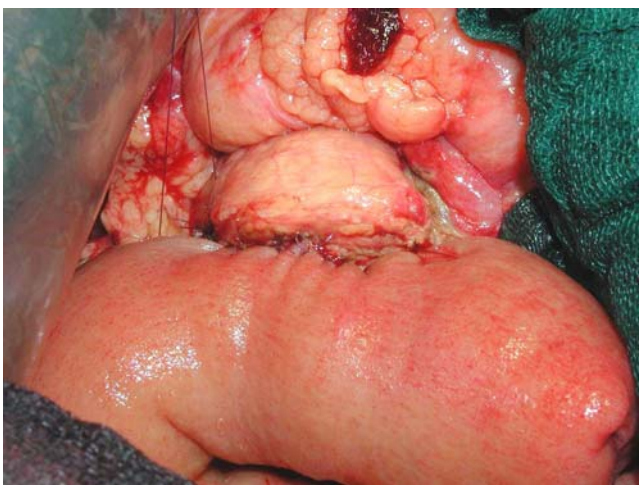

Figure 1 Duct-to-mucosa pancreaticojejunostomy: the posterior wall of the outer suture row is completed as the complete duct-to-mucosa suture. The anterior portion of the outer suture row between pancreas capsule and seromuscularis of the jejunum is still missing.

dMRI Image Evaluation

A measurement of the signal intensity (SI) was carried out in different regions of interests (RoIs) with at least 16 pixels for reliable results. The first RoI was measured in the pancreatic tissue at the estimated resection line, with and without the pancreatic duct. Further, RoIs were inside the aorta at the axial plane of the pancreas body and inside the paravertebral muscle (spinal erector muscle) for the normalization of the measurements (Fig. 2a–d). In the initial evaluation, all patients with a nondiagnostic contrast media application (all patients with an increase of the SI in the aorta after the initial arterial peak) were excluded. The measurement results in the pancreas were normalized by setting the increase in the pancreas in relation to the increase in the muscle according to the formulas described in Table 2.

The patients were classified into two groups according the pattern of perfusion following the ratio: $SI_{ratio}=\left(\frac{SI_{ea}}{SI_{pv}}\right)$. SI_{ea} was defined as the signal intensity in the early arterial phase and SI_{pv} as the portal-venous phase after the application of contrast. If the pancreatic tissue demonstrated a muscle-normalized SI^{ratio} of ≥ 1.1, the patients were assigned to group 1 (normal perfusion of the organ). Patients who demonstrated an SI^{ratio} <1.1 were assigned to group 2 (decreased perfusion of the organ). An age-matched group of 15 volunteers without history of a pancreatic disease were evaluated using the same examination and evaluation protocol.

Statistical Analyses

The primary endpoint of the study was the leakage of the pancreatic anastomosis. A Fisher's exact test was performed comparing the two groups. A chi-square test was performed comparing various patient data and the perfusion values. A multivariate analysis (logistic re-

Table 1 Examination Protocol for the MRI of the Pancreas

	T1 ax	T2 TSE ax	T1 fs ax	MRCP (HASTE)	MRCP (RARE)	T1 fs ax	T1 fs cor	T1 ax
TR/TE	121/4.1	5,000/120	132.4/2.3	4.4/64	2,800/1,100	132.4/2.3	132.4/2.3	121/4.1
Matrix	256×256	256×256	256×256	256×256	256×256	256×256	256×256	256×256
FoV (mm)	300×300	300×300	300×300	300×500	300×400	300×300	500×300	300×300
Slice thickness (mm)/gap	5/5	5/5	5/0 (pancreas)	6/0	50/na	5/0 (pancreas)	5/5	5/5
TA (s)	16	17	16	16	6	16	17	16
Contrast (time after i.v. administration)	–	–	–	–	–	+ (25 and 70 s)	140 s post	Yes

ax axial, *MRCP* magnetic resonance cholangiopancreaticography, *HASTE* half-Fourier acquisition turbo spin echo sequence, *RARE* rapid acquisition with relaxation enhancement, *fs* spectral fat saturation, *cor* coronal, *TR* time of repetition, *TE* echo time, *FoV* field of view, *TA* time of acquisition, *na* not applicable

gression) was calculated with an odds ratio (OR) for all parameters described. Predicting factors for the leakage were examined by univariate and multivariate analyses, using Cox's proportional hazards including a calculation of the odds ratio for all parameters described. Significance was accepted at the probability level of 0.05. All statistical calculations were performed using the SAS software (release 9.01; SAS Institute Inc., Cary, NC, USA).

Results

All examinations were performed with the same sequence protocol without any study violation. A total of 107 patients (median age 67.5 years, range 30–89 years, 65 men, 42 women) were included in the evaluation. In 72 patients (median age 67 years, range 30–89 years, 42 men, 30 women), the early arterial SI in the aorta was higher than the portal venous SI, showing the correct timing of the

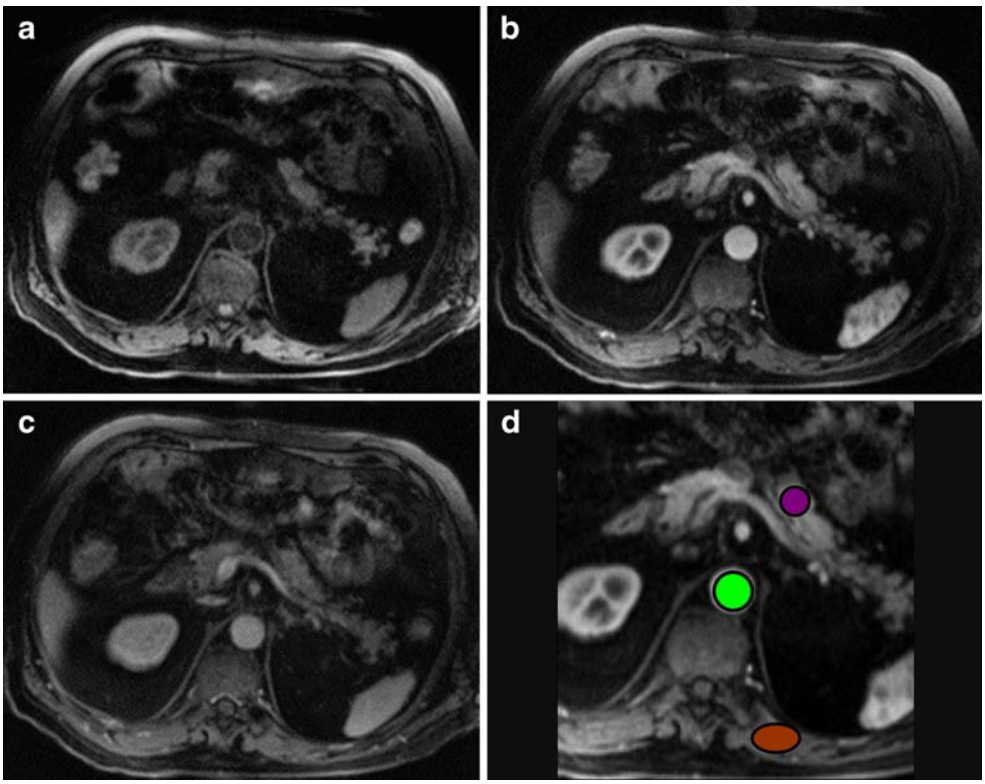

Figure 2 a–d T1-weighted images of the pancreas with fat saturation, demonstrating the contrast enhancement in the body of the pancreas. **a** Native, **b** 25 s, and **c** 60 s after b.w. adapted i.v. administration of Gd-DTPA (Magnevist®). **d** Illustrates the localization of the regions of interest for the measurement of the signal intensities. The *colors* indicate the different tissues: *purple* = pancreatic parenchyma at the localization of the presumed resection margin, *green* = abdominal aorta at the height of the pancreas, and *brown* = muscle tissue of the paravertebral spine muscle.

Table 2 Formulae for the Evaluation of the Signal Intensity Measurements

Native: $SI_{native}=\left\{\left[\frac{SI(pancreas_{nativ})}{SI(muscle_{nativ})}\right]-\left[\frac{SI(pancreas_{nativ})}{SI(muscle_{nativ})}\right]\right\}\times 100\%$

"Nativ" in der Formel muss noch durch "native" ersetzt warden

Early arterial: $SI_{ea}=\left\{\left[\frac{SI(pancreas_{ea})}{SI(muscle_{ea})}\right]-\left[\frac{SI(pancreas_{nativ})}{SI(muscle_{nativ})}\right]\right\}\times 100\%$

Portal venous: $SI_{pv}=\left\{\left[\frac{SI(pancreas_{pv})}{SI(muscle_{pv})}\right]-\left[\frac{SI(pancreas_{nativ})}{SI(muscle_{nativ})}\right]\right\}\times 100\%$

contrast media application. These 72 patients fulfilled criteria for the further examination (Table 3).

Perioperative Course

An uncomplicated postoperative course was observed in 31% of all patients (22/72). The overall morbidity rate was 69% (50/72); the postoperative mortality was 1.4% (one of 72). A classic Kausch–Whipple resection was performed in 27 patients (37.5%), a preservation of the pylorus-preserving pancreatoduodenectomy (PPPD) could be achieved in 45 patients (62.5%). Leakage of the pancreaticojejunostomy was observed in 14 patients (19.4%): grade A leakage in nine patients, grade B leakage in three, and grade C leakage requiring relaparotomy in two patients. In one of the latter patients, the anastomosis was converted; in the other patient, a complete pancreatectomy was necessary. This patient died subsequently on the 24th postoperative day. A leakage of the hepaticojejunostomy occurred in four patients (5.5%; Table 4). Seven (9.7%) patients required relaparotomy for complications, postoperative bleeding occurred in three (4.2%) patients, nine (12.5%) patients developed a delayed gastric emptying, and five (6.9%) patients presented with an intraabdominal abscess (Table 4).

Table 3 Correlation of Demographic, Histological, and Preoperative Parameters with SI_{ratio}

	SI_{ratio} ≥1.1 (n=37)	SI_{ratio} <1.1 (n=35)	p value
Age (years)	67 (30–89)	68 (40–85)	0.65
Gender (men vs. women)	21 vs. 16	21 vs. 14	0.76
ASA score (I/II vs. III/IV)	28 vs. 9	17 vs. 18	0.004
Diabetes preoperative	9	14	0.22
Bilirubin preoperative (g/dl)	1.5 (±10.7)	3.5 (±15.9)	0.48
CA 19.9 preoperative (U/l)	22 (±1.233)	152 (±2.724)	0.01
Albumin preoperative (g/dl)	33 (±5)	34 (±4)	0.79
Malignancy	30	27	0.64
Chronic pancreatitis	3	6	0.23
Benign tumor	7	2	0.05
Size of tumor (mm)	23 (±14)	32 (±16)	0.007

Table 4 Correlation of Procedural and Postoperative Parameters with SI_{ratio}

	SI_{ratio} ≥1.1 (n=37)	SI_{ratio} <1.1 (n=35)	p value
Procedure (Whipple vs. PPPD)	7 vs. 30	9 vs. 26	0.09
Complications (all)	29	20	0.07
Leakage pancreaticojejunostomy[a]	12	2	0.006
ISGPS leakage grade A[a]	7	2	
ISGPS leakage grade B[a]	3	0	
ISGPS leakage grade C[a]	2	0	
Leakage of the hepaticojejunostomy	3	1	0.35
Intraabdominal abscess	3	2	1
Blood loss (ml)	800 (±483)	750 (±587)	0.27
Operation time (min)	360 (±74)	351 (±113)	0.97
Mortality	2 (of 107)	0	0.49
Hospital stay (days)	20 (12–167)	17 (9–60)	0.05

[a] According to ISGPS definition of leakage[19]

Histopathology revealed cancer in 54 patients (75%): 33 ductal adenocarcinoma, five distal bile duct carcinoma, five carcinoma of Vater's papilla, 11 miscellaneous malignant tumors. Nine (12.5%) patients were diagnosed with a chronic pancreatitis, and nine (12.5%) patients had a benign lesion (for example noninvasive intraductal papillary mucinous neoplasm).

Evaluation of dMRI and Correlation with Clinical Parameters

Thirty-seven of the 72 patients who qualified for the final analysis (median age 67 years, range 30–89 years, 21 men, 16 women) revealed a pancreatic perfusion with an SI_{ratio} ≥1.1. Thirty-five patients (median age 68 years, range 40–85 years, 21 men, 14 women) had an SI_{ratio} <1.1. All pancreas-healthy patients in the control group showed an SI_{ratio}≥1.1. An SI_{ratio}≥1.1 was therefore equivalent to a "normal" pancreatic perfusion.

A comparison of the perfusion in dMRI and the clinical parameters revealed the following statistically significant results. In comparison to patients with a delayed perfusion (SI_{ratio} <1.1), those with a "normal" perfusion (SI_{ratio} ≥1.1) were significantly more often classified as ASA group I/II (no or mild comorbidities, p=0.004). These patients had lower preoperative CA 19-9 levels (22 vs. 152 U/l, p=0.01) and a smaller tumor size (23 vs. 32 mm, p=0.007).

Regarding the postoperative results, patients with a normal perfusion (SI_{ratio}≥1.1) had statistically significant higher rate of leakage of the pancreaticojejunostomy (p=0.006); 12 of 14 leakages (86%) occurred in patients with a normal perfusion (SI_{ratio}≥1.1) compared to only two of 14 leakages in patients with a delayed (SI_{ratio} <1.1) perfusion. All grade B and C leakages occurred in patients with a normal

perfusion. Two of 12 patients required relaparotomy (grade C) and three patients were discharged with drains in place, or needed a reintervention (grade B). In contrast to these findings, only in two patients with an signal intensity curve (SIC) <1.1 that a "biochemical" leakage (grade A) occurred. Patients with a normal perfusion had a significantly longer hospital stay (20 vs. 17 postoperative days, $p=0.05$) and were more likely to have other postoperative complications, resulting in an overall morbidity rate of 78% (29/37 vs. 21/35). This difference, however, was of no statistical significance ($p=0.07$; Table 4).

In order to reveal predictive factors of an anastomotic leakage, all preoperative parameters were evaluated in a multivariate analysis. The $SI_{ratio} \geq 1.1$ was shown to be the only parameter with a strong statistically significant correlation with the postoperative leakage ($p=0.0042$, odds ratio (OR) 7.92). All other parameters, such as ASA score, chronic pancreatitis, pancreatic cancer, tumor size, diabetes, etc., revealed no significant correlation (Table 3). The perfusion pattern in dMRI was therefore the only preoperative parameter predicting the probability of having a postoperative leakage (OR 7.92). The risk of developing a leakage was 7.9-folds higher in patients with a normal pancreatic perfusion and an $SI_{ratio} \geq 1.1$ in dMRI, in comparison to those with an SI_{ratio} <1.1 in dMRI (Table 5).

Discussion

One of the challenges following a pancreaticointestinal reconstruction is the prevention of an anastomotic leakage. A leakage is a critical factor influencing postoperative morbidity and mortality.[7,20,21] As a result, over 70 different techniques for reconstruction of the pancreatic remnant following pancreatic head resection have been described.[7] The multitude of the suggested modifications, however, reflects that none of the techniques is perfect enough to convince every pancreatic surgeon for every intraoperative situation ("soft" or "firm" gland). Furthermore, there are no objective criteria to assess the texture of the pancreas prior to the operation, in order to adapt the surgical technique adequately and to inform the patients at risk for anastomotic leakage. The texture of the pancreatic tissue is explained by its pathophysiology. The natural texture is "soft" with a main pancreatic duct of a maximum diameter of 3 mm. The perfusion of this type of gland is not impaired. Following a chronic pancreatitis, the gland is usually fibrotic and firm with an impaired perfusion.[14] Other pancreatic disorders such as solid or cystic pancreatic tumors can lead to a variety of texture changes from "soft" to firm" along with different perfusion pattern.[22–24] Various pancreatic perfusion behavior in dMRI correlates with changes of the pancreatic texture.[15] Pancreatic perfusion in dMRI, calculated as SIC by measuring the SI_{ratio} was therefore studied as a predictor for an anastomotic failure. It was examined as a possible objective measure for the assessment of the texture of the pancreatic remnant.

Table 5 Multivariate Analysis (Logistic Regression) of Preoperative Parameters Correlated with Leakage of the Pancreaticojejunostomy

Parameter	*p* value
$SI_{ratio} \geq 1.1$	0.0042 (OR 7.92)
Diabetes	0.75
Malignancy	0.29
Chronic pancreatitis	0.14
Size of tumor (mm)	0.65
ASA I+II vs. III/IV	0.09
Albumin preoperative (g/dl)	0.21
CA 19.9 preoperative (U/l)	0.47

dMRI Pancreatic Imaging

The main protocol in 1.5-T MRI consists of a standard evaluation with T2-weighted (turbo-) spin echo sequences and diffusion-weighted images of the upper abdomen, with a calculation of the resulting apparent diffusion coefficients. The magnetic resonance cholangiopancreaticography is performed by fast T2-weighted images in half-Fourier acquired T2-weighted single-shot turbo spin-echo sequences technique and rapid acquisition with relaxation enhancement technique. The native protocol is completed by T1-weighted images, with and without fat saturation for the delineation of the pancreas tissue. These sequences are followed by application of an MR contrast media, usually Gd-DTPA, in order to describe the contrast kinetics of tumors in terms of them being hypo-, iso-, or hyperintense after contrast media application. The examination is terminated by repeating the T1-weighted sequences in axial and coronal planes.[25] The examination can be performed with an axial thin-sliced T1-weighted sequence with fat saturation in order to visualize the pancreas in the early arterial, as well as in the portal-venous phase with excellent delineation of the tissue. The limitations, however, are in the exact description of vessel involvement, in case of an abnormal localization of the pancreas tissue, or of the upper abdominal vessels.[25–28] Another examination mode is the use of a coronal three-dimensional (3D) sequences as an angiographic examination, usually as a 3D volume interpolated breath-hold examination sequence. The advantage of this sequence is the high resolution with a voxel size of 1 mm^3. The disadvantage, however, is the sequence inherent signal-to-noise ratio, leading to a decrease in the quality of the evaluation of the pancreatic tissue. The results of the described techniques are, nevertheless, encouraging,

and both methods are used in the imaging technique of the pancreas.[25,26] The protocol used in this study consisted of the described thin slice axial T1-weighted sequence with the advantage of integrating delineation of morphology and the dynamic contrast enhancement aspect.

Exact imaging is essential for the exact differentiation of the tumor, the vessel infiltration of the arterial and venous vessels, and for staging of possible metastases.[25,29,30] Only a small number of previous investigators, however, have assessed pancreatic perfusion by performing a semiquantitative analysis of gadolinium enhancement parameters.[31–33] The quantitative analysis of regional blood perfusion using dMRI has been described for different tissues.[31–33] Although the study of Bali et al.[34] proposed an approach to quantify parameters with a so-called "one compartment model" for the pancreatic parenchyma, there is currently no standard of reference available for the perfusion parameters of the pancreas. Using semiquantitative methods, Coenegrachts and coworkers described a statistically significant difference between patients with chronic pancreatitis and healthy volunteers in the so-called "wash in time" as well as in the "time to inflow deceleration". They demonstrated a better contrast media enhancement in healthy volunteers in all parts of the pancreas.[31] Other studies from Tajima and his coworkers[32,33] applied the so-called "time intensity curves". This parameter was calculated as a function of signal intensity (SI post−SI pre)/SI pre×100%) and lead to a differentiation between two various tissue types: those with a good perfusion (rapid rise to a peak in the early arterial phase followed by a rapid decline) and those with a restricted perfusion (slow rise to a peak beginning at the portal-venous phase followed by a slow decline or very slow rise to a late peak followed by a decline or a plateau). These groups could be differentiated using different contrast media behavior 25 and 60 s after contrast media application. Similar to the present study the study of Tajima and his coworkers was aimed to predict possible anastomotic leakage. Their study, however, had major limitations concerning the reliability. The authors did not mention the measurement of the pancreatic duct, which was obviously inside the RoI. This leads to false measurements, since the content of the duct, which is water like, shows no contrast media enhancement, resulting in reduced signal intensity. Furthermore, the authors did not consider the different normalization levels of the images, or the different circulation times of the patients. These issues alter the signal intensity curves as well. As a significant modification, the present study included only patients who had an increase of the signal intensity in the aorta in the first arterial phase and revealed a decrease of the values in the second measurement. In the current study, only the tissue and not the duct was measured. This led to RoI which included only 6 to 8 pixels in some patients. The measurement was therefore more reliable than measuring the duct. Furthermore, the signal intensities were normalized in every patient with a very slow enhancing muscle tissue, in order to obtain more intra- as well as interindividually comparable measurements. The image-inherent noise level was also taken into consideration.[35]

Prediction of Anastomotic Leakage

In this series of 72 pancreatic head resections, 14 patients (19.4%) developed a leakage (nine grade A, three grade B, two grade C) postoperatively. This was a reasonable value compared to 1,507 patients of a multicenter database having a leakage rate of 26.7% according to the ISGPF definition.[9] In this study, the less severe type of leakage (grade A) occurred more frequently (64% vs. 48%). As a main result, it could be demonstrated that patients with a normal perfusion ($SI_{ratio} \geq 1.1$) had significantly higher rate of leakage ($p=0.006$) and a higher rate of more severe leakage types. All grade B and C leakages occurred in patients with $SI_{ratio} \geq 1.1$. Consecutively, patients with a normal perfusion ($SI_{ratio} \geq 1.1$) had a significantly longer hospital stay ($p=0.05$) and were more likely to have other postoperative complications ($p=0.07$). In a multivariate analysis, it could be shown that the $SI_{ratio} \geq 1.1$ was the only parameter revealing a strong statistically significant correlation with postoperative leakage ($p=0.0042$) with an odds ratio of 7.92. This implies that the risk of anastomotic failure in patients with a normal pancreatic perfusion is 7.92-folds higher than those with an impaired perfusion. The cutoff value for the SI ratio was chosen as a consequence of, and an improvement to the studies by Tajima,[32,33] who did not include the normalization of the values according to the muscle tissue.

Type of Resection

A recent meta-analysis[36] demonstrated no differences between the types of anastomosis (pancreatojejunostomy or pancreatogastrostomy) regarding gastric emptying time, pancreatic exocrine or endocrine insufficiency, or findings of ulcerative disorders in the endoscopy. The rate of pancreatic remnant related relaparotomies was, however, higher in the group of the patients who underwent pancreatojejunostomy.[37,38] Although in the present study pancreaticojejunostomy using a duct-to-mucosa technique was performed in all cases, there was a rate of 14/72 anastomotic leakages. Other groups such as Hayashibe and coauthors[39] described a series of 55 consecutive patients without a pancreatic anastomotic leakage after duct-to-mucosa anastomosis in all cases. The cited group considered this kind of anastomosis to be safe, having low complication rates, being reliable and favorable for the

anastomosis after pancreatoduodenectomy. The findings of this study are in accordance with the leakage rate described in the literature,[40–42] which lies between 5% and 25% in patients after pancreaticojejunostomy.

Prediction of a Soft Pancreas

As a main result, a strong correlation was found between an $SI_{ratio} \geq 1.1$ and a pancreas parenchyma of age-correlated healthy volunteers showing the same contrast enhancement. A similar finding has been described by Tajima et al.,[32] who described the perfusion of the pancreas to be the only independent variable for the prediction of leakage. As mentioned above, this was, however, performed with a technique which was less elaborate and reliable than the one in the present study. Patients with pancreas tumors addressed to have a resection of the pancreatic head can be categorized into two groups: (1) patients with a soft, fragile pancreas, and/or small pancreatic duct and (2) those with a fibrotic, firm pancreas, and/or dilated pancreatic duct. The first group is described to have a high risk for postoperative pancreatic anastomotic leakage, the second group to have a lower risk.[23,43,44] In the present study, there were better preoperative conditions described, along with an "objective" classification such as ASA classification, in the group with a better perfusion, which revealed a higher rate of anastomotic failure. This could lead to the assumption that objectively healthier patient are at a higher risk for anastomotic complications, due to a well-perfused soft gland. There is therefore a necessity for having other therapeutic options for patients at risk for a leakage. The change of the anastomotic technique in these patients (for instance from pancreaticojejunostomy to pancreatogastrostomy) could be a possible option (Fig. 3).

In summary, the present study demonstrated in particular a high rate of anastomotic leakage in patients with a regular perfusion of the pancreas parenchyma. This was contradictory to the fact that these patients had a lower surgical risk in general. Using a simple method of relative perfusion quantification, based on the contrast media enhancement of

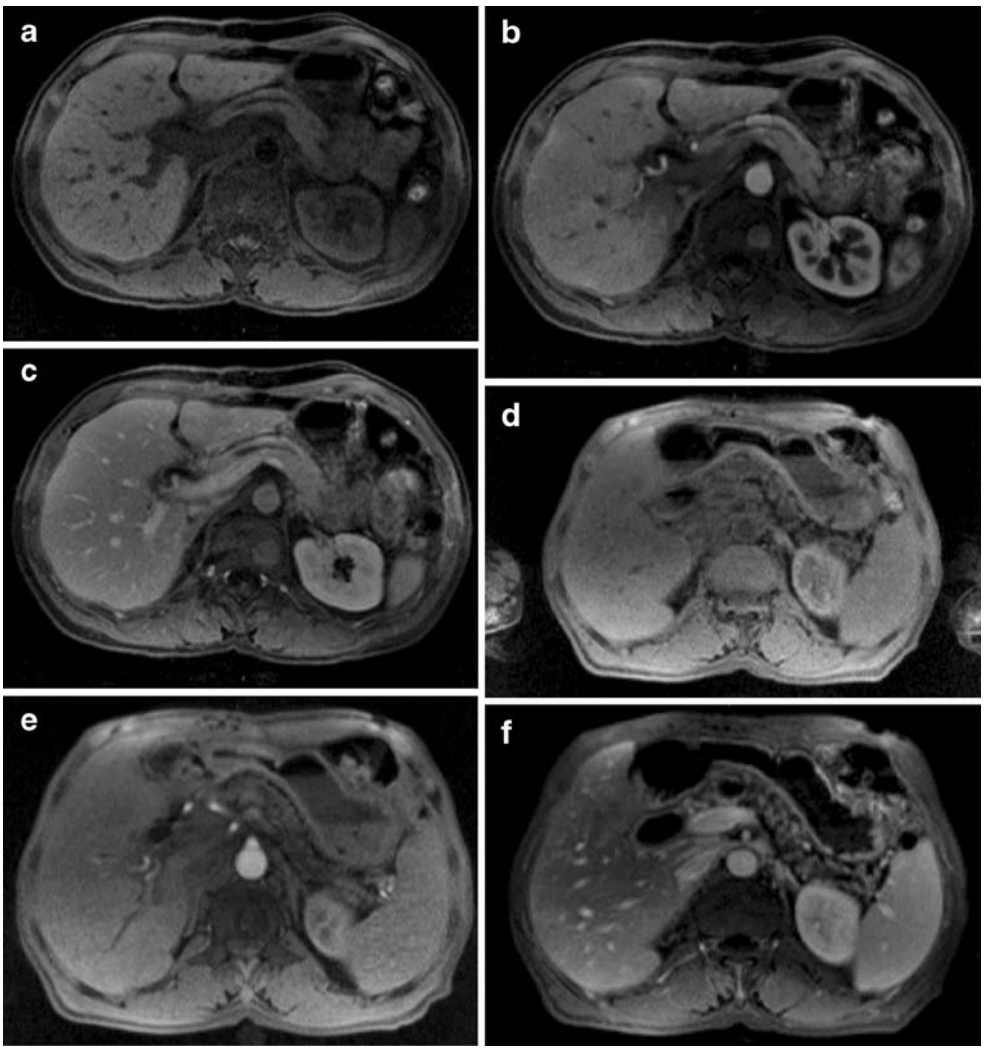

Figure 3 a–f T1-weighted images of the pancreas in a patient with a rapid increase of the SIC and a SI_{ratio} of ≥1.1 ("soft pancreas"; **a–c**) and in a patient with a delayed increase of the SIC and a SI_{ratio} of <1.1 ("firm pancreas"; **d–f**). Images **a** and **d** are native images, **b** and **e** demonstrate the early arterial phase, and **c** and **f** show the portal-venous phase.

the pancreas in relation to the aorta and the muscle tissue, it is possible to identify patients at risk for postoperative anastomotic leakage. Through applying the described dMRI technique, pancreatic surgeons can therefore preoperatively inform patients about their risk and possibly stratify these patients for other anastomotic techniques in the future.

References

1. Richter A, Niedergethmann M, Sturm JW, Lorenz D, Post S, Trede M. Long-term results of partial pancreaticoduodenectomy for ductal adenocarcinoma of the pancreatic head: 25-year experience. World J Surg 2003;27(3):324–329. doi:10.1007/s00268-002-6659-z.
2. Trede M, Schwall G, Saeger HD. Survival after pancreatoduodenectomy. 118 consecutive resections without an operative mortality. Ann Surg 1990;211(4):447–458. doi:10.1097/00000658-199004000-00011.
3. Trede M, Schwall G. The complications of pancreatectomy. Ann Surg 1988;207(1):39–47. doi:10.1097/00000658-198801000-00009.
4. 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.
5. 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(6):931–937. doi:10.1097/01.sla.0000246856.03918.9a, discussion 937–939.
6. Callery MP, Pratt WB, Vollmer CM Jr. Prevention and management of pancreatic fistula. J Gastrointest Surg 2008 (in press).
7. Niedergethmann M, Farag Soliman M, Post S. Postoperative complications of pancreatic cancer surgery. Minerva Chir 2004;59(2):175–183.
8. Strasberg SM, Linehan DC, Clavien PA, Barkun JS. Proposal for definition and severity grading of pancreatic anastomosis failure and pancreatic occlusion failure. Surgery 2007;141(4):420–426. doi:10.1016/j.surg.2006.12.001.
9. Reid-Lombardo KM, Farnell MB, Crippa S, Barnett M, Maupin G, Bassi C, et al. Pancreatic anastomotic leakage after pancreaticoduodenectomy in 1,507 patients: a report from the Pancreatic Anastomotic Leak Study Group. J Gastrointest Surg 2007;11(11):1451–1458. doi:10.1007/s11605-007-0270-4, discussion 1459.
10. Shinchi H, Wada K, Traverso LW. The usefulness of drain data to identify a clinically relevant pancreatic anastomotic leak after pancreaticoduodenectomy? J Gastrointest Surg 2006;10(4):490–498. doi:10.1016/j.gassur.2005.08.029.
11. Traverso LW. Pancreatic cancer: surgery alone is not sufficient. Surg Endosc 2006;20(Suppl 2):S446–449. doi:10.1007/s00464-006-0052-1.
12. Yang YM, Tian XD, Zhuang Y, Wang WM, Wan YL, Huang YT. Risk factors of pancreatic leakage after pancreaticoduodenectomy. World J Gastroenterol 2005;11(16):2456–2461.
13. Bartoli FG, Arnone GB, Ravera G, Bachi V. Pancreatic fistula and relative mortality in malignant disease after pancreaticoduodenectomy. Review and statistical meta-analysis regarding 15 years of literature. Anticancer Res 1991;11(5):1831–1848.
14. Murakami H, Suzuki H, Nakamura T. Pancreatic fibrosis correlates with delayed gastric emptying after pylorus-preserving pancreaticoduodenectomy with pancreaticogastrostomy. Ann Surg 2002;235(2):240–245. doi:10.1097/00000658-200202000-00012.
15. Sittek H, Heuck AF, Folsing C, Gieseke J, Reiser M. Static and dynamic MR tomography of the pancreas: contrast media kinetics of the normal pancreatic parenchyma in pancreatic carcinoma and chronic pancreatitis. Rofo 1995;162(5):396–403.
16. Hartel M, Niedergethmann M, Farag-Soliman M, Sturm JW, Richter A, Trede M, et al. Benefit of venous resection for ductal adenocarcinoma of the pancreatic head. Eur J Surg 2002;168(12):707–712. doi:10.1080/00000000000000007.
17. Niedergethmann M, Richter A, Wendl K, Schmidt B, Post S, Trede M. Rare indications for a Kausch–Whipple procedure. Eur J Surg 2001;167(2):115–119. doi:10.1080/110241501750070565.
18. Niedergethmann M, Shang E, Farag Soliman M, Saar J, Berisha S, Willeke F, et al. Early and enduring nutritional and functional results of pylorus preservation vs classic Whipple procedure for pancreatic cancer. Langenbecks Arch Surg 2006;391(3):195–202. doi:10.1007/s00423-005-0015-3.
19. 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(1):8–13. doi:10.1016/j.surg.2005.05.001.
20. Bassi C, Butturini G, Molinari E, Mascetta G, Salvia R, Falconi M, et al. Pancreatic fistula rate after pancreatic resection. The importance of definitions. Dig Surg 2004;21(1):54–59. doi:10.1159/000075943.
21. Yeo CJ. Management of complications following pancreaticoduodenectomy. Surg Clin North Am 1995;75(5):913–924.
22. de Castro SM, Kuhlmann KF, Busch OR, van Delden OM, Lameris JS, van Gulik TM, et al. Incidence and management of biliary leakage after hepaticojejunostomy. J Gastrointest Surg 2005;9(8):1163–1171. doi:10.1016/j.gassur.2005.08.010, discussion 1171–1163.
23. Lin JW, Cameron JL, Yeo CJ, Riall TS, Lillemoe KD. Risk factors and outcomes in postpancreaticoduodenectomy pancreaticocutaneous fistula. J Gastrointest Surg 2004;8(8):951–959. doi:10.1016/j.gassur.2004.09.044.
24. 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.
25. Schima W, Ba-Ssalamah A, Goetzinger P, Scharitzer M, Koelblinger C. State-of-the-art magnetic resonance imaging of pancreatic cancer. Top Magn Reson Imaging 2007;18(6):421–429. doi:10.1097/rmr.0b013e31816459e0.
26. Gaa J, Wendl K, Tesdal IK, Meier-Willersen HJ, Lehmann KJ, Bohm C, et al. Combined use of MRI and MR cholangiopancreatography and contrast enhanced dual phase 3-D MR angiography in diagnosis of pancreatic tumors: initial clinical results. Rofo 1999;170(6):528–533.
27. Sahani DV, Shah ZK, Catalano OA, Boland GW, Brugge WR. Radiology of pancreatic adenocarcinoma: current status of imaging. J Gastroenterol Hepatol 2008;23(1):23–33.
28. Zhong L. Magnetic resonance imaging in the detection of pancreatic neoplasms. J Dig Dis 2007;8(3):128–132. doi:10.1111/j.1443-9573.2007.00297.x.
29. Schima W. MRI of the pancreas: tumours and tumour-simulating processes. Cancer Imaging 2006;6:199–203. doi:10.1102/1470-7330.2006.0035.
30. Trede M, Rumstadt B, Wendl K, Gaa J, Tesdal K, Lehmann KJ, et al. Ultrafast magnetic resonance imaging improves the staging of pancreatic tumors. Ann Surg 1997;226(4):393–405. doi:10.1097/00000658-199710000-00001, discussion 405–397.

31. Coenegrachts K, Van Steenbergen W, De Keyzer F, Vanbeckevoort D, Bielen D, Chen F, et al. Dynamic contrast-enhanced MRI of the pancreas: initial results in healthy volunteers and patients with chronic pancreatitis. J Magn Reson Imaging 2004;20(6):990–997. doi:10.1002/jmri.20212.
32. Tajima Y, Kuroki T, Tsutsumi R, Fukuda K, Kitasato A, Adachi T, et al. Risk factors for pancreatic anastomotic leakage: the significance of preoperative dynamic magnetic resonance imaging of the pancreas as a predictor of leakage. J Am Coll Surg 2006;202(5):723–731. doi:10.1016/j.jamcollsurg.2006.01.008.
33. Tajima Y, Matsuzaki S, Furui J, Isomoto I, Hayashi K, Kanematsu T. Use of the time-signal intensity curve from dynamic magnetic resonance imaging to evaluate remnant pancreatic fibrosis after pancreaticojejunostomy in patients undergoing pancreaticoduodenectomy. Br J Surg 2004;91 (5):595–600. doi:10.1002/bjs.4461.
34. Bali MA, Metens T, Denolin V, De Maertelaer V, Deviere J, Matos C. Pancreatic perfusion: noninvasive quantitative assessment with dynamic contrast-enhanced MR imaging without and with secretin stimulation in healthy volunteers—initial results. Radiology 2008;247(1):115–121.
35. Noworolski SM, Henry RG, Vigneron DB, Kurhanewicz J. Dynamic contrast-enhanced MRI in normal and abnormal prostate tissues as defined by biopsy, MRI, and 3D MRSI. Magn Reson Med 2005;53(2):249–255. doi:10.1002/mrm.20374.
36. Wente MN, Shrikhande SV, Muller MW, Diener MK, Seiler CM, Friess H, et al. Pancreaticojejunostomy versus pancreaticogastrostomy: systematic review and meta-analysis. Am J Surg 2007;193 (2):171–183. doi:10.1016/j.amjsurg.2006.10.010.
37. Aranha GV, Hodul P, Golts E, Oh D, Pickleman J, Creech S. A comparison of pancreaticogastrostomy and pancreaticojejunostomy following pancreaticoduodenectomy. J Gastrointest Surg 2003;7(5):672–682. doi:10.1016/S1091-255X(02)00432-8.
38. Fang WL, Su CH, Shyr YM, Chen TH, Lee RC, Tai LC, et al. Functional and morphological changes in pancreatic remnant after pancreaticoduodenectomy. Pancreas 2007;35(4):361–365.
39. Hayashibe A, Kameyama M. The clinical results of duct-to-mucosa pancreaticojejunostomy after pancreaticoduodenectomy in consecutive 55 cases. Pancreas 2007;35(3):273–275.
40. 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(5):430–435. doi:10.1097/00000658-199305010-00002,, discussion 435–438.
41. Gouma DJ, van Geenen RC, 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.
42. Yeo CJ, Cameron JL, Lillemoe KD, Sauter PK, Coleman J, Sohn TA, et al. Does prophylactic octreotide decrease the rates of pancreatic fistula and other complications after pancreaticoduodenectomy? Results of a prospective randomized placebo-controlled trial. Ann Surg 2000;232(3):419–429. doi:10.1097/00000658-200009000-00014.
43. Fujino Y, Suzuki Y, Ajiki T, Tanioka Y, Ku Y, Kuroda Y. Risk factors influencing pancreatic leakage and the mortality after pancreaticoduodenectomy in a medium-volume hospital. Hepatogastroenterology 2002;49(46):1124–1129.
44. Hosotani R, Doi R, Imamura M. Duct-to-mucosa pancreaticojejunostomy reduces the risk of pancreatic leakage after pancreatoduodenectomy. World J Surg 2002;26(1):99–104. doi:10.1007/s00268-001-0188-z.

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ORIGINAL ARTICLE

Reduced Postoperative Pancreatic Fistula Rate After Pancreatogastrostomy Versus Pancreaticojejunostomy

U. Wellner · F. Makowiec · E. Fischer · U. T. Hopt · T. Keck

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Abstract
Introduction Metaanalysis of retrospective studies employing various definitions of pancreatic fistulas demonstrated a reduced postoperative pancreatic fistula rate after pancreatogastrostomy versus pancreaticojejunostomy. Prospective trials failed to do so, which causes an ongoing debate on the superiority of one or the other procedure. The aim of this study was to compare the two types of anastomosis at our institution with regard to postoperative pancreatic fistula and other complications.
Materials and Methods From 2001 to 2007, 114 pancreatogastrostomies and 115 pancreaticojejunostomies were performed. For retrospective analysis, the ISGPS definitions were employed. Primary endpoint was the occurrence of postoperative pancreatic fistula grade B or C. Secondary endpoints were postpancreatectomy hemorrhage, delayed gastric emptying, intraabdominal fluid collection, reoperation, and mortality. Operative time, intensive care unit stay, and overall hospital stay were also compared.
Results With pancreatogastrostomy, there were significantly less postoperative pancreatic fistulae grade B and C (pancreatogastrostomy (PG) versus pancreaticojejunostomy (PJ), 11.4% versus 22.6%, $p=0.03$), more intraluminal hemorrhage (PG versus PJ, 10.5% versus 0%, $p<0.001$) and more delayed gastric emptying grade B and C (PG versus PJ, 18.3% versus 7.9%, $p=0.03$). Operative time was shorter (PG versus PJ, median 420 versus 450 min, $p<0.01$), and intensive care unit stay was longer (PG versus PJ, median 4 days versus 5 days, $p<0.01$), with a tendency toward reduced overall hospital stay (PG versus PJ, median 17 versus 19 days, $p=0.08$).
Conclusion Surgeons should be aware of a higher rate of delayed gastric emptying and perform meticulous hemostasis to prevent intraluminal bleeding with pancreatogastrostomy. Pancreatogastrostomy is superior to pancreaticojejunostomy in terms of relevant postoperative pancreatic fistula.

Keywords Surgery · Pancreatic surgery · Pancreaticoduodenectomy · Postoperative pancreatic fistula · Postpancreatectomy haemorrhage · Delayed gastric emptying

Introduction

Since the first description of a successful pancreatoduodenectomy (PD) by Kausch in 1912,[1] there has been a debate among surgeons about which anastomotic procedure should be used to reinsert the pancreatic remnant. Among the various methods, only anastomosis to the jejunum or stomach has gained widespread international acceptance.[2] One, if not the most important, goal of all described procedures has been the reduction of the postoperative pancreatic fistula (POPF) rate to a minimum.

Reported perioperative mortality after pancreatic surgery has decreased to below 5% in centers, while occurrence of pancreatic fistula remains a significant problem, with incidences reported around 30% in the most recent series.[3–5] A metaanalysis of studies comparing pancreatogastrostomy (PG) and pancreaticojejunostomy (PJ) has shown a significant reduction of the POPF rate in favor of PG when retrospective studies were pooled. However, three prospective randomized trials failed to prove a superiority

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of PG over PJ.[6] This obvious discrepancy may be attributed to several factors. There may be a publication bias preventing nonsignificant retrospective data from being published. Furthermore, in the past and also for the prospective trials, authors have used many different definitions of POPF, which makes direct comparison of and pooling of data from several studies difficult.[7] The case number of the prospective trials was around 150,[8–10] which is lower than that of many retrospective studies and does not provide enough power to prove differences between incidence rates, which are between 10% and 20%. Last but not least, the operative technique varies in detail between the studies. Taken together, there remains an active discussion concerning the optimal anastomotic technique.

A major step toward standardization of perioperative outcome measurement in pancreatic surgery has been the publication of consensus definitions for POPF, delayed gastric emptying (DGE), and postpancreatectomy hemorrhage (PPH) by the International Study Group of Pancreatic Surgery.[7,11,12] The aim of this retrospective study was to compare the perioperative outcome of PD with PG versus PJ at our institution by using a large case number and the new consensus definitions.

Materials and Methods

Data The data of our prospectively maintained database for pancreatic surgery was used as a basis to perform a retrospective analysis for PD performed from 2001 to 2007. For correct assessment of POPF, DGE, and PPH grading according to the ISGPS,[7,11,12] the patient's records had to be reviewed, which are completely digitalized in our institution after patient discharge.

Operative Technique The technique of completely intragastric pancreatogastrostomy consisted of a purse string suture in the gastric wall (2-0 PDS) and a second intragastric line of interrupted sutures (4-0 PDS). Therefore, an additional anterior gastrotomy was necessary. PJ was performed to a Roux-Y-loop of the jejunum by single layer suture (4-0 PDS; SL-PJ) or with additional duct-mucosa-suture (5-0 PDS; DM-PJ) as described by Cartell. For SL-PJ, a decompression tube was placed in the jejuna limb, and for DM-PJ, pancreatic duct stenting was performed. For hepaticojejunostomy (single layer, interrupted, 5-0 PDS) and gastrojejunostomy (single layer, continuous, 4-0 PDS), the same jejunal Roux-Y-loop was used. In the observed time period, only four surgeons performed all pancreatoduodenectomies, and every surgeon was trained to perform all aforementioned pancreatoenteric anastomoses. The preferred anastomotic techniques were SL-PJ from 2001 to 2003, DM-PJ from 2003 to 2004, and PG from 2004 to 2006.

The decision of which procedure to chose between 2001 and 2004 was solely based on the surgeon's preference. Since 2006, patients, if eligible, were included in a prospective randomized trial that is still currently recruiting in our institution. Since 2006, 75 patients were included in this prospective randomized trial. In patients not included in the trial, the decision of which procedure should be used again was based on the surgeon's preference in the individual case. Peritoneal drains were placed in close proximity to the pancreato- and bilioenteric anastomosis.

Standard Postoperative Patient Care All patients were transferred to the intermediate care unit for postoperative surveillance for at least 3 days. Amylase activity in peritoneal drainage fluid was measured daily during the first postoperative week until removal of drains. At the beginning of the observation period, Sandostatin (3× 100 μg s.c.) was administered routinely, but after 2002, only in case of elevated amylase activity (>1,000 U/l) on day 3 or later was it administered routinely. Amylase activity was also measured routinely if fluid samples were obtained by puncture of intraabdominal collections or ascites. Every patient received a double lumen tube for gastric decompression and early jejunal feeding, which was removed depending on tolerance for oral food intake, the goal being removal by postoperative day 3 or 4.

Standard Treatment of Postoperative Complications Abdominal computed tomography was performed in case of clinical suspicion of intraabdominal complication. Intraabdominal collections caused by POPF or other reason were preferably drained interventionally. DGE was treated by application of erythromycin and stepwise increasing oral food intake. In refractory cases, dilatation of the pylorus was the primary invasive treatment option. PPH was treated depending on severity, and first-line management of severe postoperative bleeding consisted of angiographic intervention.

Endpoints The primary endpoint was defined as the occurrence of POPF grade B or C. Secondary endpoints were DGE and PPH, reoperation, intraabdominal collection with the necessity for invasive treatment (IAC), postoperative mortality, length of ICU stay, and overall postoperative hospital stay. Patient demographics, comorbidity, and pathology reports were also evaluated with special regard to known risk factors for POPF. For POPF, DGE, and PPH, definitions and classification of the *ISGPS* were used.

Briefly, *POPF* is defined as an amylase activity in peritoneal drainage fluid greater than three times the upper serum normal value (300 U/l) on or after postoperative day (POD) 3. Grade A POPF does not require specific medical or invasive therapy or diet restriction, and POPF grade B is managed by specific conservative treatment and typically

Table 1 Patient and Operation Characteristics

	PG	PJ	*p*
Preoperative parameters			
Number of cases	114	115	ns
Age (median, years)	67.6	65.5	0.02
Male/female ratio	5:6	6:5	ns
Preoperative bilirubin (mg/dl)	3.7	3.3	ns
Preoperative biliary drainage (%)	47.4	59.1	ns
Preoperative creatinine (median, mg/dl)	0.8	0.7	0.04
Preoperative diabetes mellitus (%)	21.1	22.6	ns
Operative technique			
Pylorus-preserving operation (%)	90.4	86.1	ns
Portal vein resection (%)	22.8	26.1	ns
Intraoperative blood transfusion (%)	21.1	27.8	ns
Histopathologic diagnosis			
Adenocarcinoma of the pancreas (%)	41.2	45.2	ns
Ampullary carcinoma (%)	16.7	11.3	ns
Duodenal carcinoma (%)	7.0	3.5	ns
Distal bile duct carcinoma (%)	10.5	16.5	ns
Neuroendocrine tumors (%)	2.6	1.7	ns
IPMN (%)	2.6	0.9	ns
Chronic pancreatitis (%)	11.4	15.7	ns
Other diagnosis (%)	7.9	5.2	ns
Type of lesion			
Benign (%)	16.7	18.3	ns
Malignant (%)	79.8	80.9	ns
Borderline (%)	3.5	0.9	ns

PG pancreatogastrostomy, *PJ* pancreatojejunostomy, *IPMN* intraductal papillary mucinous neoplasia, *p* derived from statistic tests, *ns* not significant

leads to prolonged hospital stay or readmission, whereas POPF grade C requires invasive treatment such as percutaneous drainage or reoperation. Because in the beginning of this study Sandostatin treatment was performed routinely as described above, this was not considered a criterion for POPF grade B.

DGE was defined as the necessity of gastric tube decompression after POD 3 or later or the inability to tolerate solid oral intake (SOI) on POD 7 or later. If the gastric tube could only be removed by day 7, 14, or 21 and SOI was only possible by POD 14, 21, or later, DGE was graded A, B, or C, respectively. DGE grade A requires only prokinetic drugs, DGE grade B requires diagnostic measures or prolonged hospital stay, and invasive treatment leads to classification as DGE grade C.

PPH is defined as every bleeding event after pancreatic surgery. PPH grade A does not require specific treatment but only diagnostic measures, PPH grade B requires treatment, and PPH grade C is considered life threatening. Early or late PPH occur within or later than 24 h after the operation. Intraluminal PPH has an intraluminal origin, in contrast to extraluminal PPH.

Statistical Analysis All data were collected and analyzed in a SPSS Version 15.0 database. The two-sided Fishers exact test was used for dichotomous variables, the Mann–Whitney *U* test for scale variables, Spearman's method for rank correlation, and binary logistic regression for multivariate analysis.

Results

Patients and Operations From 2001 to 2007, 229 PD were performed at the University Hospital Freiburg. Of these, 114 were reconstructed with PG and 115 with PJ (66 SL-PJ and 49 DM-PJ). Patient characteristics are shown in Table 1. There were no significant differences between the groups PG and PJ except for preoperative creatinine and age at

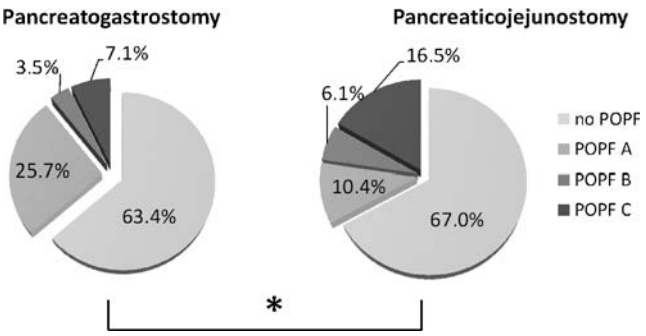

Figure 1 POPF with PG and PJ. *PG* pancreatogastrostomy, *PJ* pancreaticojejunostomy. Grade of POPF (A, B, C) is given according to the ISGPS classification. *p=0.03 for POPF grade B or C.

Table 2 Occurrence of the Primary Endpoint with Different Types of Anastomoses

	PG	PJ	*p*	SL-PJ	DM-PJ	*p*
POPF grade B or C	11.4%	22.6%	0.03	24.2%	20.4%	ns

Postoperative pancreatic fistula grade B or C (POPF B or C) after pancreatogastrostomy (PG) or pancreatojejunostomy (PJ)
SL-PJ PJ with single suture line, *DM-PJ* PJ with duct-mucosa anastomosis; *p* derived from statistic tests, *ns* not significant

operation, which were slightly higher in the PG group. Around 90% of operations were performed with preservation of the pylorus, and in about one fourth of cases, a portal vein resection was carried out because of malignant invasion. Most of the operations were carried out for malignant lesions.

Postoperative Pancreatic Fistula (POPF) The distribution of POPF by definition of the ISGPS is shown in Fig. 1 and Table 2. There were significantly less POPF of grade B and C (PG versus PJ, 11.4% versus 22.6%, $p=0.03$) in the PG group compared to the PJ group. The overall fistula rate (grade A, B, and C) was not statistically different (PG versus PJ, 36.8% versus 33.0%, p=ns). Intraabdominal collections were associated with POPF ($p<0.001$) and less frequently with PG (PG versus PJ, 9.6% versus 16.5%), but this reduction did not reach the significance level (p=ns). Comparison of SL-PJ and DM-PJ for the primary endpoint did not show a significant reduction with duct-to-mucosa technique (SL-PJ versus DM-PJ, 24.2% versus 20.4%, p= ns). The underlying pancreatic disease had a significant influence on the rate of POPF grade B and C. There was a negative correlation with pancreatic carcinoma and a positive correlation with ampullary carcinoma, as outlined in Table 3. Univariate analysis for factors known to influence POPF rate also disclosed a significant positive correlation for the preoperative creatinine level. In multivariate analysis, type of anastomosis and pancreatic carcinoma were the only independent predictors of the primary endpoint, as outlined in Table 4.

Postpancreatectomy Hemorrhage (PPH) A summary of PPH events is given in Table 5. None of the PPH episodes was considered grade A because there was always a therapeutic intervention. There were no significant differences between PG and PJ, except for significantly more intraluminal PPH in the PG group than in the PJ group (PG versus PJ, 10.5% versus 0%). This was in part caused by bleeding from the pancreatogastric anastomosis site, which required relaparotomy in four cases (3.5% of PG). There was no case of disruption of the anastomosis by bleeding events as described by other authors.[13] In all four cases that required relaparotomy, the bleeding from the anastomotic site was occurring within the first or second day after the operation, and within the first 20 cases, we performed this procedure. The source of bleeding was in all these cases the cut surface of the pancreas. Since we changed our regimen of bleeding control on this surface intraoperatively from electrocautery to 5-0 PDS sutures, we did not experience this complication any more. Relaparotomy in these cases was preferred to endoscopy as we were worried about additional damage to the pancreatogasrostomy, the gastrojejunostomy, or the ventral gastrostomy.

Delayed Gastric Emptying (DGE) There was a significantly higher rate of DGE of grade B and C in the PG group than in the PJ group (PG versus PJ, 18.3% versus 7.9%, p= 0.03), as outlined in Fig. 2. Interestingly, an association of DGE with other complications, namely POPF and IAC, could only be demonstrated for PJ but not for PG (Table 6).

Relaparotomy, Overall Mortality, and Hospital Stay Relaparotomy rates were not statistically different comparing PG and PJ (15.8% versus 10.4%, p=ns). Indications for relaparotomy are shown in Fig. 3. The slightly, but not significantly higher reoperation rate for PG, was for the greatest part caused by relaparotomy for intraluminal bleeding (four cases, 3.5% of PG). Reoperation rates were

Table 3 Occurrence of the Primary Endpoint with Different Histopathologic Diagnoses

Histopathologic diagnosis	Occurrence of POPF grade B or C (%)	Correlation coefficient	*p*
Pancreatic CA	9.1	−0.18	<0.01
Ampullary CA	31.3	0.15	0.02
Distal bile duct CA	29.0	0.13	ns
Chronic pancreatitis	19.4	0.02	ns
Other	13.9	−0.04	ns

Shown are the results of correlation analysis for specific histopathologic diagnoses and the occurrence of the primary endpoint POPF grade B or C
POPF postoperative pancreatic fistula, *CA* carcinoma, *p* derived from statistic tests, *ns* not significant

Table 4 Analysis of Factors Influencing POPF Rate

Factor		*p*
Univariate analysis		
	Correlation coefficient	
Type of anastomosis: PG or PJ (=0/1)	0.15	0.02
Age (years)	0.02	ns
Gender (m/f=0/1)	0.09	ns
Preop. creatinine (mg/dl)	0.14	0.04
Preop. bilirubin (mg/dl)	0.09	ns
Preop. diabetes mellitus	0.01	ns
Intraop. blood transfusion	0.09	ns
Multivariate analysis		
	Odds ratio	
Type of anastomosis: PG or PJ (=0/1)	2.58	0.01
Pancreatic carcinoma	0.39	0.03
Ampullary carcinoma	2.01	ns
Preop. creatinine (mg/dl)	1.19	ns

Primary endpoint was postoperative pancreatic fistula (POPF) grade B or C (0 = no and 1 = yes). The upper panel shows the results of univariate analysis; the lower panel shows the results of multivariate analysis. *PG* pancreatogastrostomy, *PJ* pancreatojejunostomy, *preop.* preoperative, *intraop.* Intraoperative, *ns* not significant

high mainly due to postoperative hemorrhage in the pancreatogastrotomy group as specified above. Reoperation rates in general may be higher than in other studies from pancreatic centers. This might reflect our aggressive approach to postoperative complications. We prefer open revisions when we face problems with the pancreatic or biliodigestive anastomosis. We also prefer operative revisions for very early gastrointestinal bleeding from the pancreatic remnant after pancreatogastrostomy. This aggressive approach results in higher reoperation rates but might indeed contribute to our low mortality rates. Overall, perioperative mortality was 2.6%. Causes were late PPH (two cases), peritonitis with sepsis (two cases), liver failure due to stent occlusion after stent placement in the common hepatic artery for arrosion of the gastroduodenal artery (one case), and acute myocardial infarction (one case). There was no significant difference in perioperative mortality between PG (1.8%) and PJ (3.5%).

Operation time was 30 min shorter when PG was performed (PG versus PJ, median 420 versus 450 min, $p<0.01$). Postoperative ICU stay was significantly longer after PG than after PJ (PG versus PJ, median 4 days versus 5 days, $p<0.01$). Length of ICU stay correlated positively with PPH, POPF, and also with occurrence of DGE grade B and C ($p<0.05$). Overall, postoperative hospital stay was shorter with PG, but this was only a statistic trend (PG versus PJ, 17 versus 19 days, $p=0.08$).

Table 5 Occurrence of Postpancreatectomy Hemorrhage (PPH) According to the ISGPS Classification

	PG (%)	PJ (%)	*p*
PPH grade A	0	0	ns
PPH grade B	11.4	4.3	ns
PPH grade C	5.3	4.3	ns
Mild PPH	6.1	2.6	ns
Severe PPH	10.5	6.1	ns
Intraluminal PPH	10.5	0	<0.001
Extraluminal PPH	6.1	8.7	ns
Early PPH	3.5	0	ns
Late PPH	13.2	8.7	ns

PG pancreatogastrostomy, *PJ* pancreatojejunostomy, *p* derived from statistic tests, *ns* not significant

Discussion

Many retrospective reports have compared PG and PJ, and recent metaanalysis disclosed lower POPF rates in favor of PG.[6] Nevertheless, three prospective, randomized studies failed to demonstrate a better outcome regarding POPF or perioperative mortality, also if pooled for metaanalysis.[6] The results of most of all studies are not directly comparable, as POPF definitions and operative techniques vary.[7] Prospective studies were maybe underpowered to find small differences in POPF rates. Only few recent studies have employed the ISGPS consensus definitions yet.[3–5] The aim of this

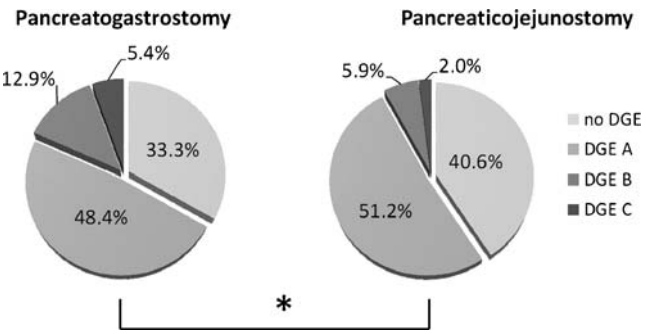

Figure 2 DGE with PG and PJ. *PG* pancreatogastrostomy, *PJ* pancreaticojejunostomy. Grade of DGE (A, B, C) is given according to the ISGPS classification. *$p=0.03$ for DGE grade B or C.

Table 6 Type of Anastomosis Affects the Association of DGE with Other Postoperative Complications

	DGE (%)	*p* value for association with	
		POPF	IAC
PG	66.7	ns	ns
PJ	59.4	0.03	0.02

PG pancreatogastrostomy, *PJ* pancreatojejunostomy, *DGE* delayed gastric emptying (all grades), *POPF* postoperative pancreatic fistula (all grades), *IAC* intraabdominal collection requiring invasive treatment, *p* derived from statistic tests, *ns* not significant

study was to compare the perioperative outcomes of PG versus PJ at our institution, using the ISGPS definitions and a case number large enough to demonstrate small differences. For proper adherence to these definitions, a review of all patient records was necessary.

By definition, the clinical impact of POPF grade A is low, as this implies only "biochemical" self-limited fistulae.[7] Therefore, we decided to use POPF grade B and C as the primary endpoint. Our analysis showed a significantly lower rate of the clinically relevant POPF of grade B and C in the PG group, suggesting that PG is superior to PJ in terms of POPF. Of note, the type of anastomosis and pancreatic carcinoma were the only independent factors, which showed an influence on POPF rate, in contrast to other known factors. Pancreatic carcinoma, which is often associated with hard pancreatic texture, was a protective factor; surprisingly, however, chronic pancreatitis, which is well known for its fibrotic pancreatic tissue, was not. Within the PJ group, the duct-to-mucosa technique did not lead to a significant reduction in POPF rate. The lower rate of POPF after PG did not translate into a significantly reduced rate of IAC or reoperations, however. The rationale behind a reduced POPF rate with PG (as performed at our institution) may be the effective inversion of the pancreatic remnant into the stomach and the fact that the complete anastomosis, including all suture line stitch channels, are situated intragastric, in contrast to the transmural sutures involved in SL-PJ or DM-PJ. It is noteworthy that for the aforementioned three prospective studies of PG versus PJ, different PG techniques were performed. One also has to reflect that each of the anastomosic procedures has a learning curve that should, as the learning effect occurs for each method, not lead to improved insults of one of these techniques over time. However, we are aware that we are presenting a retrospective study that is not free of this potential bias.

Concerning PPH, analysis showed that there was more intraluminal bleeding in the PG group, which was in part caused by bleeding from the PG site requiring relaparotomy. However, disruption of the pancreatoenteric anastomosis, as described in other series,[13] did not occur. Relaparotomy in these cases was considered necessary because air insufflation and gastric distension during gastroscopic hemostatic measures would have constituted a thread to the freshly established PG. Bleeding at the PG site was mainly an initial problem of this technique, which can be circumvented by proper intraoperative hemostasis by small 5-0 sutures on the surface of the pancreatic remnant. In our experience with PG, single stitches rather than electrocoagulation provide sufficient hemostasis at the pancreatic cut surface and pancreatoenteric anastomosis site.

The incidence of clinically relevant DGE (grade B and C) was higher in the PG group. This result seems reasonable, as PG requires more extensive mobilization of the stomach along the lesser curve, which is associated with disruption of autonomous nerve fibers mediating gastric motility. There are also two additional gastrotomies (anterior and posterior) with PG, increasing gastric traumatization. PG furthermore leads to a fixation of the posterior stomach wall to the retroperitoneum, potentially limiting gastric wall motility. However, DGE has also been reported to be less frequent with PG than with PJ in other prospective and retrospective trials.[6] Interestingly, the known association of DGE with other postoperative

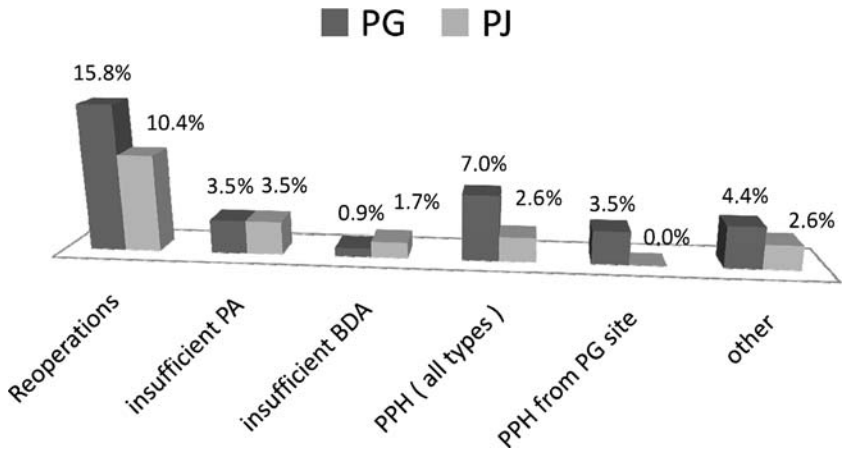

Figure 3 Reoperations and indications with PG and PJ. Given are the percentages in the groups of PG and PJ. *BDA* biliodigestive anastomosis, *PPH* postpancreatectomy hemorrhage according to the ISGPS classification.

complications such as POPF or IAC could only be demonstrated for the PJ group and not for PG. This is important to notice as DGE raises the suspicion for intraabdominal complications especially for PJ, but less so if the anastomosis is a PG. DGE in the PG group might have contributed to the longer ICU stay in this group, as shown by a positive correlation. Nevertheless, there was a trend toward shorter overall postoperative hospital stay with PG.

Perioperative mortality was low in both groups, and lower after PG than after PJ, but not statistically significant. An important factor contributing to postoperative mortality was late extraluminal PPH, as this was the responsible inciting event for 50% of the perioperative mortality. Late PPH leads to lethal hemorrhagic shock in one patient. In the second case, bleeding could be controlled by stent placement in the common hepatic artery, but stent occlusion caused lethal liver failure. The third patient suffered from repeated massive venous intraabdominal bleeding, which led to multiorgan failure and ultimately abdominal sepsis. The potentially fatal role of delayed PPH is in line with the observations of other authors.[12–16] In summary, the pancreatogastrostomy provides a good, simple, and easy to perform anastomosis as an alternative to the pancreaticojejunostomy. We are still including patients for our prospective randomized trial on pancreatic anastomosis. Our preferred technique for patients not eligible for the trial is the pancreatogastrostomy for the soft pancreas and the pancreaticojejunostomy for the hard pancreas. For the soft pancreas, the pancreatogastrostomy is especially easy to perform as the pancreas is invaginated into the stomach. For the hard pancreas, the Warren Cartell anastomosis seems more effective as an extended mobilization of the pancreatic remnant can sometimes be difficult in these patients. Reoperations and complications in the pancreatogastrostomy group were mainly encountered in the beginning of the application of this technique. In our prospective study, which started after the learning curve, we might not anymore encounter these drawbacks of the pancreatogastrostomy as presented in this current retrospective study.

Conclusion

The ISGPS definitions are well suited for comparative studies in pancreatic surgery. In concordance with previous findings, the present study suggests that PG is superior to PJ in terms of POPF. When performing PG, surgeons should be aware of a higher rate of DGE and proper intraoperative hemostasis to prevent intraluminal PPH. Mortality rates for pancreatoduodenectomy are low in centers and did not differ significantly between PG and PJ. These findings have to be confirmed by an additional ongoing prospective trial.

References

1. Kausch. Das Carcinom der Papilla duodeni und seine radikale Entfernung. Beitr Klinischen Chir 1912;78:439–486.
2. Shrikhande SV, Qureshi SS, Rajneesh N, Shukla PJ. Pancreatic anastomoses after pancreaticoduodenectomy: do we need further studies? World J Surg 2005;29(12):1642–1649. doi:10.1007/s00268-005-0137-3.
3. Pratt WB, Maithel SK, Vanounou T, Huang ZS, Callery MP, Vollmer CM Jr. Clinical and economic validation of the International Study Group of Pancreatic Fistula (ISGPF) classification scheme. Ann Surg 2007;245(3):443–451. doi:10.1097/01.sla.0000251708.70219.d2.
4. Pratt WB, Callery MP, Vollmer CM Jr. Risk prediction for development of pancreatic fistula using the ISGPF classification scheme. World J Surg 2008;32(3):419–428. doi:10.1007/s00268-007-9388-5.
5. Reid-Lombardo KM, Farnell MB, Crippa S, Barnett M, Maupin G, Bassi C, et al. Pancreatic anastomotic leakage after pancreaticoduodenectomy in 1,507 patients: a report from the Pancreatic Anastomotic Leak Study Group. J Gastrointest Surg 2007;11(11):1451–1458. doi:10.1007/s11605-007-0270-4, discussion 1459.
6. Wente MN, Shrikhande SV, Muller MW, Diener MK, Seiler CM, Friess H, et al. Pancreaticojejunostomy versus pancreaticogastrostomy: systematic review and meta-analysis. Am J Surg 2007;193(2):171–183. doi:10.1016/j.amjsurg.2006.10.010.
7. 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(1):8–13. doi:10.1016/j.surg.2005.05.001.
8. Yeo CJ, Cameron JL, Maher MM, Sauter PK, Zahurak ML, Talamini MA, et al. A prospective randomized trial of pancreaticogastrostomy versus pancreaticojejunostomy after pancreaticoduodenectomy. Ann Surg 1995;222(4):580–588. discussion 588–92.
9. Bassi C, Falconi M, Molinari E, Salvia R, Butturini G, Sartori N, et al. Reconstruction by pancreaticojejunostomy versus pancreaticogastrostomy following pancreatectomy: results of a comparative study. Ann Surg 2005;242(6):767–771. doi:10.1097/01.sla.0000189124.47589.6d, discussion 771–3.
10. Duffas JP, Suc B, Msika S, Fourtanier G, Muscari F, Hay JM, et al. A controlled randomized multicenter trial of pancreatogastrostomy or pancreatojejunostomy after pancreatoduodenectomy. Am J Surg 2005;189(6):720–729. doi:10.1016/j.amjsurg.2005.03.015.
11. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 2007;142(5):761–768. doi:10.1016/j.surg.2007.05.005.
12. Wente MN, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, et al. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery 2007;142(1):20–25. doi:10.1016/j.surg.2007.02.001.
13. Yekebas EF, Wolfram L, Cataldegirmen G, Habermann CR, Bogoevski D, Koenig AM, et al. Postpancreatectomy hemorrhage: diagnosis and treatment: an analysis in 1669 consecutive pancreatic resections. Ann Surg 2007;246(2):269–280. doi:10.1097/01.sla.0000262953.77735.db.
14. van Berge Henegouwen MI, Allema JH, van Gulik TM, Verbeek PC, Obertop H, Gouma DJ. Delayed massive haemorrhage after pancreatic and biliary surgery. Br J Surg 1995;82(11):1527–1531. doi:10.1002/bjs.1800821124.
15. Tien YW, Lee PH, Yang CY, Ho MC, Chiu YF. Risk factors of massive bleeding related to pancreatic leak after pancreaticoduodenectomy. J Am Coll Surg 2005;201(4):554–559. doi:10.1016/j.jamcollsurg.2005.05.007.
16. Trede M, Schwall G. The complications of pancreatectomy. Ann Surg 1988;207(1):39–47. doi:10.1097/00000658-198801000-00009.

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ORIGINAL ARTICLE

Determining Pattern of Recurrence Following Pancreaticoduodenectomy and Adjuvant 5-Flurouracil-Based Chemoradiation Therapy: Effect of Number of Metastatic Lymph Nodes and Lymph Node Ratio

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Abstract
Background There are limited data on patterns of recurrence and factors associated with local recurrence following pancreaticoduodenectomy for pancreatic adenocarcinoma and adjuvant 5-flurouracil-based chemoradiation therapy.
Methods and Materials Between 1995 and 2005, 905 patients underwent pancreaticoduodenectomy for pancreatic adenocarcinoma; 154 patients had complete pattern of recurrence data available.
Results At median follow-up of 20.2 months, 103 (66.9%) patients recurred with median time to recurrence of 16.2 months. Most patients recurred with distant disease only (68.9%), while 21.4% patients recurred with local disease only; ten (9.7%) patients recurred with local and distant disease. Several factors were associated with local recurrence: poor tumor differentiation (hazards ration [HR] 2.39) and presence of metastatic lymph nodes (HR 1.89, both $p<0.05$). Among N1 patients, poor tumor differentiation (HR 3.92), >5 metastatic LN (HR 3.75), and lymph node ratio (LNR) >0.4 (HR 2.96) had the highest risk of local recurrence (all $p<0.05$). Increasing LNR was associated with an incremental increased risk of local recurrence (LNR <0.2, 21.3% versus LNR ≥0.2 to 0.4, 25.2% versus LNR >0.4, 40.4%; $p<0.05$).
Conclusions Although most patients who receive standard 5-flurouracil-based chemoradiation therapy will ultimately succumb to distant disease, about 30% recur locally. Poor tumor differentiation, a high number of metastatic LN (>5), and LNR >0.4 are associated with the highest risk of local failure. In these patients, radiation dose escalation and/or a combination of radiation with novel chemotherapeutic agents may be necessary to improve outcomes.

Keywords Lymph node · Pancreatic · Adenocarcinoma · Recurrence · Adjuvant chemoradiation · 5-Flurouracil

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Introduction

Pancreatic adenocarcinoma is associated with a crude overall 5-year survival rate of less than 5%.[1] In a subset of patients in whom surgical resection is feasible, long-term survival may approach 20%–25%.[2–4] Unfortunately, even in patients who successfully undergo pancreatic resection, the local failure rate may be as high as 50%–80%.[5–8] Local failure can be a major postoperative problem, causing pain, obstruction, and a poor quality of life. Traditionally, adjuvant chemotherapy and radiation therapy have been advocated as a potential means to lower the risk of local recurrence. The addition of adjuvant chemoradiation has been reported to decrease local recurrence rates to 20%–

40%,[5,9,10] with some studies even reporting local recurrence rates as low as 10%.[11–15] Despite this, the routine utilization of radiation remains controversial. Data from the European Study Group for Pancreatic Cancer (ESPAC)[16] have shown no overall benefit for adjuvant chemoradiation therapy. As such, the routine use of chemoradiation therapy remains contested.

Most institutional reports on outcome following pancreaticoduodenectomy have focused on overall survival. In fact, there are limited data[6,7,17,18] on patterns of recurrence and the factors associated with local recurrence following pancreaticoduodenectomy for pancreatic adenocarcinoma. In addition, data on recurrence have mostly examined the impact of resection margin status on pattern of failure.[17] Lymph node status has been demonstrated to be one of the strongest factors associated with survival.[2–4,19] In addition, our group[20,21] as well as others[22,23] have suggested that lymph node ratio (LNR) may better substratify patients with regard to prognosis. Despite this, the association between pattern of recurrence and lymph node status has not been well examined.

The objective of the current study was to examine patterns of recurrence following pancreaticoduodenectomy and adjuvant 5-flurouracil (5-FU)-based chemoradiation for pancreatic adenocarcinoma. Specifically, we sought to identify factors that were associated with specific patterns of disease failure. In particular, we were interested in examining whether the number of metastatic lymph nodes or the LNR determined the pattern of recurrence following pancreaticoduodenectomy and adjuvant 5-FU-based chemoradiation.

Patient and Methods

Data were collected prospectively on 905 patients at Johns Hopkins Hospital who underwent pancreaticoduodenectomy with curative intent for pancreatic adenocarcinoma in the head of the pancreas between 1995 and 2005. The study was approved by the Johns Hopkins Institutional Review Board. To ensure accurate and homogeneous follow-up data with regard to pattern of recurrence, only patients who were treated and followed up at Johns Hopkins Hospital were included in the current study. Based on inclusion criteria, 154 patients were identified. According to our standard postoperative approach at the time, all patients received 5-FU-based chemoradiation therapy. Specifically, 4 to 6 weeks following resection, 3,400–5,700 cGy were administered in fractionated daily doses of 1.8–2.4 cGy. Table 1 outlines the radiation treatment information. Patients receiving 40 Gy or less were treated per the classic Gastro-Intestinal Study Group regimen in which patients received 2,000 cGy followed by a 2-week break and then another 2,000 cGy. The decision to deliver above 4,000 cGy was made by the individual treating radiation oncologist based on whether the patient had positive margins and/or the assessment that the dose could be safely escalated. The majority of patients during this time period were treated with conformal radiation using four or more fields (Table 1). All patients were treated on a linear accelerator with most plans utilizing 15 MV photon beams.

Table 1 Details of Radiation Treatment (n=154)

Variable	Number of patients (%)
Number of fields	
4 or more	123 (79.9)
2 or 3	25 (16.2)
Unknown	6 (3.9)
Fractionation (Gy)	
1.8	88 (57.1)
2.0	25 (16.2)
>2.0	41 (26.7)
Total dose (Gy)	
52.2–57.6	46 (29.9)
50–50.4	63 (40.9)
<50	45 (29.2)
Treatment break	
No	74 (48.1)
Yes (unplanned)	46 (29.9)
Yes (planned)	29 (18.8)
Unknown	5 (3.2)

For radiation planning, the clinical treatment volume was defined as follows: the hepatojejunostomy, pancreaticojejunostomy, and the proximal celiac and superior mesenteric arteries. The retroperitoneum from the level of the paraaortic nodes to the third lumbar vertebrae encompassing the porta hepatis, pancreaticojejunostomy anastomosis, and the celiac axis were routinely encompassed in the radiation field.

These structures, plus the retroperitoneal lymph nodes, were expanded by 1.5 cm for the final planning treatment volume. Over the time period of the study, a majority of patients were treated on several 5-FU-based in-house protocols. In general, patients were seen postoperatively by a medical and radiation oncologist. Patients received continuous infusion fluorouracil (225–250 mg/m^2 per day) with conformal radiation therapy followed by maintenance fluorouracil (250 mg/m^2) for an additional 2 to 6 months.

Patients were routinely followed every 3 to 4 months according to a standardized protocol, including both clinical assessment, laboratory exams (e.g., CA19-9), and cross-sectional imaging. In general, cross-sectional imaging included a three-dimensional (3-D) computed tomography

scan of the abdomen and pelvis. The following data were collected for each patient: demographics; tumor characteristics (size, grade, vascular invasion, perineural invasion), and pathologic margin status (R0: grossly complete resection with microscopically negative margins; R1: grossly complete resection with microscopically positive margins; R2: grossly incomplete resection).[24] The retroperitoneal margin was handled as a perpendicular margin.[25] A positive retroperitoneal margin was defined as infiltrating carcinoma at the margin. The posterior margin was always sampled. The anterior margin was only sampled if the lesion grossly extended anteriorly, and the anterior surface of the gland appeared disrupted. Other pathologic data collected included presence of lymph node metastasis, number of metastatic lymph nodes, and LNR. LNR was defined as the number of positive nodes divided by the number of total nodes harvested. Patients were subclassified into four LNR groups: LNR 0 (e.g., N0 subgroup), LNR >0–0.2, LNR >0.2–0.4, LNR >0.4 based on previous work that had established these cutoff values as being the most discriminating.[20,21]

The primary outcome of interest was pattern of recurrence. The first site or sites of disease recurrence were classified as local or distant. Local recurrence was defined as any recurrence in the region of the pancreatic bed, root of mesentery, or soft tissues/lymph nodes within the pancreatic bed area. A patient was considered to have local recurrence in the presence of a local soft tissue mass that was biopsy proven adenocarcinoma or if the mass was enlarging on repeat short-term cross-sectional imaging in the setting of an elevated CA19-9. Distant recurrence was defined as recurrence in the liver, lungs, distant organs, or malignant ascites. Radiographic findings consistent with recurrent disease were considered adequate proof of recurrence, and pathologic confirmation was rarely obtained. Only first sites of recurrence were documented and recorded for the purposes of this study.

Summary statistics were obtained using established methods. Univariate (Student *t* test, chi-square test) and multivariate analyses were performed to identify potential factors associated with the pattern of recurrences (e.g., local versus distant). Particular emphasis was placed on analyzing the relationship between lymph node status, number of metastatic lymph nodes, and LNR as potential factors associated with local recurrence. Other factors, including tumor grade, tumor size, and margin status, were also evaluated. Local recurrence rates were estimated using the cumulative incidence method. Disease-free survival was analyzed using the Kaplan–Meier method (univariate log-rank). Cox proportional hazards models were used to assess independent variables impacting patterns of recurrence. All calculations were performed using the SPSS statistical software package version 11.5 (SPSS, Chicago, IL, USA).

Results

Patient Clinicopathologic Characteristics

Table 2 shows the clinicopathologic features of the 154 patients included in the study. There were 93 (60.4%) men and 61 (39.6%) women. The mean age of the cohort was 63 years. Of the 154 patients, 136 (88.3%) were white, 11 (7.2%) were black, and 7 (4.5%) were Asian. All patients underwent surgical resection for pancreatic adenocarcinoma. The majority of patients (n=106; 68.6%) underwent a pylorus-preserving pancreaticoduodenectomy procedure. In comparison, 39 (25.3%) underwent a classic pancreaticoduodenectomy, and nine (5.8%) underwent a total pancreatectomy. The median operative time was 6.3 h (range, 5.3 to 7.2 h), and the median estimated blood loss was 800 ml (range, 550 to 1,200 ml). The mean length of stay was 10 days (range, 9–13 days). There were no deaths within 30 days of resection.

Final pathologic analysis revealed a median tumor size of 3.0 cm (range, 0.7 to 7.0 cm), and the majority of

Table 2 Clinical and Morphologic Features of Patients (n=154)

Variable	Number of patients (%)
Age	
Median (range)	63 year (55 to 77)
Sex	
Female	61 (39.6)
Male	93 (60.4)
Type of pancreaticoduodenectomy	
Classic	39 (25.3)
Pylorus-preserving	106 (68.6)
Total	9 (5.8)
Tumor size	
Median (range)	3.0 cm (0.7 to 7.0)
Tumor differentiation	
Well/moderate	94 (61.0)
Poor	60 (39.0)
Resection margin	
R0	103 (66.9)
R1	51 (33.1)
R2	0 (0)
Lymph node status	
N0	29 (18.8)
N1	125 (81.2)
Median number of lymph nodes evaluated	
Overall (range)	18 (2 to 57)
N0 patients	14
N1 patients	19
Lymph node ratio	
0	29 (18.8)
>0 to 0.2	61 (39.6)
>0.2 to 0.4	29 (18.8)
>0.4	35 (22.9)

carcinomas were either moderately or well differentiated (n=94; 61.0 %). With regard to pathologic staging, most patients had either a T2 or T3 carcinoma (n=120; 77.9%), and all were staged as AJCC I or II (n=154; 100%). Regarding surgical margin status, most resections were categorized as R0 (n=103; 66.9%) or R1 (n=51; 33.1%). No patient underwent an R2 resection.

The median number of lymph nodes evaluated was 18 (range, 2 to 57). Of the 154 patients, 29 (18.8%) had no peripancreatic lymph node metastasis (N0). In contrast, 125 (81.2%) patients had at least one lymph node metastasis (N1). The median number of lymph nodes examined in the N0 group was 14 compared with a median of 19 lymph nodes in the N1 group (p=0.003). Most N1 patients had a LNR ratio <0.2 (n=61; 48.8%); however, other patients had an LNR of >0.2 to 0.4 (n=29; 23.2%) or >0.4 (n=35; 28.0%).

Patterns of Recurrence

With a median follow-up of 20.2 months, 103 of 154 (66.9%) patients developed a recurrence. The median disease-free survival for the entire cohort was 16.2 months. The cumulative 1-, 3-, and 5-year actuarial disease-free survival were 65.4%, 27.5%, and 20.7%, respectively (Fig. 1). Among those patients who recurred, 71 (68.9%) developed distant disease as a first site of recurrence (liver, n=41; lung, n=29; other distant site, n=21). In contrast, 32 (31.1%) patients developed local disease as a component of the first site of recurrence. Ten (9.7%) of these patients initially recurred with local and distant disease, while 22 (21.4%) had local disease alone. The median time to disease recurrence was similar between patients who recurred with distant disease as a first site of recurrence (12.5 months) versus those patients who developed local disease as a component of the first site of recurrence (10.1 months; p=0.13).

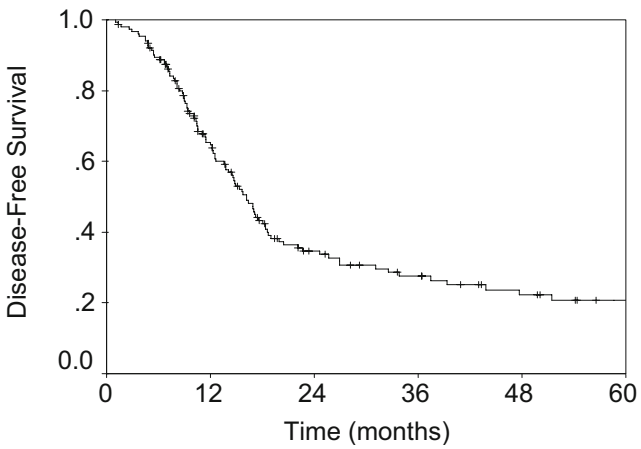

Figure 1 With a median follow-up of 20.2 months, 103 of 154 (66.9%) patients developed a recurrence. The cumulative 1-, 3-, and 5-year actuarial disease-free survival were 65.4%, 27.5%, and 20.7%, respectively.

Factors Associated with Recurrence

Several clinicopathologic factors were associated with any site recurrence following pancreaticoduodenectomy. By univariate analysis, poor tumor grade differentiation (HR 1.69, p=0.009), R1 resection status (HR 1.78, p=0.005), and the presence of metastatic lymph nodes (HR 1.07, p=0.001) were significantly associated with overall recurrence. By multivariate analysis, poor tumor grade (HR 1.66, p=0.01) and the presence of metastatic lymph nodes (HR 1.12, p=0.001) maintained prognostic significance. R1 resection status did not remain associated with an increased risk of any site recurrence (HR 1.55, p=0.07; Table 3). Of note, no clinicopathologic factor was specifically associated with risk of distant recurrence (all p>0.05).

Among all patients (n=154), univariate analysis did reveal several factors that were associated with local recurrence. Specifically, poor tumor differentiation (HR 2.39, p=0.01) and metastatic lymph nodes (HR 1.08, p=0.02) were associated with local recurrence. R1 resection status (HR 1.89, p=0.07) was marginally associated with local recurrence. There was no association between the incidence of local failure and radiation dose. By multivariate analysis, poor tumor differentiation approached statistical significance (HR 2.35, p=0.02); the presence of metastatic lymph nodes (HR 3.75, p=0.006) remained independently associated with local recurrence. In contrast, after controlling for competing risk factors, R1 resection status was not associated with local recurrence (HR 1.41, p=0.36; Table 4).

Since lymph node status was one of the strongest factors associated with recurrent disease, a subset analysis was performed to assess the risk of recurrence as it specifically related to lymph node status. Looking at the entire cohort, the incidence of any site of recurrence at 2 years of follow-up was 30.5% in patients with N0 disease compared with 26.4% in patients with N1 disease (p=0.88). Among patients with no metastatic lymph nodes (N0; n=29), seven (24.1%) patients developed local recurrent disease as a first site of recurrence. Among patients with N0 disease, patients who underwent an R1 resection tended to have a higher risk of local recurrence (HR 4.21, p=0.05).

Of the patients with metastatic nodal disease (N1; n=125), 25 (20.0%) developed local disease as a first site of recurrence. For patients with N1 disease, local recurrence was associated with poorly differentiated tumors (HR 3.92, p=0.002). R1 margins status had no effect on risk of local recurrence (HR 0.99, p=0.98). In contrast, increasing number of metastatic lymph nodes was strongly associated with the risk of local/recurrence (HR 1.09 per metastatic

Table 3 Factors Associated with Any Site Recurrence (n=154)

Variable	Univariate			Multivariate		
	Crude HR	CI	p value	Adjust HR	CI	p value
Total nodes harvested	1.01	0.98–1.03	0.60	–	–	–
Grade: poorly differentiated	1.69	1.14–2.52	0.009	1.66	0.84–2.17	0.01
Tumor size >2 cm	1.26	0.77–2.06	0.35	–	–	–
N1 disease	1.26	0.78–2.06	0.34	–	–	–
Number of N1 nodes	1.07	1.03–1.11	0.001	1.12	1.06–1.18	0.001
More than 5 N1 nodes	1.91	1.28–2.86	0.002	–	–	–
R1 resection	1.78	1.18–2.67	0.005	1.55	0.96–2.51	0.05
Vascular invasion	1.53	0.97–2.39	0.06	0.87	0.51–1.48	0.60
Perineural invasion	2.02	0.73–5.54	0.17	–	–	–

node, p=0.01). Specifically, even after controlling for competing risk factors, N1 patients with more than five metastatic lymph nodes were more likely to recur with local disease (HR 3.75, p=0.006). LNR was also strongly associated with risk of local recurrence. Increasing LNR was associated with an incremental increased risk of local recurrence (LNR <0.2, 21.3% versus LNR ≥0.2 to 0.4, 25.2% versus LNR >0.4, 40.4%; all p<0.05). Patients with an LNR >0.4 had about a threefold increased risk of local failure (HR=2.96, p=0.02) compared with patients who had an LNR of <0.2 (Fig. 2). By multivariate analysis, LNR >0.4 remained strongly associated with local recurrence compared with LNR <0.2 (HR 3.72, p=0.001) in patients with N1 disease.

Discussion

Data on both patterns of failure and factors associated with disease recurrence following pancreaticoduodenectomy remain ill-defined. Most reports on outcome have focused on survival.[2–4] Even following a "curative" pancreaticoduodenectomy, survival rates are poor with 5-year survival rates ranging from 20% to 25%.[2–4] Given the poor overall survival following pancreaticoduodenectomy, as well as the high rate of systemic recurrence, little attention has been focused on the issue of local recurrence. Locoregional recurrence can, however, have important clinical implications. Local recurrence can cause obstruction, pain, and bleeding, and can significantly worsen patients' quality of life. As such, data on the incidence and factors associated with local recurrence are important.

Similar to other reports,[7,18,26,27] we noted that systemic recurrence was the most common pattern of recurrence (distant as component of failure, 52.6%). The risk of any site recurrence was increased in those patients with more aggressive tumor characteristics such as poor histological tumor grade and metastatic lymph nodes. Although not as common, the incidence of local failure was not inconsequential. In fact, 20.8% of patients developed local recurrence as a component of failure. The incidence of local recurrence reported in the literature varies significantly. Some series[5–8] have reported local recurrence rates as high as 50% to 80%. In contrast, other studies[5,9–15] in which patients have received adjuvant chemoradiation therapy have noted a lower risk of local recurrence. In fact, most studies that utilize radiation therapy[5,9–15] have noted local recurrence rates of 10% to 40%. In the current study, the

Table 4 Factors Associated with Local Recurrence: All Patients (n=154)

Variable	Univariate			Multivariate		
	Crude HR	CI	p value	Adjust HR	CI	p value
Total nodes harvested	0.98	0.94–1.02	0.280	–	–	–
Grade: poorly differentiated	2.39	1.18–4.81	0.01	2.35	1.14–4.84	0.02
Tumor size >2 cm	1.34	0.55–3.25	0.52	–	–	–
N1 disease	1.06	0.46–2.47	0.88	–	–	–
Number of N1 nodes	1.08	1.01–1.14	0.02	–	–	–
More than 5 N1 nodes	2.68	1.33–5.42	0.006	2.48	1.10–5.59	0.02
R1 resection	1.89	0.93–3.85	0.07	1.41	0.67–2.94	0.36
Vascular invasion	2.12	0.92–4.86	0.07	1.18	0.48–2.93	0.71
Perineural invasion	1.02	0.24–4.40	0.97	–	–	–

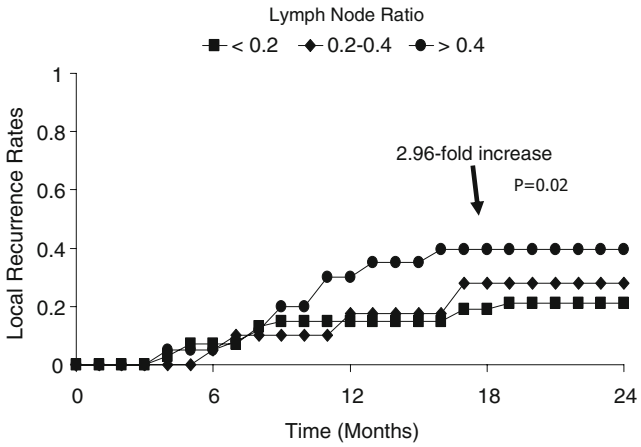

Figure 2 LNR was strongly associated with risk of local recurrence. Patients with an LNR greater than 0.4 had about a threefold increased risk of local failure (HR 2.96, p=0.02) compared with patients who had an LNR of <0.2.

overall incidence of local recurrence (20.8%) was similar to previous reports in which patients received adjuvant chemoradiation therapy.

Identification of patients who are at higher risk of local recurrence may be important. Interestingly, after adjusting for competing risk factors, margin status (R1) was found not to be independently associated with local recurrence (HR 1.41, p=0.36). Raut et al.[17] have similarly reported that surgical margin status did not significantly impact patient survival or pattern of recurrence. In the study by Raut and colleagues,[17] resection margin status was not independently associated with survival or pattern of recurrence (local/regional recurrence: R0, 16.7% versus R1, 13.4%; p=0.83). In the current study, surgical margin status was marginally associated with local recurrence on univariate analysis (HR, 1.89, p=0.07). After adjusting for other factors such as the presence of lymph node metastasis, surgical margin status was found not to be important (Table 4). In aggregate, our data and that of Raut et al.[17] do not support the conclusion of the ESPAC trial[16] that tumors with positive resection margins represent a biologically more aggressive cancer independent of patient selection/other tumor factors.

As noted, the presence of lymph node metastasis was strongly associated with local recurrence. Lymph node status is an established prognostic factor in patients undergoing resection for pancreatic adenocarcinoma. Numerous studies[2–4,15,19,28,29] have demonstrated that patients with lymph node metastases have a significantly worse survival. Specifically, most studies[2,4,21] report a median survival of just over 1 year for patients with lymph node metastasis (N1). Furthermore, patients with N1 disease have a significantly lower 5-year survival compared with patients who do not have metastatic disease to the regional lymph nodes.[4,15,21,28,29] Little data exist, however, on the effect of lymph node status on patterns of disease recurrence. De Castro et al.[30] reported that lymph node metastases were associated with high recurrence rates in patients with ampulla of Vater adenocarcinoma. To our knowledge, however, no study has previously examined the effect of lymph node status or degree of lymph node disease burden as it relates to pattern of disease recurrence in patients with pancreatic adenocarcinoma. Data from the current study demonstrated that the extent of tumor burden within the nodal basin was strongly associated with risk of local recurrence in patients with N1 disease. Specifically, those patients who had more than five metastatic lymph nodes had a 2.5-fold increased risk of local recurrence. However, our group[20,21] as well as others[22,23] has shown that reporting only the number of metastatic lymph nodes may be problematic. Instead, we have advocated the use of LNR as more strongly associated with survival following pancreaticoduodenectomy.[20,21] In contrast to previous studies that examined LNR relative to long-term overall survival, the current study assessed the association of LNR and local recurrence. In the current study, LNR was indeed noted to be associated with local recurrence even after controlling for other patient- and tumor-level factors. In fact, N1 patients with LNR >0.4 had nearly a threefold increased risk of local recurrence compared with N1 patients with LNR <0.2 (Fig. 2). LNR, rather than total node count or total number of metastatic lymph nodes, may be advantageous as it combines data on the number of positive lymph nodes, but also provides a denominator that accounts for some degree of adequacy of the lymph node dissection.

The current paper had several limitations. The study included only a small number of patients with N0 disease. As in our previous reports[4,21], only about 20% of patients undergoing pancreaticoduodenectomy for adenocarcinoma have N0 disease. As such, evidenced-based conclusions regarding patterns and factors associated with recurrence in this small cohort of N0 patients are limited. Perhaps more importantly, the current study could not directly address the natural pattern of recurrence history of patients who are chemoradiation therapy naïve. Given that chemoradiation is the standard of care at our center, as well as most centers in the United States, such data were not feasible to attain. It is possible that factors associated with local recurrence may differ in chemoradiation-therapy-naïve patients. It seems biologically feasible, however, that patients with large local tumor burdens (many metastatic lymph nodes, high LNR) would still remain at highest risk of local recurrence.

Recurrence following curative pancreaticoduodenectomy and adjuvant 5-FU chemoradiation therapy is common. Although most patients will ultimately succumb to distant disease; about 20% recur locally. We herein report that

patients with poor tumor differentiation, a high number of metastatic LN (>5), and LNR >0.4 have a significantly increased risk of developing local recurrence despite having received 5-FU-based chemoradiation therapy. While our group recently reported that 5-FU-based chemoradiation therapy was associated with an improved overall survival compared with surgery alone,[31] data from the current study suggest that standard 5-FU-based chemoradiation therapy may be inadequate in patients with certain clinicopathologic characteristics. Regine et al.[32] noted that the addition of gemcitabine before and after 5-FU-based chemoradiation therapy resulted in a nonsignificant improvement in survival compared with 5-FU-based chemoradiation therapy alone, although local control was not specifically reported in this study. Others[33–35] have reported that combining irradiation with gemcitabine[33,34] or targeted agents[35] may result in improved local and distant control in patients with resected pancreatic adenocarcinoma. Although in the current study we did not find any association between local recurrence and radiation dose (40 versus 50.4 Gy), doses of >54 Gy may be necessary to improve locoregional outcomes.[36] With intensity-modulated radiation therapy, it is now possible to deliver doses of 45 to 50 Gy while escalating the dose to the tumor bed to 54 to 60 Gy.[37] Based on data from the current study, such dose escalation may be necessary in patients with poor tumor differentiation, a high number of metastatic LN (>5), and LNR >0.4. For these patients, standard adjuvant 5-FU-based chemoradiation therapy may be inadequate. Dose escalation ≥54 Gy, as well as radiation integrated with newer chemotherapeutic and targeted agents, may be needed to improve both local control as well as overall outcome in this subset of patients.

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References

1. Gudjonsson B. Cancer of the pancreas. 50 years of surgery. Cancer 1987;60:2284–2303. doi:10.1002/1097-0142(19871101)60:9<2284::AID-CNCR2820600930>3.0.CO;2-V.
2. Lim JE, Chien MW, Earle CC. Prognostic factors following curative resection for pancreatic adenocarcinoma: a population-based, linked database analysis of 396 patients. Ann Surg 2003;237:74–85. doi:10.1097/00000658-200301000-00011.
3. Sohn TA, Yeo CJ, Cameron JL, et al. Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. J Gastrointest Surg 2000;4:567–579. doi:10.1016/S1091-255X(00)80105-5.
4. Yeo CJ, Cameron JL, Sohn TA, et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. Ann Surg 1997;226:248–257. doi:10.1097/00000658-199709000-00004, discussion 257–260.
5. Whittington R, Bryer MP, Haller DG, et al. Adjuvant therapy of resected adenocarcinoma of the pancreas. Int J Radiat Oncol Biol Phys 1991;21:1137–1143.
6. Kayahara M, Nagakawa T, Ueno K, et al. An evaluation of radical resection for pancreatic cancer based on the mode of recurrence as determined by autopsy and diagnostic imaging. Cancer 1993;72:2118–2123. doi:10.1002/1097-0142(19931001)72:7<2118::AID-CNCR2820720710>3.0.CO;2-4.
7. Griffin JF, Smalley SR, Jewell W, et al. Patterns of failure after curative resection of pancreatic carcinoma. Cancer 1990;66:56–61. doi:10.1002/1097-0142(19900701)66:1<56::AID-CNCR2820660112>3.0.CO;2-6.
8. Tepper J, Nardi G, Sutt H. Carcinoma of the pancreas: review of MGH experience from 1963 to 1973. Analysis of surgical failure and implications for radiation therapy. Cancer 1976;37:1519–1524. doi:10.1002/1097-0142(197603)37:3<1519::AID-CNCR2820370340>3.0.CO;2-O.
9. Gastrointestinal Tumor Study Group. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. Gastrointestinal Tumor Study Group. Cancer 1987;59:2006–2010. doi:10.1002/1097-0142(19870615)59:12<2006::AID-CNCR2820591206>3.0.CO;2-B.
10. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 2004;350:1200–1210. doi:10.1056/NEJMoa032295.
11. Talamonti MS, Small W Jr, Mulcahy MF, et al. A multi-institutional phase II trial of preoperative full-dose gemcitabine and concurrent radiation for patients with potentially resectable pancreatic carcinoma. Ann Surg Oncol 2006;13:150–158. doi:10.1245/ASO.2006.03.039.
12. Hoffman JP, Lipsitz S, Pisansky T, et al. Phase II trial of preoperative radiation therapy and chemotherapy for patients with localized, resectable adenocarcinoma of the pancreas: an Eastern Cooperative Oncology Group Study. J Clin Oncol 1998;16:317–323.
13. Spitz FR, Abbruzzese JL, Lee JE, et al. Preoperative and postoperative chemoradiation strategies in patients treated with pancreaticoduodenectomy for adenocarcinoma of the pancreas. J Clin Oncol 1997;15:928–937.
14. Massucco P, Capussotti L, Magnino A, et al. Pancreatic resections after chemoradiotherapy for locally advanced ductal adenocarcinoma: analysis of perioperative outcome and survival. Ann Surg Oncol 2006;13:1201–1208. doi:10.1245/s10434-006-9032-x.
15. Breslin TM, Hess KR, Harbison DB, et al. Neoadjuvant chemoradiotherapy for adenocarcinoma of the pancreas: treatment variables and survival duration. Ann Surg Oncol 2001;8:123–132. doi:10.1007/s10434-001-0123-4.
16. Neoptolemos JP, Dunn JA, Stocken DD, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. Lancet 2001;358:1576–1585. doi:10.1016/S0140-6736(01)06651-X.
17. Raut CP, Tseng JF, Sun CC, et al. Impact of resection status on pattern of failure and survival after pancreaticoduodenectomy for pancreatic adenocarcinoma. Ann Surg 2007;246:52–60. doi:10.1097/01.sla.0000259391.84304.2b.
18. Westerdahl J, Andren-Sandberg A, Ihse I. Recurrence of exocrine pancreatic cancer—local or hepatic. Hepatogastroenterology 1993;40:384–387.
19. Pawlik TM, Abdalla EK, Barnett CC, et al. Feasibility of a randomized trial of extended lymphadenectomy for pancreatic

cancer. Arch Surg 2005;140:584–589. doi:10.1001/archsurg.140.6.584, discussion 589–591.
20. Slidell MB, Chang DC, Cameron JL, et al. Impact of total lymph node count and lymph node ratio on staging and survival after pancreatectomy for pancreatic adenocarcinoma: a large, population-based analysis. Ann Surg Oncol 2008;15:165–174. doi:10.1245/s10434-007-9587-1.
21. Pawlik TM, Gleisner AL, Cameron JL, et al. Prognostic relevance of lymph node ratio following pancreaticoduodenectomy for pancreatic cancer. Surgery 2007;141:610–618. doi:10.1016/j.surg.2006.12.013.
22. Berger AC, Watson JC, Ross EA, et al. The metastatic/examined lymph node ratio is an important prognostic factor after pancreaticoduodenectomy for pancreatic adenocarcinoma. Am Surg 2004;70:235–240. discussion 240.
23. Sierzega M, Popiela T, Kulig J, et al. The ratio of metastatic/resected lymph nodes is an independent prognostic factor in patients with node-positive pancreatic head cancer. Pancreas 2006;33:240–245. doi:10.1097/01.mpa.0000235306.96486.2a.
24. AJCC. General information on cancer staging and end-results reporting. In Greene FL, Page DL, Flemming ID, eds. AJCC cancer staging manual. Springer: Chicago, 2002, pp 1–16.
25. Westra WH, Hruban RH, Phelps TH, et al. Surgical pathology dissection. An illustrated guide, 2nd ed. New York: Springer, 2003.
26. Sperti C, Pasquali C, Catalini S, et al. CA 19-9 as a prognostic index after resection for pancreatic cancer. J Surg Oncol 1993;52:137–141. doi:10.1002/jso.2930520302.
27. Takahashi S, Ogata Y, Miyazaki H, et al. Aggressive surgery for pancreatic duct cell cancer: feasibility, validity, limitations. World J Surg 1995;19:653–659. doi:10.1007/BF00294750, discussion 660.
28. Benassai G, Mastrorilli M, Mosella F, et al. Significance of lymph node metastases in the surgical management of pancreatic head carcinoma. J Exp Clin Cancer Res 1999;18:23–28.
29. Gebhardt C, Meyer W, Reichel M, et al. Prognostic factors in the operative treatment of ductal pancreatic carcinoma. Langenbecks Arch Surg 2000;385:14–20. doi:10.1007/s004230050004.
30. de Castro SM, Kuhlmann KF, van Heek NT, et al. Recurrent disease after microscopically radical (R0) resection of periampullary adenocarcinoma in patients without adjuvant therapy. J Gastrointest Surg 2004;8:775–784. doi:10.1016/j.gassur.2004.08.006, discussion 784.
31. Herman JM, Swartz MJ, Hsu CC, et al. Analysis of fluorouracil-based adjuvant chemotherapy and radiation after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas: results of a large, prospectively collected database at the Johns Hopkins Hospital. J Clin Oncol 2008;26:3503–3510. doi:10.1200/JCO.2007.15.8469.
32. Regine WF, Winter KA, Abrams RA, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. JAMA 2008;299:1019–1026. doi:10.1001/jama.299.9.1019.
33. Blackstock AW, Mornex F, Partensky C, et al. Adjuvant gemcitabine and concurrent radiation for patients with resected pancreatic cancer: a phase II study. Br J Cancer 2006;95:260–265. doi:10.1038/sj.bjc.6603270.
34. Allen AM, Zalupski MM, Robertson JM, et al. Adjuvant therapy in pancreatic cancer: Phase I trial of radiation dose escalation with concurrent full-dose gemcitabine. Int J Radiat Oncol Biol Phys 2004;59:1461–1467. doi:10.1016/j.ijrobp.2004.01.015.
35. Ma WW, Herman JM, Laheru DA, et al. A phase I tolerability and pharmokinetic study of adjuvant erlotinib and capecitabine with concurrent radiation in resected pancreatic cancer. American Society of Clinical Oncology Gastrointestinal Symposium Meeting, 2008.
36. Ben-David MA, Griffith KA, Abu-Isa E, et al. External-beam radiotherapy for localized extrahepatic cholangiocarcinoma. Int J Radiat Oncol Biol Phys 2006;66:772–779. doi:10.1016/j.ijrobp.2006.05.061.
37. Ben-Josef E, Shields AF, Vaishampayan U, et al. Intensity-modulated radiotherapy (IMRT) and concurrent capecitabine for pancreatic cancer. Int J Radiat Oncol Biol Phys 2004;59:454–459. doi:10.1016/j.ijrobp.2003.11.019.

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ORIGINAL ARTICLE

Surgery for Recurrence of Periampullary Malignancies

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Abstract
Aim Few studies have addressed the surgical treatment of recurrent disease after pancreatic resection. The aim of this study was to evaluate the indications, the short- and long-term outcome, and the prognostic factors impacting survival in patients undergoing a re-laparotomy for recurrence of periampullary malignancies.
Methods Between 1990 and 2007, 16 re-laparotomies were performed in 15 patients (one patient had a second re-laparotomy) with a median age of 61 years (range 31–84). Patients were identified from a prospective database and records were reviewed retrospectively.
Results Seven re-laparotomies were performed for a surgical emergency and nine patients had a re-laparotomy for recurrence found at imaging studies. Perioperative mortality was observed in three patients presenting with surgical emergency and a poor performance status (Eastern Cooporative Oncology Group score ≥3). Perioperative morbidity was 40%. Median survival after the first re-laparotomy for the 15 patients was 7.4 months, and was not different for patients presenting a surgical emergency versus no emergency. Patients with peritoneal carcinomatosis had a median survival of 1.4 month. In a univariate analysis of survival, a performance status of ECOG score ≥2 and a pre-operative hemoglobin level <12 g/dl were predictors of poor survival.
Conclusion In selected patients, a re-laparotomy for recurrence of periampullary malignancies is feasible. Peritoneal recurrence was not a good indication for surgery. The predictors of poor survival after the re-laparotomy were a poor performance status and a low preoperative hemoglobin level.

Keywords Laparotomy · Recurrence · Periampullary malignancies

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Introduction

Pancreatoduodenectomy remains the only potential cure for periampullary malignancies. Results and prognostic factors after pancreatoduodenectomy have been published for a variety of pathological types of tumors.[1–3] Following a curative resection (R0), a 5-year survival rate of 10% to 36% was reported for ductal adenocarcinoma.[4–7] This suggests that the majority of patients are not cured by a pancreatoduodenectomy and will have recurrence.[8–10] Patients presenting with recurrent disease after pancreatoduodenectomy are offered palliative chemotherapy or radiochemotherapy, palliative care, and in selected cases surgery, depending on symptomatology and performance status. A median survival of 6.6 to 7.1 months was reported after palliative chemotherapy with gemcitabine for locally advanced or metastatic pancreatic cancer.[11,12] However,

few studies have specifically addressed the treatment of recurrent disease after pancreatic resection.[13,14] The place of surgery, for the palliative treatment of these patients, is not defined. One study and some case reports were published about surgery for patients with recurrent periampullary malignancies.[15–23] Therefore, the aim of this study was to evaluate the indications leading to a re-laparotomy, as well as the morbidity, the mortality, and the survival in patients with recurrence of periampullary malignancies after initial pancreatoduodenectomy or total pancreatectomy.

Patients and Methods

Study Population

This retrospective study was performed at a single institution. Between January 1990 and May 2007, a pancreatoduodenectomy or total pancreatectomy for periampullary malignancies (ductal adenocarcinoma, cholangiocarcinoma, ampullary adenocarcinoma, and other forms of adenocarcinoma) were performed in 357 patients in our institution. Twenty-four out of these 357 patients were re-operated at least 3 months after the initial pancreatic resection. Six patients were operated on for different pathologies (rectal cancer, hysterectomy, renal transplantation, orthopedic surgery) in other institutions. These six patients were excluded from analysis. Three further patients had a laparotomy for intestinal obstruction, obstructive jaundice, and bleeding ileal stenosis. During laparotomy, however, no recurrence was found. These three patients were also excluded from analysis. The study population consists of the remaining 15 patients (six women and nine men). Median age at the re-laparotomy was 61 years old (range 31–84). Medical comorbidities registered in the 15 patients at the re-laparotomy were: diabetes mellitus (n=5), ischemic heart disease (n=2), chronic pulmonary disease (n=1), heart insufficiency (n=1), and other cancers (n=3) including seminoma, Hodgkin lymphoma and colon cancer in one patient each.

Initial Pancreatic Resection

In this series, 14 pancreatoduodenectomies and one total pancreatectomy were initially performed in the 15 patients. A total pancreatectomy was necessary in one patient to achieve a R0 resection, as repeated frozen section examinations of the pancreatic margin were positive. Pathologic examination of the specimen showed ductal adenocarcinoma (n=6), cholangiocarcinoma (n=3), ampullary adenocarcinoma (n=1), cystadenocarcinoma (n=2), and other types of adenocarcinoma: acinous, mucinous, papillary (n=3). Tumors were well differentiated in five patients, moderately differentiated in eight patients and poorly differentiated in two patients, according to the World Health Organization Union criteria.[24] There were two patients with pT1, three patients with pT2, and ten patients with pT3 tumors according to the 2002 TNM classification system.[25] Lymph node dissection and analysis were performed in all 15 patients and revealed positive lymph nodes in nine patients (60%). In all 15 patients, a potentially curative R0 resection was realized. Seven patients had adjuvant therapy (five radiochemotherapies and two chemotherapies).

Endpoints and Follow-Up

Primary endpoints were overall survival from initial pancreatectomy, survival after the re-laparotomy, mortality, and morbidity. Secondary endpoints were indications for surgery, site of recurrence, and length of hospital stay. No patient was lost to follow-up. Outcome data were recorded from follow-up consultations. Contact was maintained by mail and telephone calls to referring physicians, general practitioners, and directly to the patients or their families. Patients were followed after their operation by referring physicians, including oncologists, gastroenterologists, surgeons, and general practitioners. The follow-up schedule included an abdominal ultrasound or CT scan and CA 19.9 measurements every 6 months. Performance status was classified as 0, 1, 2, or 3 according to the Eastern Cooperative Oncology Group (ECOG) score. Patients with an excellent performance status had 0 and patients with a poor performance status had 3.[26] A detailed quality of life analysis was not performed due to the retrospective study design.

Statistical Analysis

Survival rates were calculated by the Kaplan–Meier method and were compared using the log-rank test for univariate analysis. The level of significance was defined as P less than 0.05. Only variables independent of each other in a chi-square test were analyzed in univariate analysis of survival. A multivariate analysis of survival was not performed because of the small number of patients. Median hospital stay was compared with the Mann–Whitney test. All analyses were performed with the Statview® software.

Results

Preoperative Treatment

In three patients, a preoperative therapy was performed: radiochemotherapy with 5-FU for local retroperitoneal

recurrence in one patient (no. 4 in Table 1) and chemotherapy with GEMOX or FOLFOX+AVASTIN in two patients (nos. 13 and 15) for isolated liver metastases. A partial response of the liver metastases to preoperative chemotherapy was observed in both patients.

Indications for Surgery

A total of 16 re-laparotomies were performed in the 15 patients, as one patient had a second re-laparotomy (13* in Table 1). In seven cases (six first re-laparotomies+one second re-laparotomy), the patients were presenting a surgical emergency: peritonitis by intestinal perforation (nos. 3 and 5 in Table 1), intestinal obstruction (nos. 4, 9, and 14), jaundice by obstruction of the biliodigestive anastomosis (no. 10), and massive ascites with an ovarian metastasis (no. 13*). In these seven re-laparotomies, the aim was to relieve symptoms and to save life. Patients presenting with a surgical emergency had a significantly poorer performance status (median ECOG score=3) compared with the other patients (median ECOG score=1; $p=0.0001$).

The other re-laparotomies were motivated either by a completely asymptomatic recurrence ($n=6$) or a symptom-

Table 1 Sixteen Re-laparotomies in 15 Patients after Pancreatoduodenectomy or Total Pancreatectomy (no. 3) for Periampullary Malignancies

No	TNM	Pathology	ECOG score[a]	Presentation	Time[b]	Site of recurrence[c]	Procedures[d]	Survival[e]	Other treatments[f]	Hospital stay[g]
First re-laparotomy										
1	pT2N1	ductal ADK	2	pain	9	retroperitoneal	exploration	6.3	–	15
2	pT1N1	ampullary ADK	1	asympt	36	pancreas, hep	splenopancreatectomy	6.5	post op CT	9
3	pT3N0	cystadenoK	3	peritonitis	44	celiac, pulm	gastroenteroanastomosis	34 days	–	Until death
4	pT3N1	ductal ADK	2	int obstruct	37	retroperitoneal	section of adhesions	7.4	pre op RCT	65
5	pT3N1	ductal ADK	3	peritonitis	3	peritoneal, hep	exploration	40 days	–	Until death
6	pT2N0	acinous ADK	1	asympt	23	hep	segmentectomy 7	58	post op CT, hep RF	6
7	pT3N1	mucinous ADK	2	pain	14	peritoneal	exploration	16	post op CT	6
8	pT3N0	cystadenoK	1	asympt	62	celiac, hep	lymph node dissection	40	post op CT	11
9	pT3N1	cholangioK	2	int obstruct	19	celiac, gastr, pulm	antropylorectomy	6.2	post op CT	16
10	pT2N0	cholangioK	2	jaundice	37	biliodig anast	biliodigestive anastomosis	18	–	10
11	pT3N0	ductal ADK	2	colonic stenosis	25	peritoneal	left colectomy	3.6	–	23
12	pT1N0	papillary ADK	1	asympt	78	pancreas	splenopancreatectomy	9.8	post op RCT	14
13	pT3N1	ductal ADK	1	asympt	30	hep	segmentectomy 4+5	20	pre, post op CT, stent	6
14	pT3N1	ductal ADK	3	int obstruct	9	peritoneal	jejunal resection	40 days	–	Until death
15	pT3N1	cholangioK	0	asympt	18	hep	segmentectomy 5 +6	3	pre op CT	6
Second re-laparotomy										
13*	pT3N1	ductal	3	massive ascites	6	ovary	bilateral ovariectomy	14	post op CT	7

asympt asymptomatic, *int obstruct* intestinal obstruction, *ADK* adenocarcinoma, *cystadenoK* cystadenocarcinoma, *cholangioK* cholangiocarcinoma

[a] Performance status was classified according to the Eastern Cooperative Oncology Group[26]

[b] Time between initial pancreatic resection to re-laparotomy in months

[c] Five patients had more than one site of recurrence (*biliodig anast* biliodigestive anastomosis, *hep* hepatic, *pulm* pulmonary, *celiac* celiac lymph nodes, *gastr* gastric involvement)

[d] In some patients, more than one procedure was realized. Only the main procedure was noted

[e] Survival in months after the re-operation

[f] *CT* chemotherapy, *RCT* radiochemotherapy, *stent* biliary stent, *RF* radiofrequency ablation

[g] Hospital stay in days after the re-operation (all patients except the three patients who died perioperatively left the hospital)

atic recurrence (n=3) found at imaging studies. Three patients (nos. 6, 13, and 15) were re-operated on for isolated, asymptomatic liver metastases, two patients (nos. 2 and 12) were re-operated on for asymptomatic local recurrence in the pancreas, and one patient (no. 8) for celiac lymph node recurrence. Symptomatic patients (nos. 1, 7, and 11) were presenting abdominal pain or a colonic stenosis. In the patients without a surgical emergency, the re-laparotomies were performed to achieve if possible a macroscopically complete resection of the tumor recurrence.

First Re-laparotomy

Fifteen patients had a re-laparotomy after a median time interval of 25 months (range 3–78 months) after initial pancreatic resection.

In three patients (nos. 1, 5, and 7 in Table 1), an explorative laparotomy was performed and showed disseminated peritoneal carcinomatosis in patient nos. 5 and 7. Patient no. 5 had peritonitis by intestinal perforation. Only drainage was realized. In patient no. 1, who was operated on for suspected recurrence in the celiac lymph nodes, no peritoneal carcinomatosis, no liver and no lymph nodes metastases were found during exploration and a chemical neurolysis of the splanchnic nerve plexus was realized for pain control. The other 12 patients underwent various procedures (Table 1).

Site of Recurrence

In 13 patients, an intra-abdominal recurrence was confirmed by pathological examination. Local recurrence (remnant pancreas, retroperitoneum, and regional lymph nodes) was found in eight patients. Metastases were observed in the liver (n=6), peritoneum (n=4), and lung (n=2). Five patients had more than one organ involved with recurrence. Two patients (nos. 1 and 4 in Table 1) had no evidence of recurrence at re-laparotomy and biopsies remained negative. These two patients died 6.3 and 7.4 months after the re-laparotomy. However, as these two patients had evidence of retroperitoneal recurrence on a preoperative CT scan they were included in the survival analysis.

Second Re-laparotomy

Patient no. 13* was re-operated on for massive ascites 6 months after the first re-laparotomy and an ovarian metastasis was removed without other sites of recurrence. Pathological examination of the right ovary showed metastasis of a ductal adenocarcinoma of the pancreas. The left ovary was normal. An ovarian primary was excluded by immunohistochemical staining. The patient died 50 months after initial pancreatoduodenectomy for ductal adenocarcinoma and 14 months after the second re-laparotomy due to disease progression with liver and peritoneal metastases. Except this patient, no other patient was re-admitted to surgery.

Mortality and Morbidity

The in-hospital mortality was 20% (n=3). All patients who died postoperatively (nos. 3, 5, and 14 in Table 1) had a surgical emergency and a poor performance status (ECOG score=3). Patients nos. 3 and 5 had a peritonitis by intestinal perforation. In patient no. 3 a resection of a perforated anastomotic ulcer was performed. She died on postoperative day 34. In patient no. 5, only an exploration with drainage was realized because of generalized carcinomatosis. He died on postoperative day 40. Patient no. 14 was re-operated on for intestinal obstruction with peritoneal carcinomatosis and a jejunal resection with anastomosis was realized. He further developed pleural effusion and pneumonia and died on postoperative day 40 due to sepsis. Three out of four patients with a poor performance status (ECOG score=3) died within 40 days after the re-laparotomy.

After a total of 16 re-laparotomies, eight postoperative complications were observed in six patients (40%) and are listed in Table 2.

Postoperative Course and Further Postoperative Treatments

Median hospital stay after the operation was 12 days (range 6–65). All patients except the three who died postoperatively were discharged from the hospital.

Efficient surgical palliation was possible in four out of seven patients presenting with a surgical emergency.

Six patients had postoperative chemotherapy and one patient a postoperative radiochemotherapy. One patient had percutaneous radiofrequency ablation for recurrent liver metastasis. In one patient a biliary stent was implanted percutaneously for jaundice (Table 1).

Table 2 Eight Complications in Six Patients after 16 Re-Laparotomies for Recurrence of Periampullary Malignancies

Surgical	
Intestinal obstruction	1[a]
Low output intestinal fistula	1
Cardiopulmonary	
Pleural effusion	3
Infections	
Pneumonia	1
Septicemia	2

[a] The patient was re-operated on at day 11, a compressive hematoma was evacuated, and a gastrointestinal bypass was realized

Survival Analysis

At last follow-up, 14 patients had died and one patient was alive. Among those patients who died, the median follow-up was 6.4 months (range 1.0–58 months). Patient no. 15 was operated on in 2007. He was disease free 3 months after the re-laparotomy.

Overall Survival from Initial Pancreatectomy

The overall survival from initial pancreatic resection for the 15 patients was 87% at 1 year, 80% at 2 years, 58% at 3 years, and 22% at 5 years. Median survival was 45 months. Patients with ductal adenocarcinoma had a median survival of 15 months. In a univariate analysis of

Table 3 Univariate Analysis for Overall Survival after the Initial Pancreatic Resection and for Survival after Re-laparotomy for Intra-abdominal Recurrence of Periampullary Malignancies in 15 Patients

	No.	Overall survival		Survival after re-laparotomy	
		Median (months)	*p*	Median (months)	*p*
Gender					
Male	9	44.8	0.821	15.8	0.276
Female	6	42.5		6.3	
Age					
<60	6	42.5	0.589	6.5	0.432
≥60	9	44.8		7.4	
Ductal adenocarcinoma					
No	9	54.8	0.021	15.8	0.144
Yes	6	14.8		3.6	
TNM T-stage					
T 1 or 2	5	54.8	0.482	9.8	0.324
T3	10	39.8		6.2	
TNM N-stage					
N 0	6	54.8	0.008	9.8	0.19
N 1	9	29.8		6.5	
Local recurrence					
No	7	29.8	0.28	15.8	0.572
Yes	8	44.8		6.5	
Peritoneal recurrence					
No	11	51	0.002	9.8	0.07
Yes	4	10.4		1.4	
Time interval to re-laparotomy					
<24 months	7	Not analyzed	–	6.3	0.943
≥24 months	8			7.4	
Perioperative chemotherapy[a]					
No	5[b]	44.8	0.202	6.3	0.136
Yes	7	51		7.4	
Hemoglobin ≥12 g/dl					
No	7	25.2	0.051	6.2	0.026
Yes	8	51		17.6	
Albumin level ≥35 g/l					
No	6	29.8	0.388	1.4	0.755
Yes	9	44.8		6.5	
Prothrombin level ≥80%					
No	6	44.8	0.851	1.4	0.632
Yes	9	42.5		6.5	
Performance status at re-laparotomy					
ECOG score 0 or 1	6	80	0.008	21	0.013
ECOG score 2 or 3	9	28.9		6.2	

ECOG Eastern Cooperative Oncology Group

[a] Pre- and/or postoperative chemotherapy for recurrence (patient nos. 2, 6, 7, 8, 9, 13, and 15). In-hospital deaths ($n=3$) were excluded from analysis

[b] Include two patients receiving radiochemotherapy

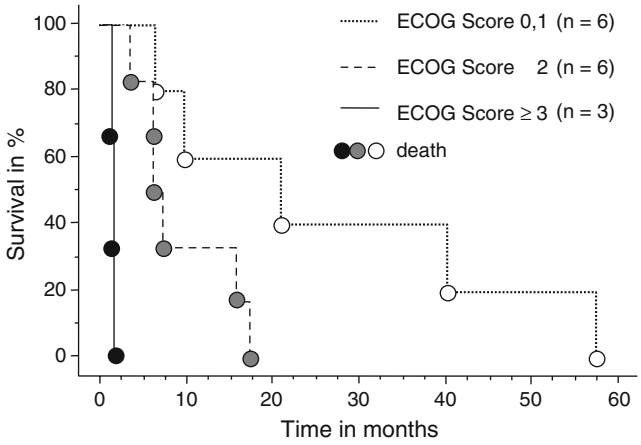

Figure 1 Influence of preoperative performance status according to the Eastern Cooperative Oncology Group[26] on survival after first re-laparotomy for recurrent periampullary malignancies in 15 patients.

survival (Table 3), ductal adenocarcinoma, positive lymph nodes of the primary tumor, peritoneal recurrence, and poor performance status were associated with poor overall survival after the initial pancreatic resection.

Survival after the Re-laparotomy

The survival after the first re-laparotomy for the 15 patients was 80% at 3 months, 73% at 6 months, 36% at 1 year, and 14% at 2 years. Median survival was 7.4 months. Median survival after the re-laparotomy in the seven patients with a surgical emergency was 6.2 months (range 1–18 months). Patients with peritoneal recurrence had a median survival of 1.4 months.

In a univariate analysis of survival (Table 3), poor performance status (Fig. 1) and pre-operative hemoglobin level <12 g/dl (Fig. 2) were significantly associated with poor survival.

Discussion

This study suggests that, in selected patients, a re-laparotomy for recurrence after initial pancreatoduodenectomy or total pancreatectomy for periampullary malignancies is feasible. Concerning the indications for surgery for recurrence of periampullary malignancies, two groups should be distinguished: (1) patients presenting with a surgical emergency and (2) patients with recurrence found at imaging studies without a surgical emergency.

1. In the seven patients presenting with a surgical emergency, a high mortality (n=3) was observed. However, these patients died because of the gravity of their disease (peritonitis with perforation, intestinal obstruction) and the poor performance status in the terminal phase of their cancer. It is then remarkable that the median survival of 6.2 months for the seven patients re-operated on for a surgical emergency was not different compared with the median survival of 6.6 to 7.1 months after palliative chemotherapy[11,12] for advanced or metastatic pancreatic adenocarcinoma. The four patients who survived emergency surgery had a survival of 6.2 to 18 months and three of them underwent a postoperative chemo- or radiochemotherapy. These patients had a benefit from the re-laparotomy.
2. The patients operated on for asymptomatic or symptomatic recurrence found at imaging studies presented a median survival of 6.5 months (range 3.6–58) (Table 1) not different from survival data after palliative chemotherapy for ductal adenocarcinoma of the pancreas. For this group of patients, only a randomized trial could show if the resection of recurrence can improve survival compared to chemotherapy alone. According to our data, cure cannot be expected after resection of recurrent periampullary malignancies, as all patients except one with a short follow-up (12 months) had a recurrence after the re-laparotomy. Patients with peritoneal recurrence had no benefit from a re-laparotomy, as the median survival was 1.4 months.

To our knowledge, this is the second series of re-laparotomy for recurrence of periampullary malignancies. Until now, only one study[15] and some cases have been reported.[16–23] The majority of the reported cases describe a re-resection of the pancreas.[16,18–23] The survival time observed in these case reports varied from 8 to 24 months. In our experience, this procedure was performed in two patients (Table 1) with localized recurrence in the pancreas diagnosed at preoperative imaging studies. In one patient, a macroscopically complete resection was performed; in the other, the resection was incomplete, as liver metastases

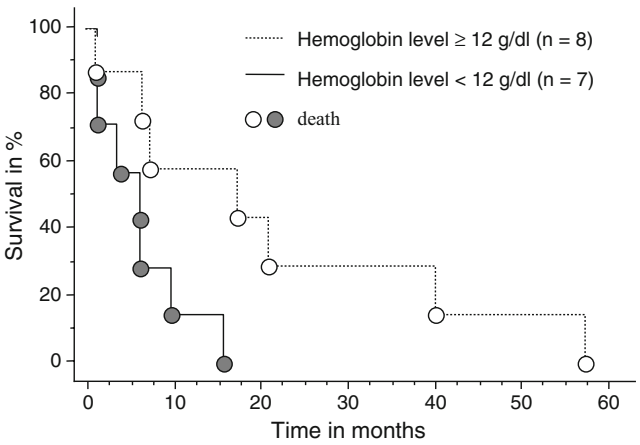

Figure 2 Influence of preoperative hemoglobin level on survival after first re-laparotomy for recurrent periampullary malignancies in 15 patients.

were discovered during the operation. Survival was 9.8 and 6.5 months, respectively.

In the study by Kleeff et al.,[15] 22 patients were re-operated on after initial pancreatoduodenectomy for ductal adenocarcinoma: nine patients had a resection, 11 an exploration, and two a bypass. A median survival after the re-laparotomy of 11.4 months was observed. Resection was not associated with better survival compared with exploration or bypass. The only factor associated with improved survival was a time interval >9 months between the initial pancreatic resection and the re-laparotomy. No data about the performance status of the patients and the symptoms leading to the re-laparotomy were presented in the study by Kleeff et al.

In the present study poor, overall survival after the initial pancreatic resection was related to characteristics of the tumor: histology of ductal adenocarcinoma, lymph node involvement, and peritoneal recurrence. These findings were confirmed by several studies.[1–3,7] On the other hand, poor survival after the re-laparotomy was associated with poor performance status and low preoperative hemoglobin level. These two factors were also found in the study by Krishnan et al. as prognostic factors after radiochemotherapy for unresectable locally advanced pancreatic adenocarcinoma.[27] A low hemoglobin level was associated with poor survival after chemoradiation of unresectable pancreatic carcinoma in the study by Morganti et al.[28] Other studies confirmed that a poor performance status was associated with poor survival for locally advanced or metastatic pancreatic cancer.[12,29]

In conclusion, the present study suggests that, in selected patients, a re-laparotomy for recurrence of periampullary malignancies is feasible. Patients presenting with a surgical emergency had a high postoperative mortality. On the other hand, surgery for emergency had provided efficient palliation for four patients.

Patients presenting without an emergency had a median survival of 6.5 months. Surgery was a palliative procedure in these patients and it remains questionable if surgery is able to improve survival compared to chemotherapy alone. Peritoneal recurrence was not a good indication for surgery.

The predictors of poor survival after re-laparotomy were a poor performance status and a low pre-operative hemoglobin level. The place of surgery for the treatment of recurrence of periampullary malignancies compared to medical therapy needs to be further defined by a prospective trial with analysis of the quality of life.

References

1. Cameron JL, Riall TS, Coleman J, Belcher KA. One thousand consecutive pancreaticoduodenectomies. Ann Surg 2006;244:10–15. doi:10.1097/01.sla.0000217673.04165.ea.
2. Yeo CJ, Cameron JL, Sohn TA et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. Ann Surg 1997;226:248–257. doi:10.1097/00000658-199709000-00004.
3. Yeo CJ, Cameron JL, Lillemoe KD et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity and mortality. Ann Surg 2002;236:355–366. doi:10.1097/00000658-200209000-00012.
4. Baumel H, Huguier M. éd. Rapport du 93e congrès de l'AFC. Le cancer du pancréas exocrine. Paris: Springer, 1991
5. Mosca F, Giulianotti PC, Balestracci T et al. Long-term survival in pancreatic cancer: pylorus preserving versus, Whipple pancreaticoduodenectomy. Surgery 1997;122:553–566. doi:10.1016/S0039-6060(97)90128-8.
6. Trede M, Schwall G, Saeger HD. Survival after pancreaticoduodenectomy. 118 consecutive resections without an operative mortality. Ann Surg 1990;211:447–458. doi:10.1097/00000658-199004000-00011.
7. Zacharias T, Jaeck D, Oussoultzoglou E, Neuville A, Bachellier P. Impact of lymph node involvement on long-term survival after R0 pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas. J Gastrointest Surg 2007;11:350–356. doi:10.1007/s11605-007-0113-3.
8. Hishinuma S, Ogata Y, Tomikawa M, Ozawa I, Hirabayashi K, Igarashi S. Patterns of recurrence after curative resection of pancreatic cancer based on autopsy findings. J Gastrointest Surg 2006;10:511–518. doi:10.1016/j.gassur.2005.09.016.
9. Sperti C, Pasquali C, Piccoli A, Pedrazzoli S. Recurrence after resection for ductal adenocarcinoma of the pancreas. World J Surg 1997;21:195–200. doi:10.1007/s002689900215.
10. Yamamoto K, Shimada S, Hirota M, Yagi Y, Matsuda M, Baba H. EIPL (extensive intraoperative peritoneal lavage) therapy significantly reduces peritoneal recurrence after pancreatectomy in patients with pancreatic cancer. Int J Oncol 2005;27:1321–1328.
11. Alberts SR, Schroeder M, Erlichman C et al. Gemcitabine and ISIS-2503 for patients with locally advanced or metastatic pancreatic adenocarcinoma: a North Central cancer Treatment Group phase II trial. J Clin Oncol 2004;22:4944–4950. doi:10.1200/JCO.2004.05.034.
12. Louvet C, Labianca R, Hammel P et al. Gemcitabine in combination with oxaliplatine compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. J Clin Oncol 2005;23:3509–3516. doi:10.1200/JCO.2005.06.023.
13. Wilkowski R, Thoma M, Bruns C, Dühmke E, Heinemann V. Combined chemoradiotherapy for isolated recurrence after primary resection of pancreatic cancer. J Pancreas Online 2006;7:34–40.
14. Menke-Pluymers MB, Klinkenbijl JH, Tjioe M, Jeekel J. Treatment of locoregional recurrence after intentional curative resection of pancreatic cancer. Hepatogastroenterology 1992;39:429–432.
15. Kleeff J, Reise C, Hinz U et al. Surgery for recurrent pancreatic ductal adenocarcinoma. Ann Surg 2007;245:566–572. doi:10.1097/01.sla.0000245845.06772.7d.
16. Dalla Valle R, Mancini C, Crafa P, Passalacqua R. Pancreatic carcinoma recurrence in the remnant Pancreas after a pancreaticoduodenectomy. J Pancreas Online 2006;7:473–477.
17. Aimoto T, Uchida E, Nakamura Y et al. Malignant afferent loop obstruction following pancreaticoduodenectomy: report of two cases. J Nippon Med Sch 2006;73:226–230. doi:10.1272/jnms.73.226.
18. Tomimaru Y, Ishikawa O, Ohigashi H et al. Advantage of pancreaticogastrostomy in detecting recurrent intraductal papillary mucinous carcinoma in the remnant pancreas: a case of successful re-resection after pancreaticoduodenectomy. J Surg Oncol 2006;93:511–515. doi:10.1002/jso.20387.

19. Takamasu S, Bad D, Irie T et al. Resection of a cancer developing in the remnant pancreas after pancreaticoduodenectomy for pancreas head cancer. J Gastrointest Surg 2005;9:263–269. doi:10.1016/j.gassur.2004.05.016.
20. D'Amato A, Gentili V, Santella S, Boschetto A, Pronio A, Montesani C. Carcinoma of the pancreatic remnant developing after pancreaticoduodenectomy for adenocarcinoma of the head of pancreas. Chir Ital 2002;54:539–544.
21. Niiyama H, Yamaguchi K, Shimizu S et al. Pancreatic carcinoma in remnant pancreas after pancreatectomy for mucinous cystadenoma. Eur J Gastroenterol Hepatol 1998;10:703–707.
22. Wada K, Takada T, Yasuda H, Amano H, Yoshida M. A repeat pancreatectomy in the remnant pancreas 22 months after pylorus-preserving pancreaticoduodenectomy for pancreatic adenocarcinoma. J Hepatobiliary Pancreat Surg 2001;8:174–178. doi:10.1007/s005340170043.
23. Eriguchi N, Aoyagi S, Imayama H et al. Resectable carcinoma of the pancreatic head developing 7 years and 4 months after distal pancreatectomy for carcinoma of the pancreatic tail. J Hepatobiliary Pancreat Surg 2000;7:316–320. doi:10.1007/s005340070055.
24. Klöppel G, Solcia E, Longnecker DS et al. Histological typing of tumours of the exocrine pancreas. WHO international histology classification of tumours. Berlin: Springer, 1996.
25. Sobin LH, Wittekind C, editors. TNM Classification of Malignant Tumours, 6th edn. New York: Wiley, 2002.
26. Oken MM, Creech RH, Tormey DC et al. Toxicity and response criteria of Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649–655. doi:10.1097/00000421-198212000-00014.
27. Krishnan S, Rana V, Janjan NA et al. Prognostic factors in patients with unresectable locally advanced pancreatic adenocarcinoma treated with chemoradiation. Cancer 2006;107:2589–2593. doi:10.1002/cncr.22328.
28. Morganti AG, Forni F, Macchia G et al. Chemoradiation of unresectable pancreatic carcinoma: impact of pretreatment hemoglobin level on patterns of failure. Strahlenther Onkol 2003;179:87–92. doi:10.1007/s00066-003-1043-y.
29. Ikeda M, Okada S, Tokuuye K, Ueno H, Okusaka T. Prognostic factors in patients with locally advanced pancreatic carcinoma receiving chemoradiotherapy. Cancer 2001;91:490–495. doi:10.1002/1097-0142(20010201)91:3<490::AID-CNCR1027>3.0.CO;2-L.

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ORIGINAL ARTICLE

A Double-blind, Placebo-controlled Trial of Ciprofloxacin Prophylaxis in Patients with Acute Necrotizing Pancreatitis

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Abstract
Background The use of prophylactic antibiotics in acute severe necrotizing pancreatitis is controversial.
Methods Prospective, randomized, placebo-controlled, double-blind study was carried out at Bellvitge Hospital, in Barcelona, Spain. Among 229 diagnosed with severe acute pancreatitis, 80 had evidence of necrotizing pancreatitis (34/80 patients were excluded of the protocol). Forty-six patients without previous antibiotic treatment with pancreatic necrosis in a contrast-enhanced CT scan were randomly assigned to receive either intravenous ciprofloxacin or placebo. Five patients were secondarily excluded, and the remaining 41 patients were finally included in the study (22 patients received intravenous ciprofloxacin and 19 patients placebo).
Results Comparing the 22 with intravenous ciprofloxacin and 19 with placebo, infected pancreatic necrosis was detected in 36% and 42% respectively (p=0.7). The mortality rate was 18% and 11%, respectively (p=0.6). No significant differences between both treatment groups were observed with respect to variables such as: non-pancreatic infections, surgical treatment, timing and the re-operation rate, organ failure, length of hospital and ICU stays.
Conclusion The prophylactic use of ciprofloxacin in patients with severe necrotizing pancreatitis did not significantly reduce the risk of developing pancreatic infection or decrease the mortality rate. The small number of patients included in this study should be considered.

Keywords Severe acute pancreatitis · Necrotizing pancreatitis · Prophylactic antibiotics · Ciprofloxacin · Infection · Mortality

Introduction

Acute pancreatitis has a broad clinical spectrum that ranges from mild to severe pancreatitis. The severe form is characterized by pancreatic or peripancreatic necrosis and may cause single or even multiple organ failure in about 20% of the cases.

This study was promoted by the "Bellvitge Hospital" and has not received any grant or payment from the pharmaceutical industry.

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The mortality rate associated with necrotizing pancreatitis increases when other organs are involved[1] (definitions adopted from the Atlanta classification);[2] moreover, the incidence of organ failure is determined by the extent of sterile necrotic parenchyma. However, when necrotic tissue gets infected, the incidence of multiple organ failure increases substantially, regardless of the extent of the necrosis.[3]

Approximately 80% of deaths in acute pancreatitis are due to septic complications secondary to a bacterial infection.[4,5] Pancreatic necrosis infection normally develops during the second or third week after the onset of symptoms, and occurs in 40–70% of all patients with necrotizing pancreatitis.[6–8] The mortality rate for patients with infected pancreatic necrosis undergoing surgical treatment is about 10% to 30%.[5,9–13]

The use of antibiotic prophylaxis is based on the rationale that reducing the pancreatic infection may decrease late morbidity and mortality. Although much attention has been given to the possibility of preventing or treating severe acute pancreatitis due to its poor prognosis, the advantages of antibiotic prophylaxis still remain controversial.

Several randomized controlled clinical trials have provided some evidence that prophylactic antibiotics may prevent the infection of necrotic pancreatic tissue[14,15] or reduce septic complications.[16] However, only one study showed significantly reduced patient mortality following treatment with antibiotics.[17] Furthermore, two meta-analyses[18,19] suggested that mortality was significantly reduced in patients with severe pancreatitis who were given antibiotic prophylaxis.

Nevertheless, only two of the published studies had a double-blind design. Isenmann et al.[20] published a double-blind multicenter trial on the use of antibiotic prophylaxis in acute pancreatitis and showed it had no benefit in avoiding the development of infected pancreatic necrosis. Recently, in a trial with 32 centers, Dellinger et al.[21] demonstrated no statistically significant difference between the treatment groups for pancreatic or peripancreatic infection, mortality, or requirement for surgical intervention. Consequently, they did not support early prophylactic antimicrobial use in patients with severe acute necrotizing pancreatitis.

We therefore performed a prospective, double-blind, placebo-controlled, randomized trial. Our aim was to assess the effects of intravenous prophylactic ciprofloxacin on the incidence of infected necrosis and mortality in patients with necrotizing pancreatitis, compared to a control population.

Patients and Methods

Setting and Study Population

Between May 1999 and December 2003, 798 patients with acute pancreatitis were admitted to the Surgical Gastrointestinal Service of Bellvitge Hospital (Barcelona, Spain). Of them 229 (29%) were diagnosed with severe acute pancreatitis (definition according to the Atlanta classification),[2] from which 80 presented pancreatic necrosis (see Fig. 1).

We studied 46 consecutive patients with acute necrotizing pancreatitis admitted during this period. Three patients were excluded because necrosis was not confirmed when a senior radiologist revised the CT. Additionally, two more patients with fulminant disease, who died within 24 h of the

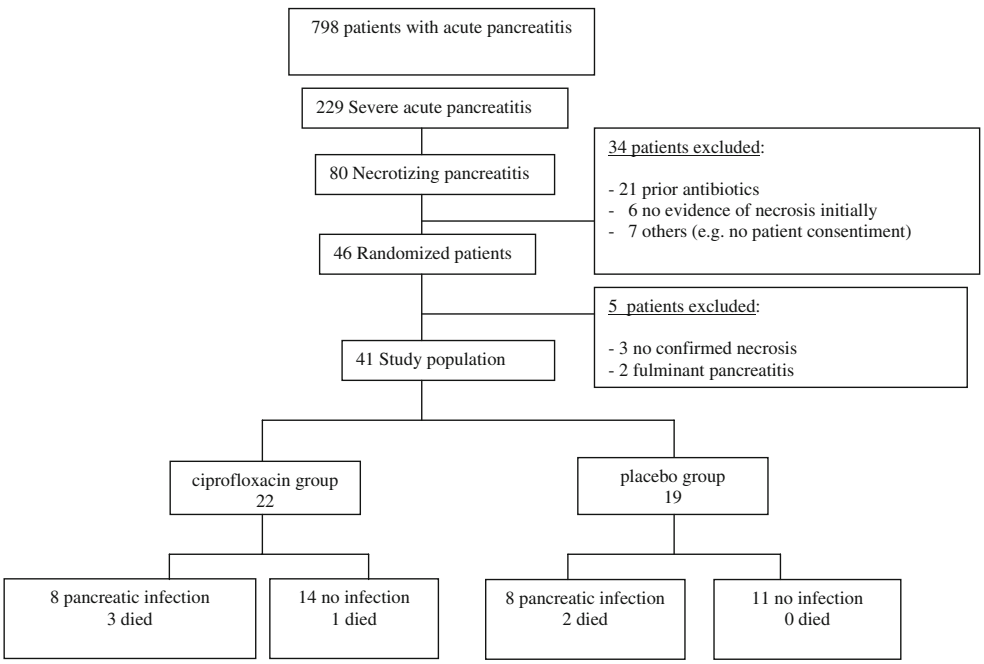

Figure 1 Patients with acute pancreatitis and those finally included in the study protocol.

beginning of the study, were not included either, as they could only follow the protocol for 1 day. Thus, 41 patients remained in the study protocol.

The reasons for discontinuing the study were: infected necrosis confirmed by cultures of CT-guided needle-aspirated material, strong clinical suspicion of pancreatic sepsis, progressive organ failure despite intensive medical treatment and extrapancreatic infection (pneumonia, urinary tract infection, intraabdominal infection).

The study protocol was reviewed and approved by the ethical committee of our hospital (no EC: 129/98, 12/12/1998). The trial has been submitted to the ISRCCTN register with the application num. ISRCTN75232398—http://www.controlled-trials.com/ISRCTN75232398.

Study Design

All patients with acute pancreatitis suspected to have the severe form of the disease underwent a dynamic contrast-enhanced CT scan within 48–72 h of admission. When the CT showed a pancreatic necrosis, patients signed a consent form, and were randomly assigned to receive either prophylactic antibiotic treatment or placebo. In the treatment group, 22 patients received 300 mg ciprofloxacin q. 12 h for 10 days, whereas in the control group 19 patients were administered placebo.

We chose ciprofloxacin because it has been proven to be clinically safe, provide appropriate antibacterial activity against the relevant pathogens of this kind of infections, and due to its good penetration of necrotic pancreatic and peripancreatic tissue.[22,23]

All patients were treated medically on admission (aggressive fluid resuscitation along with electrolyte imbalance, complete avoidance of oral intake, pain control and total parenteral nutrition). Patients with organ failure were followed in the intensive care unit (ICU). When infected necrosis was clinically suspected, a CT-guided fine-needle aspiration (FNA) followed by a Gram stain and a bacteriologic culture was carried out. If infection could be diagnosed through these procedures, we indicated surgical treatment. Further indications for surgery were: diagnostic doubt, organ failure despite intensive medical treatment and symptomatic sterile necrosis (defined as persistent abdominal pain or inability to eat after 4 to 6 weeks of medical management).[24]

Surgical debridement and postoperative lavage were performed according to the Beger procedure.[25]

Inclusion–exclusion Criteria

All patients without previous antibiotic treatment and with detectable pancreatic necrosis in a contrast-enhanced CT scan[26] performed within 48–72 h of admission were included. Patients with quinolone allergy or clinical evidence of sepsis on admission were excluded.

Outcome Variables Studied

The primary end point of this study was to determine whether prophylaxis with intravenous ciprofloxacin could reduce the incidence of infected pancreatic necrosis. Secondarily, we assessed its effects on the mortality rate; on the extrapancreatic infections; on the surgical treatment, its timing and the re-operation rate; on the development of organ failure[2] and on the in-hospital and ICU length of stay.

Statistical Analysis

A sample size of 134 patients was calculated as necessary to demonstrate that antibiotic prophylaxis reduces the proportion of patients with infected pancreatic necrosis from 40% (placebo) to 20% (ciprofloxacin), with 90% power and a one-sided 5% significance level. A pilot study of about 46 patients included in the protocol and randomized to receive either ciprofloxacin or placebo was initially planned to re-evaluate the sample size and the possibilities to continue the study.

Data analysis was performed with computer software (SPSS 11.0 for Windows). Differences in numeric variables were evaluated with parametric tests (Student *T*-test) and non-parametric ones (Mann Whitney *U* test) according to their distributional characteristics. Comparison of proportions was made using χ^2 or Fischer's exact test for string variables, when appropriate. A two-tailed p value of 0.05 or less was considered evidence not attributable to chance.

Results

The algorithm shows the total number of patients with acute pancreatitis and the final group included in the study protocol. Forty-six patients were randomly assigned to receive either ciprofloxacin or placebo. Of the 46 patients, five were excluded (see Fig. 1) and 41 were finally included in the protocol. The time of evolution for the study population from the onset of symptoms until hospital admission was 1*2.17 days (1–3-day range). The most relevant clinical data were similar in both the placebo and the ciprofloxacin group (see Table 1).

Study medication was administered during 3–10 days (mean 9.7 days) after joining the protocol in the treatment group, and during 4–10 days (mean 9.7 days) in the control group. In seven patients (7/22) within the ciprofloxacin group, and in eight (8/19) within the placebo group (p= 0.495), it had to be discontinued and open antibiotic treatment had to be started instead. Of them, one patient

Table 1 Patients Finally Included in the Study Protocol

	Group ciprofloxacin $n=22$	Group placebo $n=19$	p
Men/women	14/8	15/4	0.283
Age in years (mean, minimum–maximum)	59.5 (31–84)	67 (38–79)	0.301
Etiology (%)			
Biliary	72.7	57.9	0.213
Alcohol	9.1	26.3	
Others	18.2	15.8	
APACHE (mean)	10	14	0.135
C-reactive protein (mg/L) in first 48 h (mean, minimum–maximum)	313 (25–431)[a]	326 (106–453)[b]	0.866
Study inclusion after onset of symptoms, days (mean, minimum–maximum)	5 (2–16)	5 (2–12)	0.535
Necrosis			
<30%	11	9	0.313
30–50%	3	6	
>50%	8	4	

[a] Data from 20 patients
[b] Data from 19 patients

had an exanthema (9 days after the administration of study medication) and could not receive antibiotic treatment thereafter. Thus, open antibiotic treatment was started in six patients within the ciprofloxacin group after a mean of seven days (range 3–9 days) and in eight patients within the placebo group after a mean of 6 days (range 4–8 days). Piperacillin–tazobactam, or imipenem, was thus administered to those patients with demonstrated pancreatic infection (positive FNA) or with high pancreatic infection probability (progressive organic failure despite intensive medical treatment), this later being modified as per antibiogram results. Ciprofloxacin was begun for two placebo-group patients due to urinary tract infection. The reasons for discontinuing the study medication are listed in Table 2.

Bacterial Infection

The overall incidence of infected pancreatic necrosis was 39% (16/41; eight patients in the treatment group and eight patients in the control group, $p=0.707$). Eight extrapancreatic infections were found in six of the 22 patients (27%) within the ciprofloxacin group, whereas in the placebo group there were ten extrapancreatic infections in eight of the 19 patients (42%).

Five patients presented central line infections: two patients of the ciprofloxacine group (*Staphylococcus epidermidis* and *Staphylococcus aureus*) and three from the placebo group (*Staphylococcus aureus* in two and *Staphylococcus epidermidis* in one). No differences were observed between the groups when infectious complications were analyzed (see Table 3).

Bacteriology

Of the 16 positive pancreatic necrosis cultures, five were polymicrobial (two within the ciprofloxacin group and three in the placebo group).

Gram-positive cocci predominated in intraoperative cultures from pancreatic necrosis within the control group;

Table 2 Reasons for Discontinued of Study Medication

	Group ciprofloxacin 22 patients	Group placebo 19 patients
Total switch-overs	7	8
Progressive organ failure despite intensive medical treatment	2	1
Infected pancreatic necrosis	4	5
Urinary tract infection	0	2
Exanthema	1	0

Table 3 Infectious Complications

	Group ciprofloxacin $n=22$ n (%)	Group placebo $n=19$ n (%)	p
Infected pancreatic necrosis	8 (36)	8 (42)	0.707
Number of patients with one or more extrapancreatic infections[a]	6 (27)	8 (42)	0.318
Pneumonia	0	2	
Urinary tract infection	3	3	
Central line infection	2	3	
Positive blood-culture	3	2	

[a] Some patients had two or more extrapancreatic infections

Table 4 Bacterial Isolates from Infected Pancreatic Necrosis in 16 Patients

	Group ciprofloxacin	Group placebo
Gram-positive cocci		
Staphylococcus aureus	1	4[a]
Staphylococcus schleiferii		1
Staphylococcus epidermidis	1	
Streptococcus intermedius		1
Streptococcus sanguis I	2	
Enterococcus faecalis	1	
Gram-negative bacilli		
Escherichia coli		2
Enterobacter cloacae		1
Acinetobacter baumannii	2[b]	
Proteus mirabilis	1	
Bacteroides spp.	2	
Others		
Clostridium perfringens		1
Corynebacterium		1
Fusobacterium spp.	2	

[a] One case was a MRSA which showed also resistance to ciprofloxacin
[b] The two isolates of *Acinetobacter baumannii* multiresistant including resistance to ciprofloxacin

whereas gram-negative bacilli and gram-positive cocci were isolated in the treatment group (Table 4). One case of methicillin-resistant *Staphylococcus aureus* (MRSA) in the placebo group and two cases of multiresistant *Acinetobacter baumannii* in the ciprofloxacin group presented ciprofloxacin resistance.

Outcomes of Necrotizing Pancreatitis

A total of 19 patients had a necrosectomy, a cholecystectomy and a subsequent continuous lavage of the necrotic cavity through drainage tubes. One patient required a cystojejunostomy as well because of an associated pseudocyst.

The indications to proceed to surgical debridement were: a positive percutaneous fine-needle aspiration of pancreatic necrosis—14 patients (seven in ciprofloxacin group and seven in placebo group), progressive organ failure despite intensive medical treatment—four patients (three within the ciprofloxacin group and one in the placebo group) and finally pseudocyst, characterized by a persistent abdominal pain and inability to eat—one patient from the ciprofloxacin group.

Four patients had surgery in the first week of the disease. Three due to positive FNA, two from placebo group (one died after the first week) and one from ciprofloxacin group (died after the first week). One patient from the ciprofloxacin group due to organ failure (Atlanta classification2) in the form of severe respiratory failure despite mechanical ventilation that eventually resulted in a sterile pancreatic necrosis (died in the first week).

Overall mortality rate in this study was 15%. Three patients died during the first week due to multiple organ failure, and three died (beyond the fourth week after the onset of symptoms) due to septic complications. Of the three patients who died in the first week, the infected pancreatic necrosis was isolated in two. In one, the infection was caused by *Staphylococcus aureus* (group ciprofloxacin), and in another by *Bacteroides fragilis* (group placebo), while the third was a sterile necrosis (group ciprofloxacin).

No differences were observed between the two treatment groups with regard to secondary end points. The results are summarized in Table 5.

Discussion

Due to the high mortality rate associated with pancreatic infection, prophylactic antibiotic therapy has been suggested, during the last few years, to improve the prognosis of its severe form. As a result, many trials have been published on this issue during the last decade.[14–17,20] Pederzoli and Luiten showed a decrease in the incidence of pancreatic infection when broad spectrum antibiotics were used in severe acute pancreatitis (12.2% versus 30.3%—$p<0.01$ and 18% versus 38%—$p<0.03$, respectively). Accordingly, the Delcenserie study showed a decrease in both pancreatic and extrapancreatic infections when they were both analyzed at the same time (0% versus 58%, $p<0.03$). Nevertheless, only the Sainio study demonstrated a significantly reduced mortality rate (3% versus 33%, $p<0.03$). On the other hand, only two prospective, placebo-controlled, double blind studies performed up to now failed to show significant differences in

Table 5 Outcome of 41 Patients with Necrotizing Pancreatitis

	Group ciprofloxacin 22 patients	Group placebo 19 patients	*p*
Organ failure (%)[a]	13 (59)	10 (53)	0.678
Mortality (%)	4 (18)	2 (11)	0.668
Surgical treatment (%)	11 (50)	8 (42)	0.613
Hospital stay, days (mean, minimum–maximum	21 (7–255)	19 (9–203)	0.794
ICU stay, days (mean, minimum–maximum)	17 (0–127)	18 (0–138)	0.826
Timing to surgery, days (mean, minimum–maximum)	17 (5–80)	13 (4–21)	0.125
Re-operation (%)	6 (27)	3 (16)	0.466

[a] Bradley

the risk of developing pancreatic infection or in the mortality rate.[20]

Although many studies favor the use of imipenem for antibiotic prophylaxis in severe acute pancreatitits,[27,28] we chose ciprofloxacin due to its good penetration of the pancreatic tissue, its adequate organ concentration, its activity against frequent pathogens in this sort of infections, and the low occurrence of adverse effects associated with it.[22,23,29] Bassi et al.[30] compared pefloxacin, an antibiotic of the quinolone family, versus imipenem in a multicentric trial. The authors found a theoretical benefit with imipenem, although mortality was not significantly different in the two groups.

We selected the patients with pancreatic necrosis at the CT for this study because they were at high risk of developing a pancreatic infection. The area of necrosis was similar in both groups.

In Isenmann's study[20], all patients started medication within three days of the onset of symptoms, whereas in ours medication was started later because we included patients transferred from other centers in our sample. This also contributed to a smaller number of patients than expected, as many of the patients coming from other hospitals had already started an empirical antibiotic treatment, making them ineligible for inclusion. The main reason that forced us to finish the study after evaluation of the pilot group, without reaching the initially calculated sample size, was the difficulty in recruiting a sufficient number of patients and the increased isolation of ciprofloxacin-resistant pathogens.

In most intraoperative cultures of the control group, gram-positive cocci were isolated, whereas in the treatment group, both gram-positive cocci and gram-negative bacilli grew in similar proportions. In three of the five cases who died, a *Staphylococcus aureus* was isolated from the intraoperative culture. This might suggest that this microorganism is associated with a worse prognosis in evolution.

An important feature prompted by the use of prophylactic antibiotics is the development of resistance and the presence of uncommon organisms such as fungi, which are associated with a higher mortality rate and a longer stay in the ICU.[31,32]

In two cases within the ciprofloxacin group, a multiresistant *Acinetobacter baumannii* was isolated and an MRSA in one case in the placebo group. However, no fungus grew in any intraoperative culture.

Considering that the more localized the necrosis, the more effective the surgical debridement, generally at the third to fourth week24, one could think that antibiotic prophylaxis might permit a late debridement. However, no differences were found within the groups regarding the day of surgery. In addition, other studies suggest that an antibiotic prophylaxis is neither useful in reducing the incidence of multi organ failure, nor the need for surgery.[14,16,20]

The mean age in our sample is higher than in other centers and therefore, so is the morbidity; the mortality rate in our study is comparable to the figures published by other groups.[14,16,17,20,33]

In the present prospective, randomized, placebo-controlled, double-blind study, the prophylactic use of ciprofloxacin in patients with pancreatic necrosis did not reduce the risk of developing a pancreatic infection nor the mortality rate. No conclusion can be drawn regarding the routine use of antibiotic prophylaxis for severe acute pancreatitis from any of the available studies.[34–36]

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References

1. Poves Prim I, Fabregat Prous J, García Borobia FJ, Jorba Martí R, Figueras Felip J, Jarrieta Mas E. Early onset of organ failure is the best predictor of mortality in acute pancreatitis. Rev Esp Enferm Dig 2004;96:705–713.
2. Bradley EL III. A clinically based classification system for acute pancreatitis: Summary of the International Symposium on Acute Pancreatitis. Arch Surg 1993;128:586–590.
3. Isenmann R, Rau B, Beger HG. Bacterial infection and extent of necrosis are determinants of organ failure in patients with acute necrotizing pancreatitis. Br J Surg 1999;86:1020–1024. doi:10.1046/j.1365-2168.1999.01176.x.
4. Beger HG, Rau B, Mayer J, Pralle U. Natural course of acute pancreatitis. World J Surg 1997;21:130–135. doi:10.1007/s002689900204.
5. Gloor B, Müller CA, Worni M, Martignoni ME, Uhl W, Büchler MW. Late mortality in patients with severe acute pancreatitis. Br J Surg 2001;88:975–979. doi:10.1046/j.0007-1323.2001.01813.x.
6. Beger HG, Bittner R, Block S, Büchler M. Bacterial contamination of pancreatic necrosis: a prospective clinical study. Gastroenterology 1986;91:433–438.
7. Gerzof SG, Banks PA, Robbins AH, Johnson WC, Spechler SJ, Wetzner SM, Snider JM, Langevin RE, Jay ME. Early diagnosis of pancreatic infection by computed tomography-guided aspiration. Gastroenterology 1987;93:1315–1320.
8. Bassi C, Falconi M, Girelli R, Nifosi F, Elio A, Pederzoli P. Microbiological findings in severe pancreatitis. Surg Res Commun 1989;5:1–4.
9. Bradley EL III, Allen K. A prospective longitudinal study of observation versus surgical intervention in the management of necrotizing pancreatitis. Am J Surg 1991;161:19–25. doi:10.1016/0002-9610(91)90355-H.
10. Ashley SW, Perez A, Pierce EA, Brooks DC, Moore FD, Whang EE, Banks PA, Zinner MJ. Necrotizing pancreatitis: contemporary analysis of 99 consecutive cases. Ann Surg 2001;234:572–580. doi:10.1097/00000658-200110000-00016.
11. Ho SH, Frey CF. The role of antibiotic prophylaxis in severe acute pancreatitis. Arch Surg 1997;132:487–493.
12. Hartwig W, Werner J, Uhl W, Büchler MW. Management of infection in acute pancreatitis. J Hepatobiliary Pancreat Surg 2002;9:423–428. doi:10.1007/s005340200052.
13. Rattner DW, Legermate DA, Lee MJ, Mueller PR, Warshaw AL. Early surgical debridement of symptomatic pancreatic necrosis is beneficial irrespective of infection. Am J Surg 1992;163:105–110. doi:10.1016/0002-9610(92)90261-O.

14. Pederzoli P, Bassi C, Vesentini S, Campedelli A. A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitis with imipenem. Surg Gynecol Obstet 1993;176:480–483.
15. Luiten EJ, Hop WC, Lange JF, Bruining HA. Controlled clinical trial of selective decontamination for the treatment of severe acute pancreatitis. Ann Surg 1995;222:57–65. doi:10.1097/00000658-199507000-00010.
16. Delcenserie R, Yzet T, Ducroix JP. Prophylactic antibiotics in treatment of severe acute alcoholic pancreatitis. Pancreas 1996;13:198–201.
17. Sainio V, Kemppainen E, Puolakkainen P, Taavitsainen M, Kivisaari L, Valtonen V, Haapiainen R, Schröder T, Kivilaakso E. Early antibiotic treatment in acute necrotising pancreatitis. Lancet. 1995;346:663–667. doi:10.1016/S0140-6736(95)92280-6.
18. Golub R, Siddiqi F, Pohl D. Role of antibiotics in acute pancreatitis: a meta-analysis. J Gastrointest Surg 1998;2:496–503. doi:10.1016/S1091-255X(98)80048-6.
19. Sharma VK, Howden CW. Prophylactic antibiotic administration reduces sepsis and mortality in acute necrotizing pancreatitis: a meta-analysis. Pancreas 2001;22:28–31. doi:10.1097/00006676-200101000-00005.
20. Isenmann R, Rünzi M, Kron M, Kahl S, Kraus D, Jung N, Maier L, Malfertheiner P, Goebell H, Beger HG. Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: a placebo-controlled, double blind trial. Gastroenterology 2004;126:997–1004. doi:10.1053/j.gastro.2003.12.050.
21. Dellinger EP, Tellado JM, Soto NE, Ashley SW, Barie PS, Dugernier T, et al. Early antibiotic treatment for severe acute necrotizing pancreatitis: a randomized, double-blind, placebo-controlled study. Ann Surg 2007;245(5):674–683. doi:10.1097/01.sla.0000250414.09255.84.
22. Bassi C, Pederzoli P, Vesentini S, Falconi M, Bonora A, Abbas H, et al. Behavior of antibiotics during human necrotizing pancreatitis. Antimicrob Agents Chemother 1994;38:830–836.
23. Büchler M, Malfertheiner P, Frieb H, Isenmann R, Vanek E, Grimm H, et al. Human pancreatic tissue concentration of bactericidal antibiotics. Gastroenterology 1992;103:1902–1908.
24. Fernandez del Castillo C, Rattner DW, Makary MA, Mostafavi A, McGrath D, Warshaw AL. Débridement and closed packing for the treatment of necrotizing pancreatitis. Ann Surg 1998;228:676–684. doi:10.1097/00000658-199811000-00007.
25. Beger HG, Buchler M, Bittner R, Block S, Nevalainen TJ, Roscher R. Necrosectomy and postoperative local lavage in necrotizing pancreatitis. Br J Surg 1988;75:207–212. doi:10.1002/bjs.1800750306.
26. Balthazar EJ, Freeny PC, vanSonnenberg E. Imaging and intervention in acute pancreatitis. Radiology 1994;193:297–306.
27. Brattstrom C, Malmborg AS, Tyden G. Penetration of imipenem into human pancreatic juice following single intravenous dose administration. Chemoterapy 1989;35:83–87.
28. Büchler MW, Gloor B, Müller CA, Friess H, Seiler CA, Uhl W. Acute necrotizing pancreatitis: treatment strategy according to the status of infection. Ann Surg 2000;232:619–626. doi:10.1097/00000658-200011000-00001.
29. Mithofer K, Fernandez del Castillo C, Ferraro MJ, Lewandrowski K, Rattner DW, Warshaw AL. Antibiotic treatment improves survival in experimental acute necrotizing pancreatitis. Gastroenterology 1996;110:232–240. doi:10.1053/gast.1996.v110.pm8536862.
30. Bassi C, Falconi M, Talamini G, Uomo G, Papaccio G, Dervenis C, et al. Controlled clinical trial of pefloxacin versus imipenem in severe acute pancreatitis. Gastroenterology. 1998;115(6):1513–1517. doi:10.1016/S0016-5085(98)70030-7.
31. Robbins EG, Stollman NH, Bierman P, Grauer L, Barkin JS. Pancreatic fungal infections: a case report and review of the literature. Pancreas 1996;12:308–312. doi:10.1097/00006676-199604000-00016.
32. Grewe M, Tsiotos GG, Luque de Leon E, Sarr MG. Fungal infection in acute necrotizing pancreatitis. J Am Coll Surg 1999;188:408–414. doi:10.1016/S1072-7515(98)00334-2.
33. Nordback I, Jubani S, Saaristo R, Paajanen H. Early treatment with antibiotics reduces the need for surgery in acute necrotizing pancreatitis—a single-center randomized study. J Gastrointest Surg 2001;5:113–120. doi:10.1016/S1091-255X(01)80021-4.
34. Xiong GS, Wu SM, Wang ZH. Role of prophylactic antibiotic administration in severe acute pancreatitis: a meta-analysis. Med Princ Pract 2006;15:106–110. doi:10.1159/000090913.
35. Zhou YM, Xue ZL, Li YM, Zhu YQ, Cao. Antibiotic prophylaxia in patients with severe acute pancreatitis. Hepatobiliary Pancreat Dis Int 2005;4:23–27.
36. Mazaki T, Ishii Y, Takayama T. Meta-analysis of prophylactic use in acute necrotizing pancreatitis. Br J Surg 2006;93:674–684. doi:10.1002/bjs.5389.

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ORIGINAL ARTICLE

Exogenous Ghrelin Enhances Endocrine and Exocrine Regeneration in Pancreatectomized Rats

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Abstract
Aim Ghrelin, the most important modulator of endocrine and exocrine pancreatic functions, has a role in the development of islets of Langerhans during embryogenesis. The aim of this study was to evaluate the effects of ghrelin on pancreatic regeneration in rats with 90% pancreatectomy.
Materials and Methods Two- to 3-week-old Wistar rats were used in the study. After anesthesia, 90% pancreatectomy was performed. In the ghrelin group, 90% pancreatectomy was performed. Ten nanomoles per kilogram per day of ghrelin was administered intraperitoneally from the first postoperative day. In the antagonist group, 90% pancreatectomy was performed. From the first postoperative day, rats received the ghrelin receptor antagonists and substance P intraperitoneally at 1 μmol/kg. In the control group, 90% pancreatectomy was performed, and intraperitoneal saline was administered. The sham group did not receive pancreatectomy. Eight rats from each group were randomly selected and sacrificed on the second, third, and 30th days.
Results Blood glucose levels in pacreatectomized rats were significantly higher than in rats in the sham group. The number of beta islet cells, serum insulin levels, and PDX-1 and cytokeratin staining scores decreased in rats with pancreatectomy when compared to the sham-group rats. In the ghrelin-receiving rats, blood glucose levels tended to decrease from the 15th postoperative day. Ghrelin treatment increased insulin levels, insulin-positive islet cell number, and 5-bromo-2-deoxyuridine and PDX-1 staining, whereas ghrelin antagonist administration resulted in significant decreases in these parameters. Ghrelin treatment significantly improved glucose tolerance test results.
Conclusion Exogenous ghrelin administration decreased blood glucose levels after 90% pancreatectomy by increasing islet cell numbers and enhancing endocrine and exocrine regeneration.

Keywords Pancreatectomy · Ghrelin · Regeneration · Pancreas · Type 3 diabetes

Kerem M and Salman B contributed equally to this work; Kerem M, Salman B, and Bedirli A designed experiments; Kerem M, Salman B, Pasaoglu H, Ozsoy S, Haziroglu R, and Yilmaz Tu performed experiments; Kerem M, Salman B, and Bedirli A analyzed data; Kerem M, Salman B, and Bedirli A wrote the paper.

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Introduction

Cells in the islets of Langerhans undergo continuous turnover under physiological conditions. The pancreas is highly responsive to decreases or increases in the total number of β cells and the regulation of functional islet cell mass.[1,2] β cell hyperplasia and hypertrophy occur to compensate for increased insulin demand during pregnancy and obesity or after pancreatectomy and pancreatic inju-

ry.[1,2] Studies have shown that the pancreatic regenerative process is constituted by four complex mechanisms: (1) β cell neogenesis at the residual islet cells, (2) proliferation of duct cells and new β cell differentiation around the expanded ducts, (3) acinar cell dedifferentiation and acinar cell differentiation to β cells or transdifferentiation to islet cells, and (4) replication and proliferation of progenitor β cells in the residual islets.[3,4] On the basis of in vivo regenerative models, it is clear that there are pancreatic stem or progenitor cells (ducts, acinar, and islet cells) in the adult pancreas. Additionally, "self-duplication" is more prominent than stem cell differentiation in adult pancreatic β islet cells.[5] Various agents have been studied in order to increase pancreatic regenerative capacity; the most important are glucagon-like peptide 1, actin, members of the transforming growth factor β family, and the polypeptide growth factor betacellulin.[6–16] In this study, we aimed to evaluate the effects of a ghrelin receptor antagonist on pancreatic regeneration.

Ghrelin is a 28-amino-acid octanoylated peptide isolated from human and rat stomachs, and it is an endogenous ligand for the growth hormone secretagogue receptor (GHS-R). It also influences feeding behavior, metabolic regulation, and energy balance.[17] Ghrelin is a potent stimulator of growth hormone (GH) release and feeding. Ghrelin is involved in a wide variety of functions, including the regulation of endocrine and exocrine pancreatic functions.[18] Endogenous ghrelin has been reported to influence the embryologic development of the pancreas and to regulate pancreatic secretions. The effects of exogenous ghrelin on β cell mass and ductal pancreatic regeneration have not yet been evaluated. Data derived from in vitro studies on isolated perfused pancreas, isolated islets, or INS-1 cell culture do not allow any conclusions about whether ghrelin acts locally or systemically on β cells.[19,20] Dezaki et al.[21] injected ghrelin intraperitoneally after a glucose tolerance test and observed significantly deceased insulin levels that were inhibited by ghrelin antagonism. In these studies, both endogenous and exogenous ghrelin reduced insulin secretion from β cells. Prado et al.[22] reported that ghrelin cells could replace insulin-producing beta cells in two different models of pancreas development, raising the question of how exogenous ghrelin and ghrelin receptor antagonists could effect pancreatic regeneration. The aim of this study was to evaluate the effects of exogenous ghrelin and ghrelin receptor antagonists on regeneration of the pancreatic remnants after pancreatectomy.

Materials and Methods

All procedures were conducted following the recommendations of the Animal Research Committee at Gazi University, Ankara, Turkey. Two- to 3-week-old Wistar rats weighing 230–260 g were used in the study. Rats were housed under laboratory conditions for 1 week before the experiment. They were deprived of food for 8 h before the experiment. Intramuscular injection of 40 mg/kg ketamine (Ketalar, Parke-Davis, Eczacibasi, Istanbul, Turkey) and 5 mg/kg xylazine (Rompum, Bayer Leverkusen, Germany) were used for anesthesia. Laparotomy was performed under sterile conditions. Ninety-percent pancreatectomy was done using the technique previously described by Bonner-Weir et al. Briefly, the majority of the head and the entire tail of the pancreas were removed via microdissection. In order to maintain intra-abdominal organ perfusion, vascular structures were carefully dissected. One to 2 mm of pancreatic tissue was left along the first portion of the duodenum and near the common biliary duct. The remaining tissue was at the upper portion of the head of the pancreas. In the sham group, finger pressure was applied to the pancreas for 1 min after laparotomy. Blood glucose levels were measured daily for the first week and then weekly for up to 4 weeks. Glucose levels were measured in the whole blood from the tail vein using a GlucoCard DIA meter (Arkray, Kyoto, Japan). Blood insulin, glucagons, and pancreatic polypeptide concentrations, as well as body weight, were determined weekly. On the 28th day after surgery, a glucose tolerance test (2 g/kg) was performed following 14 h of fasting. Blood samples were collected in heparinized hematocrit tubes after 0, 30, 60, 90, and 120 min, and glucose levels were measured. The rest of the blood samples were stored for insulin measurement. On the 30th day of the experiment, pancreatic remnants were removed, and blood samples were taken from the vena cava under anesthesia. Rats were killed by bleeding. Pancreatic samples were weighed and divided into two pieces. One half was fixed in 4% paraformaldehyde and embedded in paraffin wax at 4°C. Random sections were generated with a thickness of 3 μm. The other half of the pancreatic tissue was homogenized in cold acid ethanol then heated in a 70°C saline bath. Heated samples were centrifuged and stored at −20°C. Eight rats from each group were sacrificed on the second and third days following pancreatectomy. Thus, the early and late regeneration capacity of the pancreas after pancreatectomy could be compared. Six hours before the rats were killed, 100 mg/kg 5-bromo-2-deoxyuridine (BrdU; phosphate buffer dissolved in saline, Sigma, Munich, Germany) was injected intraperitoneally. The remaining pancreas was excised and fixed as described above. Rats were divided into four groups, and each group consisted of 24 rats.

Sham Group Sham pancreatectomy was performed. Rats were fed with standard rat chow and did not receive the intraperitoneal drug. Eight rats from each group were killed,

and tissue and blood samples were taken on the second, third, and 30th days.

Control Group Ninety-percent pancreatectomy was performed. Saline was administered intraperitoneally. Eight rats from each group were killed, and tissue and blood samples were taken on the second, third, and 30th days. Blood samples were centrifuged at 3,000 rpm and stored at −20°C.

Ghrelin Group Rats received 90% pancreatectomy. Ten nanomoles per kilogram per day of ghrelin[19] was injected intraperitoneally. Eight rats from each group were killed, and tissue and blood samples were taken on the second, third, and 30th days.

Ghrelin Antagonist Group Ninety-percent pancreatectomy was performed. Rats received the ghrelin receptor antagonists [D-Lys^3]-GHRP-6 (Sigma, St. Louis, MO, USA) and [D-Arg^1, D-Phe^5, D-Trp^{7,9}, Leu^{11}] substance P (SPA; Sigma) intraperitoneally at 1 μmol/kg. Eight rats from each group were killed, and tissue and blood samples were taken on the second, third, and 30th days. Pathological and biochemical studies were performed by the researchers who did not know the groups.

Immunohistochemistry and Histophotometric Studies

Paraffin sections were deparaffinized and dehydrated. Endogenous peroxidase activity was blocked using 1% H2O2/methanol. After being washed with PBS, the sections were incubated overnight at 4°C with guinea pig anti-porcine insulin (1:1,000), rinsed with PBS, incubated 1 h at room temperature with peroxidase conjugated donkey anti-guinea pig IgG (1:500, Jackson ImmunoResearch, West Grove, PA, USA), developed with diaminobenzidine, and counterstained with hematoxylin. These sections (four per rat) were evaluated using a histophotometric method as previously described.[24] In order to define β cells and other areas, image analysis software (NIH image) was used. The β-cell area and the area of each section were determined using image analysis software (NIH image). The ratio of β-cell area in the remaining pancreas was calculated by dividing the area of all insulin-positive cells in one section by the total area of that section. The β-cell mass was calculated by multiplying the remaining pancreatic weight by the ratio of β-cell area. The β-cell size was determined for sections stained with anti-insulin antibody by evaluating the mean cross-sectional area of individual β-cells. The area of β-cells in islets was measured as described above and the number of β-cell nuclei in each islet was counted. Ten islets were counted in each animal. BrdU staining was accomplished with a cell proliferation assay kit (Amersham Pharmacia Biotech, Little Chalfont, UK). Sections were incubated for 1 h at room temperature with a mouse anti-BrdU monoclonal antibody and washed with PBS. Insulin staining was done as described previously. BrdU/insulin-positive cells in islets were counted in each section as a marker of replication of a preexisting β cell. To analyze the number of PDX-positive cells in the duct, which showed pancreatic duct proliferation, PDX-1 and duct cell-specific cytokeratin 20 (CK) double-staining was performed on cryosections. OCT (Sakura Fine Chemicals, Tokyo, Japan), rabbit anti-PDX-1 antibody (Biocompare, Cambridge, UK), monoclonal mouse anti-CK antibody (1:40, DAKO, Carpinteria, CA, USA), cy3-conjugated donkey anti-rabbit IgG (1:3,000, Jackson ImmunoResearch) and fluorescein isothiocyanate-conjugated donkey anti-mouse IgG (1:100, Jackson ImmunoResearch) were used during the procedure. Counterstaining was done with 4′,6-diamidio-2-phenylindol-HCl (Boehringer Mannheim, Mannheim, Germany). PDX-1/CK-positive cells were counted at 400× and expressed as the number of PDX-1/CK-positive cells per field. Apoptotic cells were detected by terminal deoxynucleodidyl transferase technique using an apoptosis in situ detection kit.

Biochemical Assay

Fasting blood glucose, insulin, glucagons, and pancreatic polypeptide levels were analyzed. Insulin, glucagons, and pancreatic polypeptide levels were quantitated using a RIA kit.

Statistical Analysis

Data were analyzed by a one-way analysis of variance and Mann–Whitney *U* test. $P<0.05$ was considered statistically significant. SPSS 11.00 was used for statistical analysis.

Results

Four rats died due to injury of the splenic vein and vena cava during pancreatectomy. Those subjects were replaced with new ones. Rats were prone to weakness and had no appetite for the first 24 h after pancreatectomy. Four milliliters of saline was injected into the back region of each rat after the first 24 h of the experiment. Appetite and weakness of the rats were markedly improved by the first postoperative day.

Weight Gain

Ninety percent pancreatectomy resulted in significantly decreased body weight. The weight loss might be the

consequence of the lack of appetite observed during the first 24 h of the experiment. Body weights of pancreatectomized rats were lower than those of sham group rats on the seventh postoperative day ($P<0.05$). Ghrelin-treated rats began to gain weight from the 19th day of the experiment. On the 25th day, the mean body weight of the ghrelin-group rats was similar to that of the sham-group rats ($P>0.05$). Weight loss in the control and antagonist groups proceeded throughout the course of the entire experiment. On the 19th, 25th, and 30th postoperative days, the body weights in those groups tended to be lower than those in the sham and the ghrelin groups ($P>0.05$). However, there were no statistically significant differences noted between the control and antagonist groups (Fig. 1).

Blood Glucose Concentrations

In 90% pancreatectomized rats, blood glucose levels were significantly higher than in the sham group ($P<0.05$). Treatment with ghrelin markedly reduced the plasma glucose concentration from the 11th postoperative day. In the ghrelin group on the 19th, 25th, and 30th postoperative days, blood glucose levels were lower than in the control and the antagonist groups but higher than in the sham group ($P<0.05$). Blood glucose levels in rats receiving the ghrelin antagonist were significantly higher than in the sham group ($P<0.05$). No difference was observed between the control and antagonist groups (Fig. 2).

Glucose Tolerance Test

The glucose tolerance test was performed on the last day of the experiment (or 30 days after pancreatectomy). Glucose tolerance was impaired in the control and the antagonist groups, whereas blood glucose levels decreased in the ghrelin group. However, glucose tolerance was still found to be decreased compared against the sham group ($P<0.05$, Fig. 3).

Plasma Insulin Concentrations

In pancreatectomized rats, plasma insulin concentrations were significantly lower than in the sham group ($P<0.05$). Plasma insulin concentrations in subjects receiving ghrelin treatment tended to increase from the 14th postoperative day, and were significantly higher than those in the control and ghrelin antagonist groups ($P<0.05$, Fig. 4).

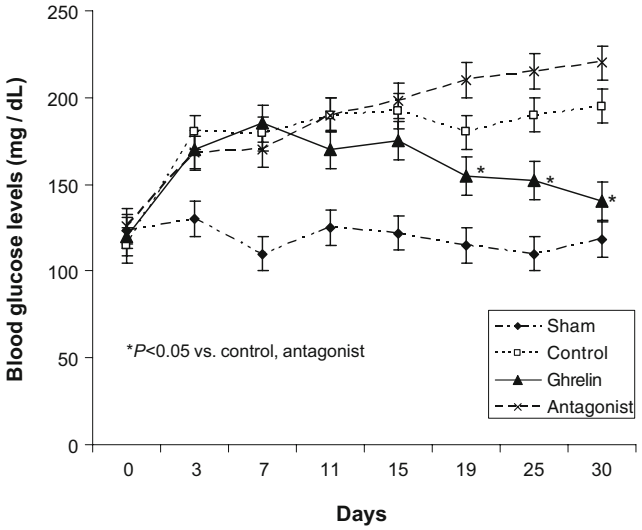

Figure 2 The results of blood glucose level measurements.

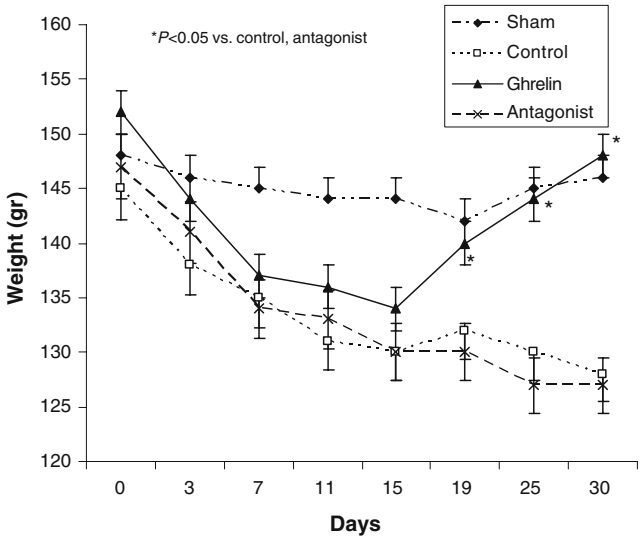

Figure 1 Weight changes of rats during the experiment are seen.

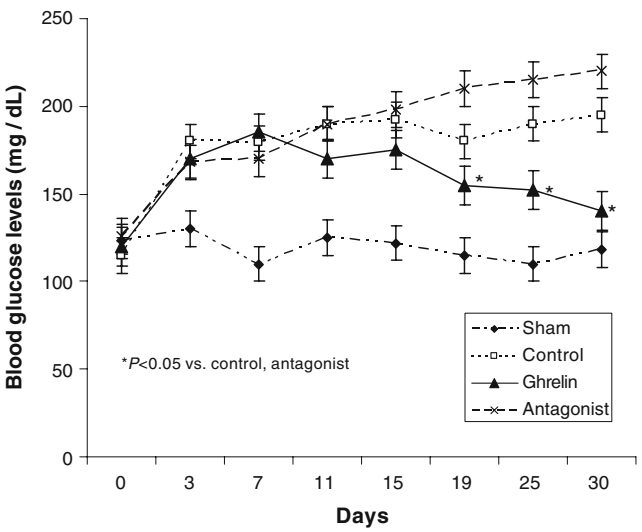

Figure 3 The results of glucose tolerance tests are seen.

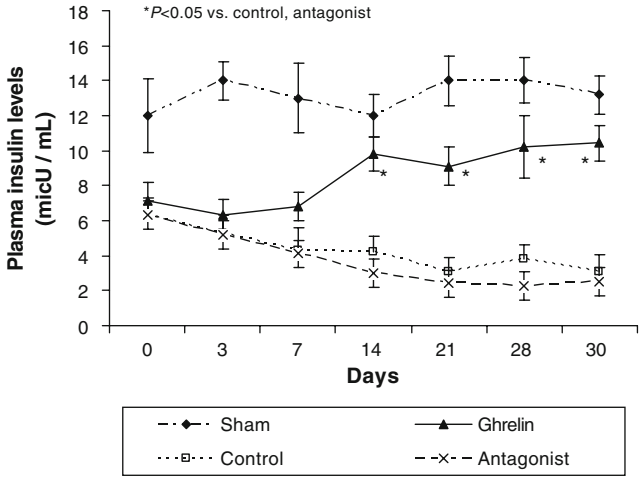

Figure 4 Insulin levels of experiments.

β Islet Numbers

The number of β cells/total number of cells in an islet was significantly decreased in pancreatectomized rats when compared with the sham group ($P<0.05$). The ratio of β cells to the total number of cells in an islet were equivalent at day 0. On the first, third, and 30th postoperative days, the ratio of β cells/total number of cells in an islet in ghrelin-treated rats was markedly higher than in the control and antagonist groups ($P<0.05$). The numbers of β cells were significantly decreased in the ghrelin antagonist group (Fig. 5).

Insulin-positive Islet Cell Number

The ratio of insulin-positive cells to islet cells in pancreatectomized rats in the ghrelin group was significantly lower than in the sham group ($P<0.05$), but they were higher than in the control and antagonist groups (Fig. 6).

Cell Proliferation

Ghrelin increased proliferation of pancreatic islet cells as the ratio of BrdU-positive cells plus β-cells over the total number of β-cells was significantly increased in the ghrelin group when compared to the sham, control, or antagonist groups on days 1, 3, or 30 after pancreatectomy ($P<0.05$, Fig. 7)

PDX-positive Cells

The effects of ghrelin and its antagonist on PDX-positive cells are depicted in Fig. 8. Ghrelin treatment resulted in an increased number of PDX-positive cells, whereas ghrelin-antagonist treatment blocked this effect ($P<0.05$, Fig. 8).

Pancreatic Polypeptide Cells

A significant decrease in the number of pancreatic polypeptide-expressing cell was observed in rats that received a pancreatectomy. Ghrelin treatment significantly increased anti-PP staining (Fig. 9). PP+ cell numbers in the control and antagonist groups were markedly lower than in the ghrelin group (Fig. 9).

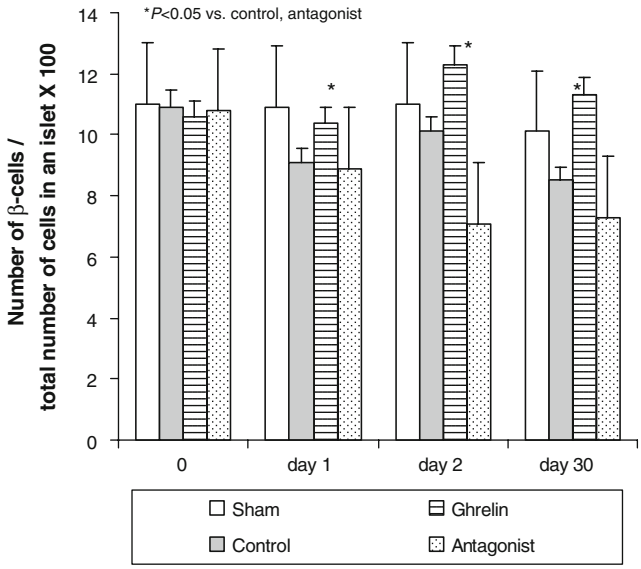

Figure 5 The ratio of number of beta cells to the total number of cells in an islet.

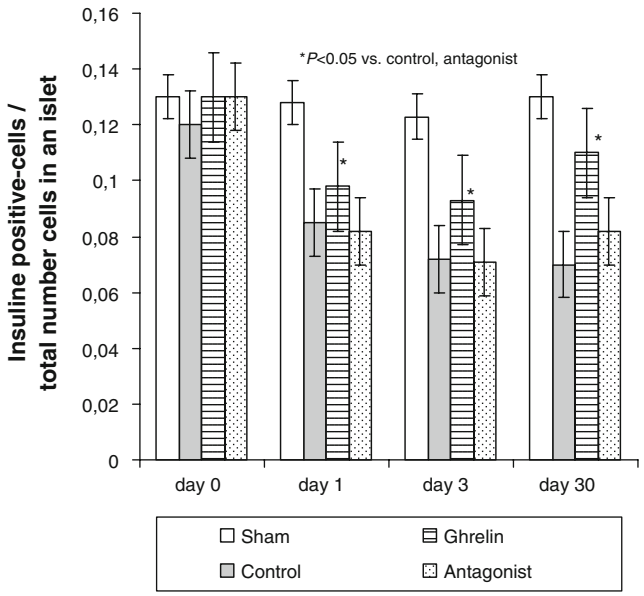

Figure 6 The ratio of insulin-positive cells to the total number cells in an islet.

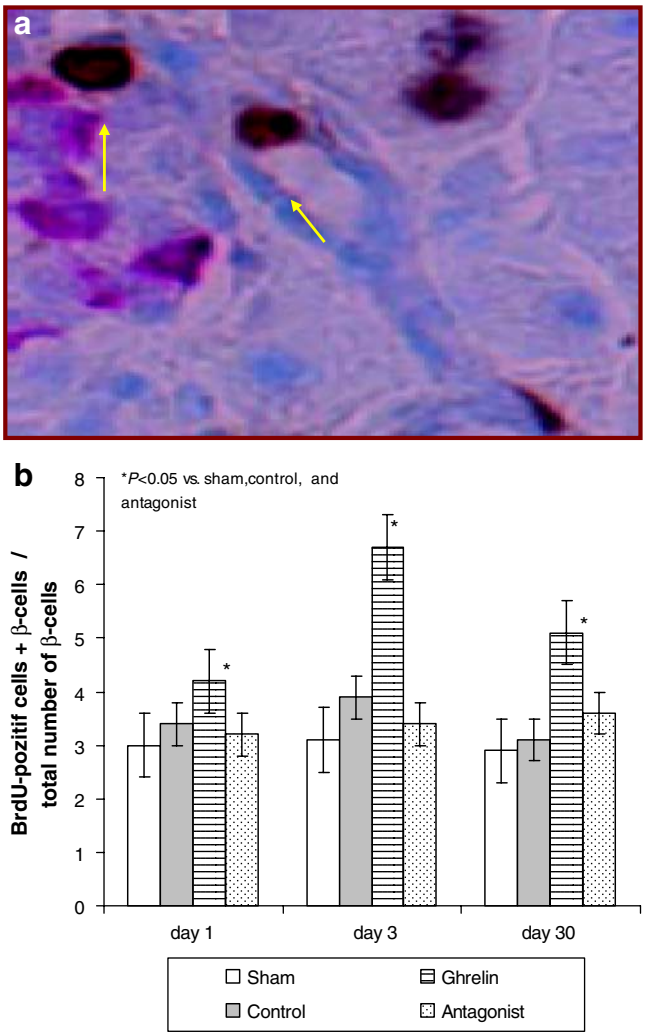

Figure 7 BrdU pozitif cells (**A**). The ratio of BrDU-positive cells + β cells to total number of β cells (**B**).

Discussion

Diabetes mellitus is the most common endocrine disorder worldwide, and its incidence is increasing rapidly. β islet replacement is the primary curative management for this disease.[25] Transplantation of islets of Langerhans or pancreas thus offers an attractive strategy for diabetes therapy.[26,27] Promotion of β cell regeneration is an alternative strategy.[23] Type 3 diabetes associated with massive islet cell loss after pancreatectomy is a very rare clinical condition but a significant model for studying pancreatic regeneration.[23,27] In our study, we used a diabetes model based on partial pancreatectomy. Diabetes mellitus that develops after pancreatectomy for periampullary carcinoma involves a different pathway from type 1 or 2 diabetes. In this type of diabetes (type 3), decreased levels of not only insulin but also pancreatic polypeptide and glucagon both of which have importance in the regulation of the blood glucose level.[23,28] This type of diabetes is characterized by sudden decreases and increases in plasma glucose levels, and it is called "brittle diabetes" because of the difficulty in regulating glucose levels. Increasing insulin concentration alone is an inadequate treatment for type 3 diabetes, therefore, and increase in the proliferation of cells that produce glucagon and pancreatic polypeptide is necessary. For this reason, in our model, we attempted to define whether various types of cells other than β cells could also regenerate from pancreatic islets. The effects of exogenous administration of ghrelin, which has been correlated with β islet development during intrauterine life,[18–20,29] was studied in pancreatic regeneration after pancreatectomy. Ghrelin plays a significant role in the development of embryologic pancreas and islet cell transformation.[18,19,29] To our knowledge, no studies thus far have evaluated the use of ghrelin and ghrelin receptor

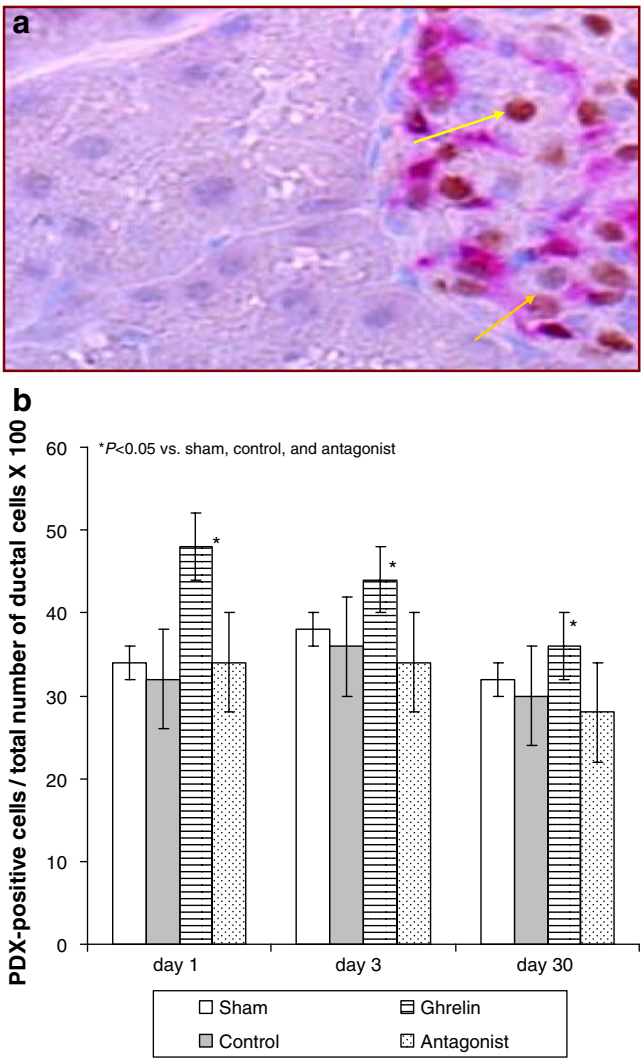

Figure 8 The PDX-Positive cells are seen by *arrow* (**A**). The ratio of PDX-positive cells to total number of ductal cells (**B**).

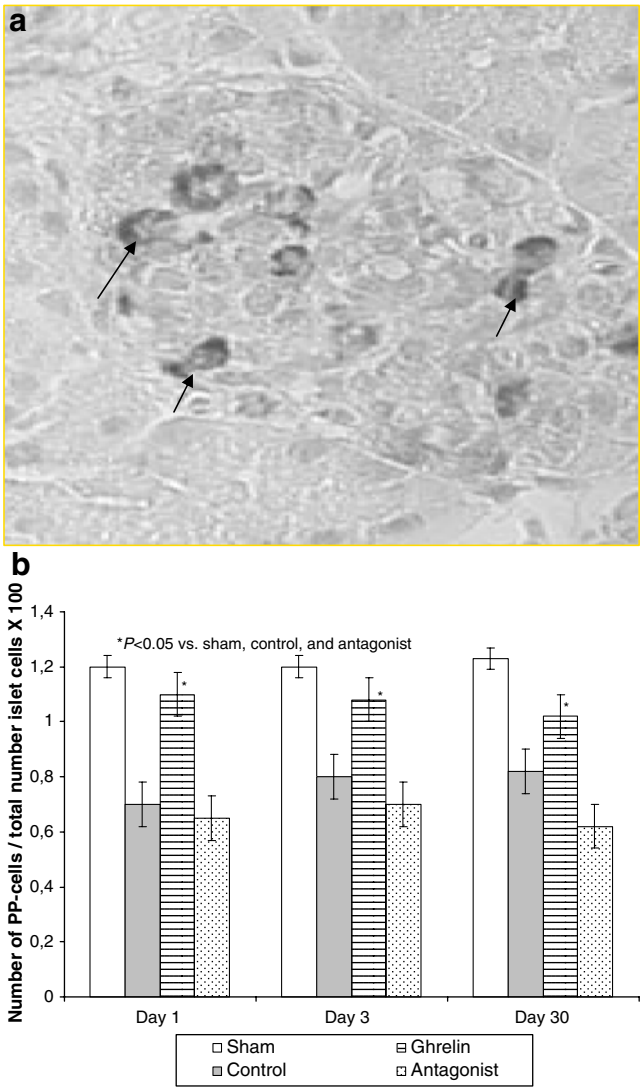

Figure 9 Cells stained by anti-PP are shown by *arrows* (**A**). The ratio of number of PP-cells to total number islet cells (**B**).

antagonist for modulation the regenerative capacity of the remaining pancreas after pancreatectomy. Therefore, our study is an original study.

Ghrelin, an endogenous ligand for GHS-Rs, regulates pituitary GH secretion.[17] It is mainly produced by the gastric fundus, and its expression is also detected in the pancreas; it has systemic and local effects on the gastrointestinal tract.[18] Its regulatory role on human pancreatic islet cells was described by Wierup et al.[18] in 2002. Various studies that evaluated the effects of ghrelin on the pancreas were subsequently performed.[19,20,29] One investigator examined fetal pancreas specimens and identified that ghrelin was produced by islet endocrine cells known as (epsilon) ε-cells, and these cells constituted the largest portion of the pancreas: the same study speculates that ghrelin may play a role.[19,20] However, various investigators have reported that ghrelin has either inhibitory or stimulatory effects on insulin secretion.[21,30–34] Here, we examined its effects on β islet masses in the remaining pancreas, as well as on plasma glucose and insulin levels in 90% pancreatectomized rats.

The weight of pancreatectomized rats significantly decreased when compared to the sham group. Exogenous ghrelin treatment attenuated weight loss, whereas ghrelin antagonist-receiving rats failed to gain weight. Like its GH-like effects, these effects of ghrelin may be attributed to its "appetite regulatory" effect.[18] Weight loss in rats receiving ghrelin antagonist was first described by Asakawa et al.[35] In our pancreatectomy study, the ghrelin antagonist-receiving rats clearly lost more weight than those in either the ghrelin or the sham group. It can be speculated that the reason for the weight gain in treatment group is that ghrelin is inducing GHS-Rs[17] and resulting GH release or directly acting on the pancreas in order to make it regulate insulin,[18] both of which result in synergic effects of these anabolic hormones.

After 90% pancreatectomy, the plasma glucose concentration was found to be significantly elevated when compared to sham rats. Plasma glucose levels of ghrelin-treated rats tended to decrease by the 11th postoperative day. On the 19th, 25th, and 30th days, plasma glucose levels were significantly lower in the ghrelin group when compared to the control and antagonist groups, but these levels were still higher than in the sham group. There was a correlation between these blood glucose levels and plasma insulin concentration, insulin-positive islet cell number, and β islet number. Cells in the islets of Langerhans undergo continuous turnover under physiological conditions.[1] β islet cell mass may increase or decrease in response to various circumstances. Increased insulin demand triggers a compensatory mechanism that results in cell proliferation and β cell hypertrophy. Better understanding of these mechanisms could allow the development of interventions that could increase the proliferation or hypertrophy rate.[1,23,25] Also, this effect may be due to the effect of ghrelin in the central system by GH secretion.[17] This hypothesis may be supported by previous studies that have shown the regeneration effect of GH over pancreas.

Ghrelin treatment increased the regeneration of exocrine and endocrine cells in the pancreas. The resulting increase in the number of PP cells and high proliferation rate of islet cells resulted in decreased plasma glucose concentration. In obese rats with type 2 diabetes, Desaki et al.[30] found that ghrelin antagonists enhanced insulin release but did not affect the number of islets or level of insulin mRNA in ghrelin knockout mice. Here, blockage of endogenous ghrelin was achieved by using GHSR antagonists. Dezaki et al.[30] induced glucose intolerance by feeding rats with a fatty diet, whereas we used a pancreatectomy model. Therefore, the different results may be the result of different

study models. Furthermore, when considering the intrauterine development of pancreatic β islet cells, it is possible that ghrelin could influence pancreatic stem cells in the remaining pancreas and promote the regeneration of endocrine and exocrine cells.

The finding of Granata et al.[31,32] that ghrelin promotes β-cell proliferation and potently inhibits apoptosis in pancreatic islet cells supports our results. Irako et al.[33] reported that administration of exogenous ghrelin prevents the development of diabetes in streptozotocin-treated newborn rats without beta cell destruction via enhanced regeneration of beta cells. Doi et al.[34] demonstrated a link between ghrelin, IA-2beta, and glucose-stimulated insulin secretion. Prado et al.[22] found that ghrelin cells play a significant role in the replacement of insulin-producing beta cells in two mouse models of pancreas development and that ghrelin has great importance in glucose synthesis. In the literature, there is much controversy regarding the interaction between ghrelin and β islet cells; this controversy may arise from the different experimental models used.

In the present study, administration of exogenous ghrelin to 90%-pancreatectomized rats attenuated diabetes symptoms by decreasing plasma glucose levels and increasing the number of islet cells. Thus, the results support our primary hypothesis. In conclusion, more studies are needed to determine a potential therapeutic use of ghrelin in type 3 diabetes.

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References

1. Terazono K, Uchiyama Y, Ide M, Watanabe T, Yonekura H, Yamamoto H, Okamoto H. Expression of reg protein in rat regenerating islets and its co-localization with insulin in the beta cell secretory granules. Diabetologia 1990;33:250–252. doi:10.1007/BF00404804.
2. Brockenbrough JS, Weir GC, Bonner-Weir S. Discordance of exocrine and endocrine growth after 90% pancreatectomy in rats. Diabetes 1988;37:232–236. doi:10.2337/diabetes.37.2.232.
3. Rafaeloff R, Pittenger GL, Barlow SW, Qin XF, Yan B, Rosenberg L, Duguid WP, Vinik AI. Cloning and sequencing of the pancreatic islet neogenesis-associated protein (INGAP) gene and its expression in islet neogenesis in hamsters. J Clin Invest 1997;99:2100–2109. doi:10.1172/JCI119383.
4. Gu D, Sarvetnick N. Epithelial cell proliferation and islet neogenesis in IFN-g transgenic mice. Development 1993;118:33–46.
5. Dor Y, Brown J, Martinez OI, Melton DA. Adult pancreatic β cells are formed by self-duplication rather than stem-cell differentiation. Nature 2004;429:41–46. doi:10.1038/nature02520.
6. List JF, Habener JF. Glucagon-like peptide 1 agonists and the development and growth of pancreatic beta cells. Am J Physiol Endocrinol Metab 2004;286:E875–E881. doi:10.1152/ajpendo.00007.2004.
7. Xu G, Stoffers DA, Habener JF, Bonner-Weir S. Exendin-4 stimulates both b-cell replication and neogenesis, resulting in increased β-cell mass and improved glucose tolerance in diabetic rats. Diabetes 1999;48:2270–2276. doi:10.2337/diabetes.48.12.2270.
8. Pospislik JA, Martin J, Doty T, Ehses JA, Pamir N, Lynn FC, Piteau S, Demuth HU, McIntosh CH, Pederson RA. Dipeptidyl peptidase IV inhibitor treatment stimulates β-cell survival and islet neogenesis in streptozotocin-induced diabetic rats. Diabetes 2003;52:741–750. doi:10.2337/diabetes.52.3.741.
9. Massague J, Chen YG. Controlling TGF-beta signaling. Genes Dev 2000;14:627–644.
10. Hebrok M, Kim SK, Melton DA. Notochord repression of endodermal sonic hedgehog permits pancreatic development. Genes Dev 1998;12:1705–1713. doi:10.1101/gad.12.11.1705.
11. Furukawa M, Eto Y, Kojima I. Expression of immunoreactive activin A in fetal rat pancreas. Endocrinol Jpn 1995;42:63–68.
12. Sanvito F, Herrera PL, Huarte J, Nichols A, Montesano R, Orci L, Vassalli JD. TGF-b1 influences the relative development of the exocrine and endocrine pancreas in vitro. Development 1994;120:3451–3462.
13. Miralles F, Czernichow P, Scharfmann R. Follistatin regulates the relative proportions of endocrine versus exocrine tissue during pancreatic development. Development 1998;125:1017–1024.
14. Mashima H, Ohnishi H, Wakabayashi K, Mine T, Miyagawa J, Hanafusa T, Seno M, Yamada H, Kojima I. Betacellulin and activin A coordinately convert amylase-secreting pancreatic AR42J cells into insulin-secreting cells. J Clin Invest 1996;97:1647–1654. doi:10.1172/JCI118591.
15. Zhang YQ, Zhang H, Maeshima A, Kurihara H, Miyagawa J, Takeuchi T, Kojima I. Up-regulation of the expression of activins in the pancreatic duct by reduction of the β-cell mass. Endocrinology 2002;143:3540–3547. doi:10.1210/en.2002-220089.
16. Shing Y, Christofori G, Hanahan D, Ono Y, Sasada R, Igarashi K, Folkman J. Betacellulin: a mitogen from pancreatic β-cell tumors. Science 1993;259:1604–1607. doi:10.1126/science.8456283.
17. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K, et al. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature 1999;402:656–660. doi:10.1038/45230.
18. Wierup N, Svensson H, Mulder H, Sundler F. The ghrelin cell: a novel developmentally regulated islet cell in the human pancreas. Regul Pept 2002;107:63–69. doi:10.1016/S0167-0115(02)00067-8.
19. Wierup N, Yang S, McEvilly RJ, Mulder H, Sundler F. Ghrelin is expressed in a novel endocrine cell type in devoloping rat islets and inhibits insulin secretion from INS-1 (832/13). J Histochem Cytochem 2004;52:301–310.
20. Wierup N, Sundller F. Cirulating levels of ghrelin in human fetus. Eur J Endocrinol 2004;150:405. doi:10.1530/eje.0.1500405.
21. Dezaki K, Hosoda H. Endogenous ghrelin in pancreatic istets resricts insulin release by attenuating Ca 2+ signaling in β-cells. Diabetes 2004;53:3142–3151. doi:10.2337/diabetes.53.12.3142.
22. Prado CL, Pugh-Bernard AE, Elghazi L, Sosa-Pineda B, Sussel L. Ghrelin cells replace insulin-producing **beta** cells in two mouse models of pancreas development. Proc Natl Acad Sci U S A 2004;101:2924–2929. doi:10.1073/pnas.0308604100.
23. Bonnes-Weir S, Trent DF, Weir GC. Partial pancreatectomy in the rat and subsequent defect in glucose-induced insulin release. J Clin Invest 1983;71:1544–1553. doi:10.1172/JCI110910.
24. Li L, Seno M, Yamada H, Kojima I. Betacellulin improves glucose metabolism by promoting conversion of intraislet precursor cells to β cells in streptozotocin-treated mice. Am J Physiol Endocrinol Metab 2003;285:E577–E583.
25. Rovertson RP. Islet transplantation as a treatment for diabetes—a work in progress. N Engl J Med 2000;350:694–705. doi:10.1056/NEJMra032425.

26. Shapiro AMJ, Lakey JRT, Ryan EA, Korbutt GS, Toth E, Warnock GL, Kneteman NM, Rajotte RV. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med 2000;27:230–238. doi:10.1056/NEJM200007273430401.
27. Ryan EA, Lakay JRT, Paty BW, Imes S, Korbutt GS, Kneteman NM, Bigam D, Rajotte RV, Shapiro AMJ. Successful islet transplantation: continued insulin reserve provides long-term glycemic control. Diabetes 2002;51:2148–2157. doi:10.2337/diabetes.51.7.2148.
28. Brockenbrough JS, Weir GC, Bonner-Weir S. Discordance of exocrine and endocrine growth after 90% pancreatectomy in rats. Diabetes 1988;37:232–236. doi:10.2337/diabetes.37.2.232.
29. Wierup N, Sundler F. Ultrastructure of islet cells in human fetus. Cell Tissue Res 2005;319:423–428. doi:10.1007/s00441-004-1044-x.
30. Dezaki K, Sone H, Koizumi M, Nakata M, Kakei M, Nagai H, Hosoda H, Kangawa K, Yada T. Blockade of pancreatic islet-derived ghrelin enhances insulin secretion to prevent high-fat diet-induced glucose intolerance. Diabetes 2006;55:3486–3493. doi:10.2337/db06-0878.
31. Granata R, Settanni F, Trovato L, Destefanis S, Gallo D, Martinetti M, Ghigo E, Muccioli G. Unacylated as well as acylated ghrelin promotes cell survival and inhibit apoptosis in HIT-T15 pancreatic beta-cells. J Endocrinol Invest 2006;29:RC19–RC22.
32. Granata R, Settanni F, Biancone L, Trovato L, Nano R, Bertuzzi F, Destefanis S, Annunziata M, Martinetti M, Catapano F, Ghè C, Isgaard J, Papotti M, Ghigo E, Muccioli G. Acylated and unacylated ghrelin promote proliferation and inhibit apoptosis of pancreatic beta-cells and human islets: involvement of 3′,5′-cyclic adenosine monophosphate/protein kinase A, extracellular signal-regulated kinase 1/2, and phosphatidyl inositol 3-Kinase/Akt signaling. Endocrinology 2007;148:512–529. doi:10.1210/en.2006-0266.
33. Irako T, Akamizu T, Hosoda H, Iwakura H, Ariyasu H, Tojo K, Tajima N, Kangawa K. Ghrelin prevents development of diabetes at adult age in streptozotocin-treated newborn rats. Diabetologia 2006;49:1264–1273. doi:10.1007/s00125-006-0226-3.
34. Doi A, Shono T, Nishi M, Furuta H, Sasaki H, Nanjo K. IA-2beta, but not IA-2, is induced by ghrelin and inhibits glucose-stimulated insulin secretion. Proc Natl Acad Sci U S A 2006;103:885–890. doi:10.1073/pnas.0502470102.
35. Asakawa A, Inui A, Kaga T. Antagonism of ghrelin receptor reduces food intake and body weight gain in mice. Gut 2003;52:547–552. doi:10.1136/gut.52.7.947.

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ORIGINAL ARTICLE

Vascular Resection in Pancreatic Cancer Surgery: Survival Determinants

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Abstract
Introduction Pancreaticoduodenectomy (PD) is the standard operation for cancer of the pancreatic head. To achieve complete tumor resection and, thus, improve long-term survival, venous resection of the portal or superior mesenteric vein with reconstruction has become routine for advanced pancreatic adenocarcinoma (PDAC). However, its clinical benefit still remains controversial. The aim of this study was to investigate morbidity, mortality, and survival of patients with advanced PDAC following PD with venous resection and to identify significant survival determinants.
Material and Methods From October 2001 to December 2007, 488 patients with PDAC of the pancreatic head underwent PD at our department. Venous resection was performed in 110 patients (22.5%). Clinical data, surgical techniques, perioperative parameters, and histopathologic data were analyzed on a prospective database.
Results Major venous reconstruction was accomplished through primary lateral venorrhaphy in 18 patients (16.3%), polytetrafluoroethylene grafting (n=14, 12.7%), primary end-to-end anastomosis (n=72, 65.5%), an autologous saphenous venous graft patch (n=4, 4.6%) or a Goretex® patch (n=2, 2.3%). In 78.1% histopathologic examination revealed cancer invasion of the vein, whereas the remainder had peritumoral inflammation extending to the vessel wall. Perioperative morbidity rate was 41.8%; and the mortality rate 3.6%. The 1-, 2-, and 3-year survival rates were 55.2%, 23.1%, and 14.4%, respectively. Operating time (>420 min) and advanced age (>70 years) were the only prognostic variables, which significantly diminished survival on multivariate analysis.
Conclusion Resection of the superior mesenteric or portal vein to achieve macroscopic tumor clearance can be performed safely with acceptable operative morbidity and mortality. However, improved local clearance in these patients cannot achieve a favorable long-term survival for all patients because distant metastases or local recurrence is frequent.

Keywords Pancreatic cancer · Vascular infiltration · Venous resection · Pancreaticoduodenectomy

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Introduction

PDAC is a highly malignant carcinoma, making it one of the five leading causes of cancer-related death.[1] Unfortunately, owing to late presentation of symptoms, only 10% to 20% of patients are candidates for surgical resection, which remains the only chance for cure.[2] Factors contributing to the low resectability rate at presentation include liver metastases, extensive lymph node involvement, and invasion of retroperitoneal tissue; the superior mesenteric artery (SMA), the celiac axis, or the superior mesenteric-portal vein (PV) region. Tumor invasion of the SMA or celiac axis is considered a general contraindication to resection because of previously documented high mortality rate and poor prognosis.[3] Distant metastases are present in

50% and locally advanced cancer in about 45%.[4] Therefore, preoperative evaluation of operability in locally advanced tumors is still a challenge regarding best prognosis and quality of life in patients with PDAC. Radical surgical resection is considered to be the only curative option in the treatment of PDAC. Over the past decade, low operative mortality (<5%) after PD has been reported from experienced centers.[5–8] Infiltration of major veins without obliteration of the PV in a locally resectable tumor is no longer considered a contraindication if the surgeon considers that venous resection and reconstruction could be performed as a margin negative (R0) resection.[9–11] Currently, venous resection has been reported in up to 20% of PD at high-volume pancreatic surgery centers.[12–14] Several series have compared PD with and without venous resection documenting feasibility and equal rates in morbidity, operative mortality, and survival.[15–17] Several studies have analyzed different determinants of long-term survival following PD in PDAC patients. Factors found to be potentially associated with survival outcomes have included demographic, perioperative, and histopathologic factors; however, they remain controversial. To evaluate the clinical implications and role of PV resection, the present study investigated demographics, operative factors, morbidity, mortality, and overall survival of a consecutive single center series of 110 patients with PDAC of the pancreatic head who underwent PD with venous resection. In subgroup analyses, independent survival determinants were examined.

Patients and Methods

Between October 2001 and December 2007, 488 consecutive patients with PDAC of the pancreas head underwent surgical resection at our institution. Venous resection for suspected tumor infiltration of the PV, confluence, superior mesenteric vein, or a combination was performed in 110 of these 488 patients (22.5%). There were 50 men and 60 women with a mean age of 62.9 years (range 37–81 years). Data on all patients were recorded prospectively in our pancreatic tumor database. Patients with ampullary adenocarcinomas, distal bile-duct carcinomas, and other malignancies were excluded from the study.

Preoperative evaluation included the performance of a physical examination, blood tests, and tumor markers (carcinoembryonic antigen (CEA), CA 19-9), chest radiography, contrast-enhanced computed tomography or magnetic resonance imaging, and American Society of Anesthesiologists (ASA) score. Sixteen patients with advanced local invasion underwent resection following neoadjuvant chemoradiotherapy (n=13) or chemotherapy (n=3). Of the remaining 94 patients, 83 had standard adjuvant treatment according to the European Study Group for Pancreatic Cancer (ESPAC)-3 or ESPAC-1 protocol or were enrolled in the CapRI-Trial that compared combined chemoradiotherapy plus interferon alpha (arm A) with fluorouracil (5-FU) bolus infusion (arm B) in patients with resected PDAC.[18–20] The demographic and clinical variables, including age, sex, preoperative jaundice, tumor markers, operative procedure, histopathology report, TNM-stage, morbidity, mortality, and hospital course were collected. All patients were regularly followed in the outpatient clinic, or the patient's primary physician was personally contacted until March 2008 or the patients' death. The median follow-up of the patients was 8.0 months (range 0.8–45.4 months).

Surgical Technique

After appropriate preoperative selection and preparation of the patients, general criteria for performing a PD were absence of hepatic metastases, macroscopic peritoneal seeding, bulky lymph node involvement, or cancer invasion to the superior mesenteric or hepatic artery. The resection of choice was a standard pylorus-preserving PD as described previously[21,22] and was performed in majority of patients (n=86, 78.2%) by a team of surgeons with significant hepatopancreatobiliary experience. Standard Kausch–Whipple operation was performed in 23 (20.9%) patients. In one patient, a pylorus-preserving total pancreatectomy was required. If separation of the tumor from SMV or PV was not possible; venous resection and reconstruction was performed to accomplish a complete resection with tumor-free margins. In this series, limited venous in growth was treated with a tangential wedge resection with reconstruction completed by primary lateral venorrhaphy or an autologous vein or polytetrafluoroethylene (PTFE) patch; in presence of more extensive venous ingrowth, a segmental resection was performed. After segmental resection and mobilization of the mesenteric root, reconstruction was performed with a primary end-to-end anastomosis or PTFE graft (10 mm ring-stabilized) in cases with long distance defects. Cross-clamp time of SMV and PV was kept to a minimum to avoid edema of the bowel. We usually performed a running suture of the posterior venous wall using 5-0 prolene with interrupted sutures of the anterior wall to avoid narrowing of the anastomosis. The standard lymphadenectomy in patients with resectable PDAC included complete dissection of the hepatoduodenal ligament, the retropancreatic tissue, and the right side of the superior mesenteric artery. Intraoperative parameters (operating time, blood loss) were obtained from anesthesiology operative records. Histological findings of the tumor were obtained from each patient's pathology report. The lymph node ratio (LNR) was determined by dividing the total

number of positive lymph nodes by the total number of examined nodes. Based on their LNR, patients were divided into four groups (LNR=0, LNR=0–0.2; LNR=0.2–0.4; and LNR>0.4).

Morbidity and Mortality

Major postoperative complications were defined as delayed gastric emptying, pancreatic fistula, intraabdominal abscess, hemorrhage, reoperation, and pneumonia. Pancreatic fistula, delayed gastric emptying, and intraabdominal hemorrhage were defined according to the International Study Group of Pancreatic Surgery.[23,24] Postoperative mortality was defined as death within 30 days of surgery.

Statistical Analysis

SAS software (Release 9.1, SAS Institute, Inc., Cary, NC, USA) was used for statistical analysis. Quantitative variables are expressed as median and range. Overall survival from the date of pancreas operation was calculated by the Kaplan–Meier estimate. Patients alive at the last follow-up were censored as were seven patients lost to follow-up after 1 (five patients), 2, and 3 months, respectively. Univariate correlation between clinicopathologic variables and overall survival were examined by the log rank test. Factors independently associated with overall survival were identified by proportional hazard regression analysis (Cox model). To analyze the impact of the quantitative variables on the overall survival, quartiles were used to divide patients into groups. Two-sided P values were always computed and a difference was considered statistically significant at $P \leq 0.05$.

Results

Details of Patients and Hospital Course

Demographic, clinical, and operative data, including age, sex, preoperative jaundice, carbohydrate antigen 19-9 (CA 19-9) level, CEA level, ASA score, and the different types of reconstruction after pancreatic head resection for the entire cohort of 110 patients are given in Table 1. The ASA score was 1–2 in 64 (58.2%), 3 in 43 (39.1%), and 4 in 2 (1.8%) patients. Tangential resection of either the PV or the SMV was performed in 24 patients. Among these, in 18 (16.3%) cases a simple primary lateral venorrhaphy was sufficient to restore portal blood flow, whereas four (4.6%) patients underwent a venous patch and two (2.3%) a Goretex® patch. A complete venous resection was performed in 86 patients. The venous axis was subsequently reconstructed by a primary end-to-end anastomosis (n=72, 65.5%) or by a Goretex® graft (n=14, 12.7%; Table 1). Intraoperative blood flow was assessed clinically at the completion of reconstruction, and Doppler-ultrasound was performed during the postoperative period to assess patency of the reconstructed veins.

Table 1 Patient Demographics, Preoperative, and Operative Data of 110 Patients with Venous Resection

Patient Demographics, Preoperative, and Operative Data		
Sex		
M	50	45.5%
F	60	54.5%
Age, median (range) yrs	62.9	37–81
Preoperative jaundice	58	52.7%
CEA, median (range), ng/ml	5.4	0.5–57
CA 19-9, median (range), U/ml	539.1	1–5312
ASA		
1	2	1.9%
2	63	57.2%
3	43	39%
4	2	1.9%
Operation		
Standard PD	23	20.9%
Pylorus-preserving pancreatectomy	1	0.9%
Pylorus-preserving PD	86	78.2%
Portal vein reconstruction technique		
End-to-end anastomosis	72	65.5%
Lateral venorrhaphy	18	16.3%
Prosthesis	14	12.8%
Saphenous vein patch	4	3.6%
Goretex® patch	2	1.8%

The median operating time was 421 min (range 257–720 min), and the median blood loss was 1,182 mL (range 100–4,500 mL). There was a 40% morbidity (n=44) and a 3.6% (n=4) postoperative mortality rate. Surgical complications occurred in ten patients (9%) and are listed in Table 2. The most common postoperative complication was delayed gastric emptying (n=15). Other complications included three intraabdominal hemorrhages Grade B and four pancreatic fistulas (two Grade A and two Grade C).[23,24] Two of the patients with pancreatic fistulas had additional pathologic findings of the colon (one patient with ischemia and one patient with perforation). Lymph fistula (n=1), pancreatic necrosis (n=1), and PV thrombosis with consecutive liver abscess (n=1) was detected in the other patients. Reoperation was necessary in ten patients (9%) after 7 days (range 1–22). The mean hospital stay for all patients was 17.9 (range: 4–64).

Histopathology

The histopathological data are summarized in Table 3. Tumor size (maximal transverse diameter) was recorded at the time of pathologic evaluation of the PD specimen.

Table 2 Surgical Morbidity and Mortality in 110 Patients Undergoing PD with Venous Resection

Morbidity	*n*	%
Hemorrhage from surgical site	3	2.8
Gastric emptying delay	15	13.6
Pancreatic fistula	4	3.6
Apoplex	2	1.8
Pneumonia	6	5.6
Wound infection	6	5.6
Intraabdominal abscess	2	1.8
Liver abscess	1	0.9
Cholangitis	5	4.6
Reoperation	10	9.0
Surgical mortality	4	3.6
Median (range) hospital stay (days)	17.9	4–64

Median tumor size was 3.3 cm (range 1.0–6.0 cm). Despite aggressive surgical resection, the surgical margin was positive (R1, microscopically positive) in 54 patients (49%); curative (R0, negative resection margins) resection was obtained in 54 patients (49%). Peripancreatic lymph nodes in the surgical specimen were positive in 90 patients (81.8%). The median number of lymph nodes evaluated following pancreatic resection was 25 (range 5–63). In those patients with lymph node metastasis (N1, n=90) the mean number of positive lymph nodes was 5 (range 1–19). Most N1 patients had a LNR less than 0.2 (n=54, 49%); however, some had a LNR of >0.2 to 0.4 (n=25, 22.7%) or >0.4 (n=11, 10%; Fig. 1). The majority of the tumors were moderately differentiated (grade II, n=69, 62.7%). Despite suspected venous invasion macroscopically in all patients, histological examination showed tumor cell infiltration of the resected venous wall in 86 patients (78.1%) of the 110 patients.

Table 3 Pathological Data of 110 Patients Undergoing PD with Venous Resection for PDAC

Data of 110 patients undergoing PD with venous resection for PDAC		
Tumor size (range) cm	3.33	1.0–6.0
T-stage		
1	0	0%
2	1	0.9%
3	104	94.6%
4	5	4.5%
Histopathologic type		
Well differentiated	4	3.7%
Moderately differentiated	70	63.5%
Poorly differentiated	36	32.8%
Curability		
Curative (R0)	54	49.1%
Non-curative (R1/R2)	54	49.1%
Rx	2	1.8%
Vascular invasion	86	78.1%
Vessel not infiltrated	24	21.9%

Survival

The median survival for PD with venous resection was 14.5 months (range 7.3–24 months). The 1-, 2-, and 3-year survival rates were 55.2%, 23.1%, and 14.4%, respectively (Fig. 2). There was no significant difference in survival after resection for PDAC between patients with tumor-positive (R1) or tumor-free (R0) resection margins (P=0.26). No significant difference in survival was seen between patients who had venous resection with histologically confirmed tumor infiltration and patients who had venous resection with suspected tumor infiltration (P=0.65). Tumor size, blood loss, lymph node status, and lymph node ratio also had no prognostic impact on survival in our study population. Furthermore, there was no significant difference in survival between the patients with neoadjuvant treatment and the patients without neoadjuvant treatment (P=0.51; Fig. 3). Marginally, significant factors were operating time longer than 420 min (p=0.08), patients older than 70 years (p=0.07), and occurrence of postoperative complications (p=0.08) (Fig. 4). The overall survival did not differ for patients undergoing different reconstruction techniques (lateral venorrhaphy versus end-to-end versus graft interposition; p=0.72, Fig. 5). Also, preoperative Ca 19-9 and CEA levels and ASA score had no statistical significance in multivariate analysis. Only age (hazard ratio (HR) 1.811, P=0.037), operating time (HR 1.743, P=0.037), and lack of major postoperative complications (HR 1.580, P=0.07) were identified as factors that were independently associated with poorer survival by multivariate analysis using a Cox proportional hazards model (Table 4).

Discussion

PDAC is one of the most aggressive human tumors and is the second most common malignancy of the gastrointestinal tract.[1] Radical resection is often precluded by the close anatomical relationship between the tumor in the pancreatic head with the portal and superior mesenteric veins and the hepatic and mesenteric arteries. Tumor adherence to the PV/SMV is common in PDAC of the pancreatic head as reflected by the rate of vein resection during PD, which rises to 20–30% in our and some previous series.[4,12,17] A more recent study found PV resection performed in 23% of the reported patients, with true PV invasion occurring in 77%.[14]

Several series have compared PD with and without venous resection, documenting similarities in morbidity,

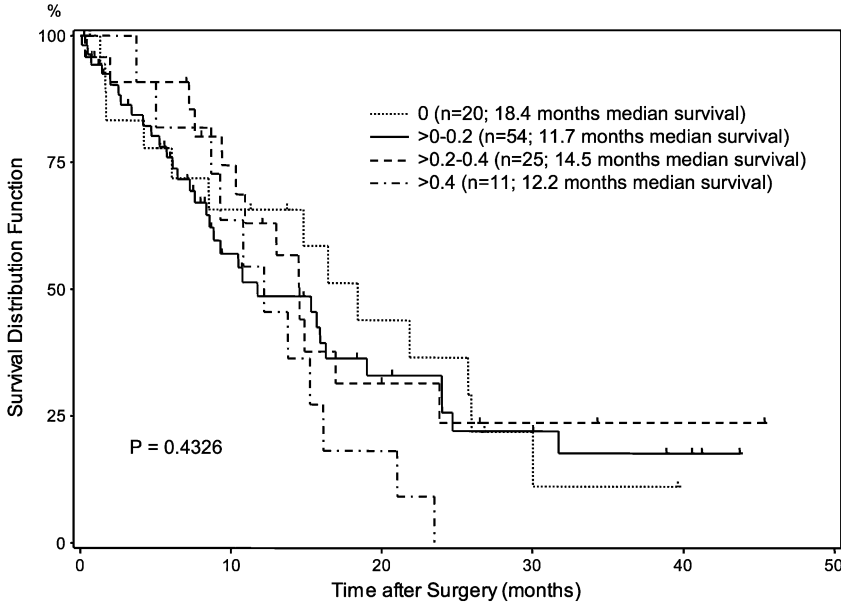

Figure 1 Overall survival and lymph node ratio.

operative mortality, and survival.[14,15,25] Overall morbidity, however, is not insignificant, ranging from 30% to 50%, and survival is often unsatisfactory with median survival rates of 11–20 months.[26,27]

Given the low operative mortality of less than 5% in experienced centers, the belief in vascular resection is still controversial which is reflected by considerable differences in venous resection rates varying from 3% to 41%.[12,15,22,28] There remains the oncological justification for PV resection. The European Study Group for Pancreatic Cancer described that there was no survival difference related to invasion of adjacent structures.[29] It is widely accepted that PV resection increases the resectability rate in cancers of the pancreatic head. Nakao et al. increased their resectability rate to 63%[30] and Takahashi et al. from 48% to 57%.[10] Over the last decade, efforts have been directed towards the development of adjuvant and neo-adjuvant therapies in an attempt to improve outcome. Adjuvant chemotherapy has proven advantageous in terms of prolonging overall survival,[20] whereas neoadjuvant treatment regimens and adjuvant chemoradiation are still considered controversial, with large randomized controlled trials required for further evaluation.[31] Previous reports have identified tumor-associated biologic characteristics which are important in

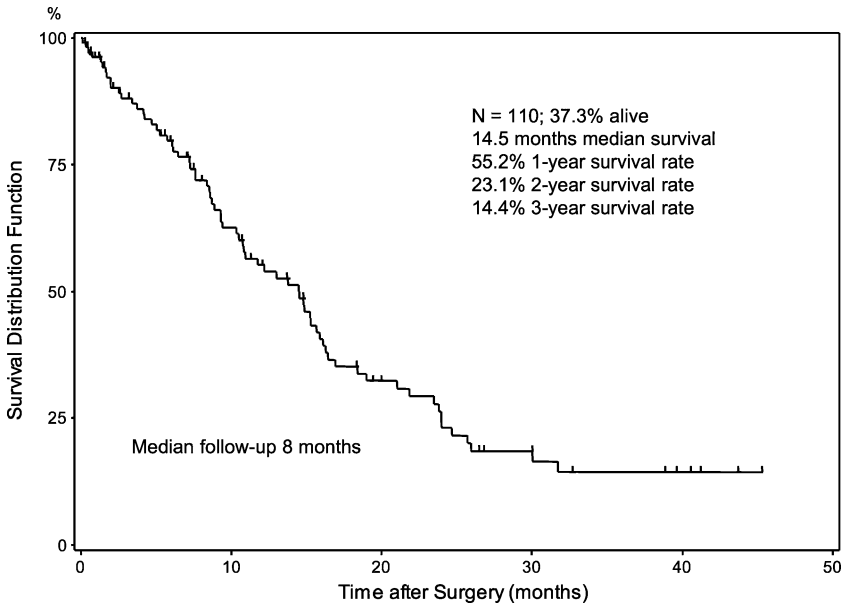

Figure 2 Overall survival after PD and venous resection in 110 patients. The 1-, 2-, and 3-year survival rates were 55.2%, 23.1%, and 14.4%, respectively.

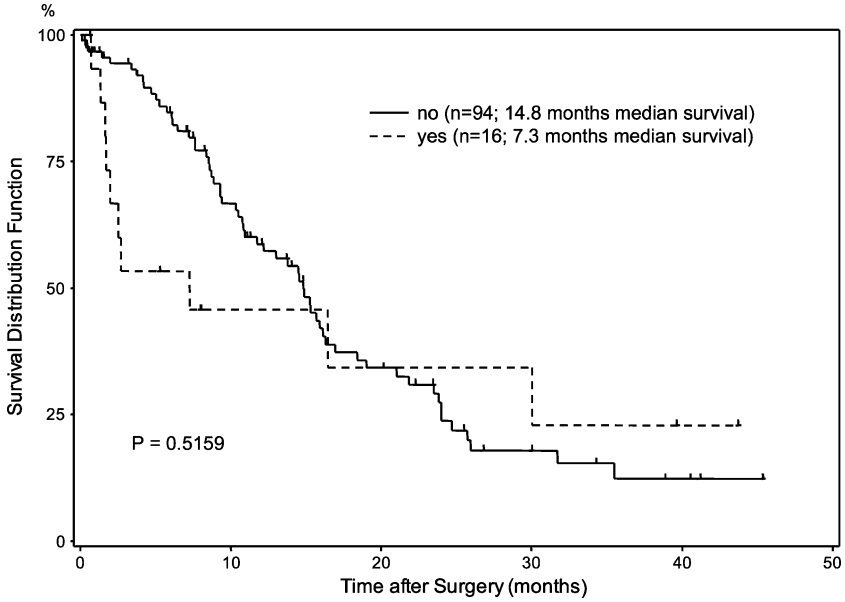

Figure 3 Overall survival after PD in patients who underwent neoadjuvant treatment (n=16) as compared with patients who did not undergo neoadjuvant treatment (n=94).

the prognosis of PDAC patients after resection. For example lymph node status, tumor size, and status of the resection have all been previously shown to be significant determinants of survival.[32–34] Recently, single center studies reported on LNR as a prognostic factor in PDAC.[35,36]

Before PDAC resection, Ca 19-9 can be considered the most important predictive factor of both recurrence and survival. Some studies have also identified a correlation between the expression of Ca 19-9 and the hepatic metastatic potential and a direct relationship between tumor burden and Ca 19-9 level in PDAC.[37] Schlieman et al. reported that a Ca 19-9 level of more than 150 kU/L may be associated with unresectability.[38]

Nakagohri et al. reported that negative microscopic invasion to the PV was associated with longer survival.[39] Tseng et al. demonstrated in a multivariate analysis that only positive lymph nodes and major perioperative complications were associated with a significant decrease in survival.[12] In the present study, the only two factors which had an independent influence on survival were operating time (<420 vs. >420 min) and age (>70 vs. <70 years). Mean operating time is comparable with data from other studies

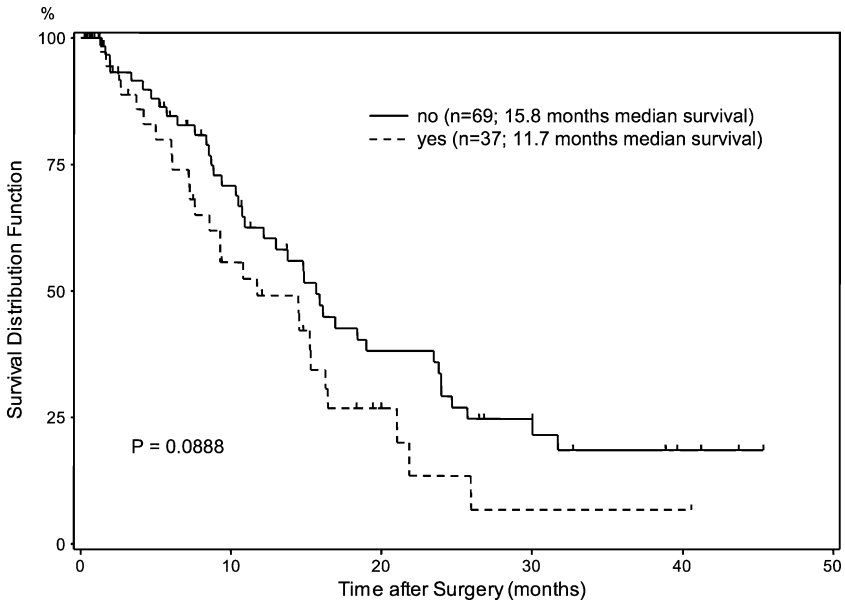

Figure 4 Overall survival and postoperative complications (30-days mortality excluded).

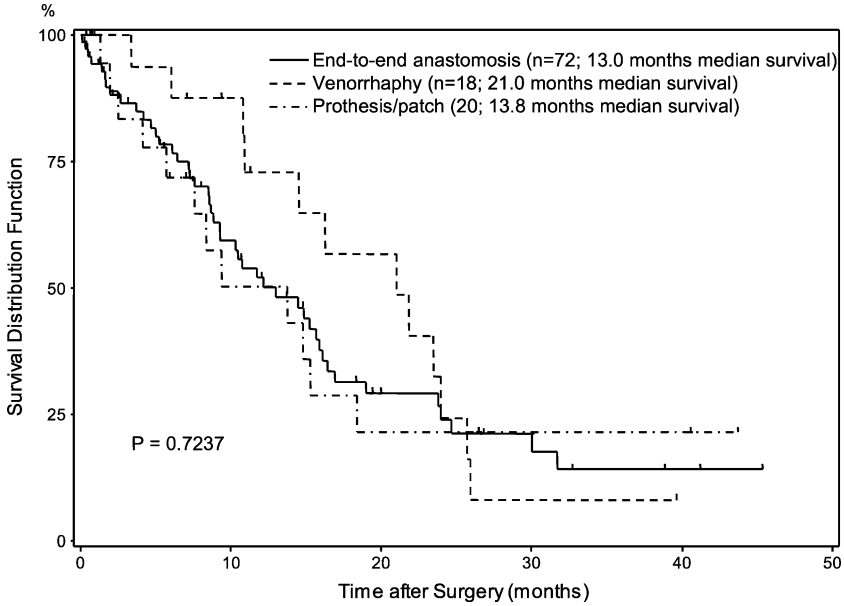

Figure 5 Overall survival and reconstruction technique of PV.

that reported operating times ranging from 500–660 min.[12,28] Multiple studies have demonstrated good outcomes in appropriate elderly candidates with little to no increase in morbidity and mortality.[40,41] The morbidity rate in our patients with venous resection is comparable to the results of most reported series.[42,43] In addition to pancreatic fistula and postoperative hemorrhage, delayed gastric emptying is one of the most common postoperative complications after pancreatic surgery occurring in 19–57% of patients.[24,39]

In our study, venous resections were mainly end-to-end anastomosis—implying removal of a full cross section vein. This and the lateral venorrhaphy technique can be performed in most cases with venous involvement and has been the preferred method by other groups.[15,44] Although lacking statistical significance, venous reconstruction with a primary lateral venorrhaphy had the longest median survival of 21 months compared to end-to-end anastomosis (13 months) and graft (14 months). This may imply a greater survival for lesser degrees of venous invasion rather than advanced venous involvement as indicated in several series of venous resection.[30,45]

The R1 rate in the present series seems remarkably high compared with the current literature.[14,34,46,47] Possible explanations for the high rate could be the lack of standardized pathology protocols for pancreatic cancer and the different definition and pathologic evaluation of the R1 status (0 vs. 1 mm from the resection margin). The recently published cohort with a R1 rate of 76%, that was examined according to a standardized protocol developed by the European Study Group for Pancreatic Cancer was partially included in the present study and might have influenced the overall resection status.[48] Thus, a high rate of R1 resections is a potential marker of high-quality pathology rather than low quality surgery.[49]

Table 4 Multivariate Analysis of Prognostic Parameters After Simultaneous Pancreatic and Venous Resection

Independent prognostic factor	Hazard ratio	95% Confidence interval	*P* value
Complication (yes vs. no)	1.580	0.953–2.621	0.0763
Age <70 vs. >70 years	1.811	1.037–3.164	0.0369
Operation time >420 vs. <420 min	1.743	1.035–2.936	0.0367

Conclusion

In summary, the results of the present study show that venous resection during PD for PDAC of the pancreatic head can be safely performed with acceptable perioperative morbidity and mortality. If segmental venous involvement is suspected macroscopically during resection, this segment should be resected, although in up to 20% of cases tumor infiltration may not be confirmed. PV resection is important for local macroscopic cancer control to achieve complete tumor clearance. However, PV resection on its own cannot achieve a favorable long-term survival in most patients requiring PV resection because distant metastases are common. With surgery alone, the success of PD with vascular resection requires careful selection of patients. Future studies are needed to identify a subgroup of patients who may have a real benefit from PD with vascular resection, while improvements in adjuvant therapies and, thus, systemic control may yet justify more radical surgical treatment of advanced local disease.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer statistics, 2008. CA Cancer J Clin 2008;58(2):71–96. doi:10.3322/CA.2007.0010.
2. Bold RJ, Charnsangavej C, Cleary KR, Jennings M, Madray A, Leach SD, Abbruzzese JL, Pisters PW, Lee JE, Evans DB. Major vascular resection as part of pancreaticoduodenectomy for cancer: radiologic, intraoperative, and pathologic analysis. J Gastrointest Surg 1999;3(3):233–243. doi:10.1016/S1091-255X(99)80065-1.
3. Weitz J, Koch M, Friess H, Büchler MW. Impact of volume and specialization for cancer surgery. Dig Surg 2004;21(4):253–261. Review, doi:10.1159/000080198.
4. Neoptolemos JP, Russell RC, Bramhall S, Theis B. Low mortality following resection for pancreatic and periampullary tumours in 1026 patients: UK survey of specialist pancreatic units. UK Pancreatic Cancer Group. Br J Surg 1997;84(10):1370–1376. doi:10.1002/bjs.1800841010.
5. Koniaris LG, Staveley-O'Carroll KF, Zeh HJ, Perez E, Jin XL, Maley WR, Zabari G, Bartlett DL, Khanna A, Franceschi D, Schoeniger LO. Pancreaticoduodenectomy in the presence of superior mesenteric venous obstruction. J Gastrointest Surg. 2005;9:915–921. doi:10.1016/j.gassur.2005.04.005.
6. Büchler MW, Wagner M, Schmied BM, Uhl W, Friess H, Z'graggen K. Changes in morbidity after pancreatic resection: toward the end of completion pancreatectomy. Arch Surg 2003;138(12):1310–1314. discussion 1315, doi:10.1001/archsurg.138.12.1310.
7. Howard TJ, Villanustre N, Moore SA, DeWitt J, LeBlanc J, Maglinte D, McHenry L. Efficacy of venous reconstruction in patients with adenocarcinoma of the pancreatic head. J Gastrointest Surg 2003;7(8):1089–1095. doi:10.1016/j.gassur.2003.07.010.
8. Launois B, Stasik C, Bardaxoglou E, Meunier B, Campion JP, Greco L, Sutherland F. Who benefits from portal vein resection during pancreaticoduodenectomy for pancreatic cancer? World J Surg 1999;23(9):926–929. doi:10.1007/s002689900601.
9. Shibata C, Kobari M, Tsuchiya T, Arai K, Anzai R, Takahashi M, Uzuki M, Sawai T, Yamazaki T. Pancreatectomy combined with superior mesenteric-portal vein resection for adenocarcinoma in pancreas. World J Surg 2001;25(8):1002–1005. doi:10.1007/s00268-001-0070-z.
10. Takahashi S, Ogata Y, Tsuzuki T. Combined resection of the pancreas and portal vein for pancreatic cancer. Br J Surg 1994;81(8):1190–1193. doi:10.1002/bjs.1800810837.
11. Harrison LE, Klimstra DS, Brennan MF. Isolated portal vein involvement in pancreatic adenocarcinoma. A contraindication for resection? Ann Surg 1996;224(3):342–347. discussion 347-349, doi:10.1097/00000658-199609000-00010.
12. Tseng JF, Raut CP, Lee JE, Pisters PW, Vauthey JN, Abdalla EK, Gomez HF, Sun CC, Crane CH, Wolff RA, Evans DB. Pancreaticoduodenectomy with vascular resection: margin status and survival duration. J Gastrointest Surg 2004;8(8):935–949. discussion 949-950, doi:10.1016/j.gassur.2004.09.046.
13. Al-Haddad M, Martin JK, Nguyen J, Pungpapong S, Raimondo M, Woodward T, Kim G, Noh K, Wallace MB. Vascular resection and reconstruction for pancreatic malignancy: a single center survival study. J Gastrointest Surg 2007;11(9):1168–1174. doi:10.1007/s11605-007-0216-x.
14. Yekebas EF, Bogoevski D, Cataldegirmen G, Kunze C, Marx A, Vashist YK, Schurr PG, Liebl L, Thieltges S, Gawad KA, Schneider C, Izbicki JR. En bloc vascular resection for locally advanced pancreatic malignancies infiltrating major blood vessels: perioperative outcome and long-term survival in 136 patients. Ann Surg 2008;247(2):300–309.
15. Van Geenen RC, ten Kate FJ, de Wit LT, van Gulik TM, Obertop H, Gouma DJ. Segmental resection and wedge excision of the portal or superior mesenteric vein during pancreatoduodenectomy. Surgery 2001;129(2):158–163. doi:10.1067/msy.2001.110221.
16. Poon RT, Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK, Yeung C, Wong J. Pancreaticoduodenectomy with en bloc portal vein resection for pancreatic carcinoma with suspected portal vein involvement. World J Surg 2004;28(6):602–608.
17. Fuhrman GM, Leach SD, Staley CA, Cusack JC, Charnsangavej C, Cleary KR, El-Naggar AK, Fenoglio CJ, Lee JE, Evans DB. Rationale for en bloc vein resection in the treatment of pancreatic adenocarcinoma adherent to the superior mesenteric-portal vein confluence. Pancreatic Tumor Study Group. Ann Surg 1996;223(2):154–162. doi:10.1097/00000658-199602000-00007.
18. Knaebel HP, Märten A, Schmidt J, Hoffmann K, Seiler C, Lindel K, Schmitz-Winnenthal H, Fritz S, Herrmann T, Goldschmidt H, Krempien R, Mansmann U, Debus J, Diehl V, Büchler MW. Phase III trial of postoperative cisplatin, interferon alpha-2b, and 5-FU combined with external radiation treatment versus 5-FU alone for patients with resected pancreatic adenocarcinoma–CapRI: study protocol [ISRCTN62866759]. BMC Cancer 2005;5(1):37. 12.
19. Neoptolemos JP, Dunn JA, Stocken DD, Almond J, Link K, Beger H, Bassi C, Falconi M, Pederzoli P, Dervenis C, Fernandez-Cruz L, Lacaine F, Pap A, Spooner D, Kerr DJ, Friess H, Büchler MW. European Study Group for Pancreatic Cancer. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. Lancet 2001;358(9293):1576–1585. 10.
20. Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, Beger H, Fernandez-Cruz L, Dervenis C, Lacaine F, Falconi M, Pederzoli P, Pap A, Spooner D, Kerr DJ, Büchler MW. European Study Group for Pancreatic Cancer. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 2004;350(12):1200–1210. Erratum in: N Engl J Med. 2004 Aug 12;351(7):726.
21. Gouma DJ, Nieveen van Dijkum EJ, Obertop H. The standard diagnostic work-up and surgical treatment of pancreatic head tumours. Eur J Surg Oncol 1999;25(2):113–23. Review, doi:10.1053/ejso.1998.0612.
22. Weitz J, Kienle P, Schmidt J, Friess H, Büchler MW. Portal vein resection for advanced pancreatic head cancer. J Am Coll Surg 2007;204(4):712–716. doi:10.1016/j.jamcollsurg.2007.01.004.
23. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W, Buchler M, International Study Group on Pancreatic Fistula Definition. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005;138(1):8–13. Review, doi:10.1016/j.surg.2005.05.001.
24. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Traverso LW, Yeo CJ, Büchler MW. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 2007;142(5):761–768.
25. Hartel M, Niedergethmann M, Farag-Soliman M, Sturm JW, Richter A, Trede M, Post S. Benefit of venous resection for ductal adenocarcinoma of the pancreatic head. Eur J Surg 2002;168(12):707–712. doi:10.1080/00000000000000007.
26. Richter A, Niedergethmann M, Sturm JW, Lorenz D, Post S, Trede M. Long-term results of partial pancreaticoduodenectomy for ductal adenocarcinoma of the pancreatic head: 25-year experience. World J Surg 2003;27(3):324–329. doi:10.1007/s00268-002-6659-z.
27. Sener SF, Fremgen A, Menck HR, Winchester DP. Pancreatic cancer: a report of treatment and survival trends for 100,313 patients diagnosed from 1985-1995, using the National Cancer Database. J Am Coll Surg 1999;189(1):1–7. doi:10.1016/S1072-7515(99)00075-7.

28. Bachellier P, Nakano H, Oussoultzoglou PD, Weber JC, Boudjema K, Wolf PD, Jaeck D. Is pancreaticoduodenectomy with mesentericoportal venous resection safe and worthwhile? Am J Surg 2001;182 (2):120–129. Review, doi:10.1016/S0002-9610(01)00686-9.
29. Neoptolemos JP, Stocken DD, Dunn JA, Almond J, Beger HG, Pederzoli P, Bassi C, Dervenis C, Fernandez-Cruz L, Lacaine F, Buckels J, Deakin M, Adab FA, Sutton R, Imrie C, Ihse I, Tihanyi T, Olah A, Pedrazzoli S, Spooner D, Kerr DJ, Friess H, Büchler MW. European Study Group for Pancreatic Cancer. Influence of resection margins on survival for patients with pancreatic cancer treated by adjuvant chemoradiation and/or chemotherapy in the ESPAC-1 randomized controlled trial. Ann Surg 2001;234 (6):758–768. doi:10.1097/00000658-200112000-00007.
30. Nakao A, Harada A, Nonami T, Kaneko T, Inoue S, Takagi H. Clinical significance of portal invasion by pancreatic head carcinoma. Surgery 1995;117(1):50–55. doi:10.1016/S0039-6060 (05)80229-6.
31. Kleeff J, Michalski CW, Friess H, Büchler MW. Surgical treatment of pancreatic cancer: the role of adjuvant and multimodal therapies. Eur J Surg Oncol 2007;33(7):817–823. Review, doi:10.1016/j.ejso.2007.01.022.
32. Pedrazzoli S, DiCarlo V, Dionigi R, Mosca F, Pederzoli P, Pasquali C, Klöppel G, Dhaene K, Michelassi F. 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.
33. Yeo CJ, Cameron JL, Lillemoe KD, Sohn TA, Campbell KA, Sauter PK, Coleman J, Abrams RA, Hruban RH. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity, and mortality. Ann Surg. 2002;236(3):355–366. discussion 366-368, doi:10.1097/00000658-200209000-00012.
34. Wagner M, Redaelli C, Lietz M, Seiler CA, Friess H, Büchler MW. Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma. Br J Surg 2004;91:586–594. doi:10.1002/bjs.4484.
35. Pawlik TM, Gleisner AL, Cameron JL, Winter JM, Assumpcao L, Lillemoe KD, Wolfgang C, Hruban RH, Schulick RD, Yeo CJ, Choti MA. Prognostic relevance of lymph node ratio following pancreaticoduodenectomy for pancreatic cancer. Surgery 2007;141(5):610–618. doi:10.1016/j.surg.2006.12.013.
36. Slidell MB, Chang DC, Cameron JL, Wolfgang C, Herman JM, Schulick RD, Choti MA, Pawlik TM. Impact of total lymph node count and lymph node ratio on staging and survival after pancreatectomy for pancreatic adenocarcinoma: a large, population-based analysis. Ann Surg Oncol 2008;15(1):165–174. doi:10.1245/s10434-007-9587-1.
37. Tian F, Appert HE, Myles J, Howard JM. Prognostic value of serum CA 19-9 levels in pancreatic adenocarcinoma. Ann Surg 1992;215(4):350–355. doi:10.1097/00000658-199204000-00008.
38. Schlieman MG, Ho HS, Bold RJ. Utility of tumor markers in determining resectability of pancreatic cancer. Arch Surg 2003;138(9):951–955. discussion 955–956, doi:10.1001/archsurg.138.9.951.
39. Nakagohri T, Kinoshita T, Konishi M, Inoue K, Takahashi S. Survival benefits of portal vein resection for pancreatic cancer. Am J Surg 2003;186(2):149–153. doi:10.1016/S0002-9610(03) 00173-9.
40. Fong Y, Blumgart LH, Fortner JG, Brennan MF. Pancreatic or liver resection for malignancy is safe and effective for the elderly. Ann Surg 1995;222(4):426–434. discussion 434–437.
41. Richter A, Niedergethmann M, Lorenz D, Sturm JW, Trede M, Post S. Resection for cancers of the pancreatic head in patients aged 70 years or over. Eur J Surg 2002;168(6):339–344. doi:10.1080/11024150260284842.
42. Kawada M, Kondo S, Okushiba S, Morikawa T, Katoh H. Reevaluation of the indications for radical pancreatectomy to treat pancreatic carcinoma: is portal vein infiltration a contraindication? Surg Today 2002;32(7):598–601. doi:10.1007/s005950200108.
43. Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA, Hruban RH, Ord SE, Sauter PK, Coleman J, Zahurak ML, Grochow LB, Abrams RA. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. Ann Surg. 1997;226(3):248–257. discussion 257–260, doi:10.1097/00000658-199709000-00004.
44. Clavien PA, Rüdiger HA. A simple technique of portal vein resection and reconstruction during pancreaticoduodenectomy. J Am Coll Surg 1999;189(6):629–634. doi:10.1016/S1072-7515 (99)00214-8.
45. Park DI, Lee JK, Kim JE, Hyun JG, Shim SG, Lee KT, Palk SW, Rhee JC, Choi KW, Lim JH, Kim YI. The analysis of resectability and survival in pancreatic cancer patients with vascular invasion. J Clin Gastroenterol 2001;32(3):231–234. doi:10.1097/00004836-200103000-00011.
46. Howard TJ, Krug JE, Yu J, Zyromski NJ, Schmidt CM, Jacobson LE, Madura JA, Wiebke EA, Lillemoe KD. A margin-negative R0 resection accomplished with minimal postoperative complications is the surgeon's contribution to long-term survival in pancreatic cancer. J Gastrointest Surg 2006;10(10):1338–1345. discussion 1345–1346, doi:10.1016/j.gassur.2006.09.008.
47. Winter JM, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J, Hodgin MB, Sauter PK, Hruban RH, Riall TS, Schulick RD, Choti MA, Lillemoe KD, Yeo CJ. 1423 pancreaticoduodenectomies for pancreatic cancer: a single-institution experience. J Gastrointest Surg 2006;10(9):1199–1210. discussion 1210–1211, doi:10.1016/j.gassur.2006.08.018.
48. Esposito I, Kleeff J, Bergmann F, Reiser C, Herpel E, Friess H, Schirmacher P, Büchler MW. Most pancreatic cancer resections are R1 resections. Ann Surg Oncol 2008;15(6):1651–1660. doi:10.1245/s10434-008-9839-8.
49. Verbeke CS, Leitch D, Menon KV, McMahon MJ, Guillou PJ, Anthoney A. Redefining the R1 resection in pancreatic cancer. Br J Surg 2006;93(10):1232–1237. doi:10.1002/bjs.5397.

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ORIGINAL ARTICLE

Resolution of Systemic Hypertension after Laparoscopic Gastric Bypass

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Abstract
Background Hypertension is a well-recognized and treatable risk factor for coronary heart disease and is one of the most common comorbidities associated with obesity. The aim of this study was to characterize the clinical outcome of a cohort of patients with documented hypertension who underwent laparoscopic gastric bypass.
Methods Ninety-five obese patients with documented hypertension and being treated with antihypertensive medication(s) underwent laparoscopic gastric bypass. Main outcome measures included length of hypertensive condition, changes in systolic and diastolic blood pressures, and changes in antihypertensive medication(s) at follow-up.
Results There were 69 (72%) females with a mean preoperative body mass index of 47 kg/m^2. The mean duration of hypertension was 73±70 months. The mean excess body weight loss at 12 months was 66%. The mean systolic blood pressure significantly decreased from 140±17 mmHg preoperatively to 120±18 mmHg at 12 months ($p<0.01$). The mean diastolic blood pressure also significantly decreased from 80±11 mmHg preoperatively to 71±8 mmHg at 12 months ($p<0.01$). At 12 months follow-up, 44 (46%) patients had complete resolution of hypertension while 18 (19%) patients had improvement. Patients with complete resolution had a shorter duration of disease as compared to patients without resolution (53 vs. 95 months, respectively, $p=0.01$).
Conclusion Weight loss associated with laparoscopic gastric bypass substantially improves and/or resolves hypertension in the majority of patients. Improvement of hypertension occurs as early as 1 month postoperatively and is more frequently in patients with a shorter preoperative duration of disease.

Keywords Bariatric surgery · Morbid obesity · Systemic hypertension · Gastric bypass

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Background

The prevalence of obesity in the USA is on the rise. It is estimated that one-third of the adult population in the USA is obese.[1,2] Obesity has been associated with a number of comorbid conditions such as hypertension, hyperlipidemia, obstructive sleep apnea, type 2 diabetes, arthritis, and coronary artery disease.[3,4] Of these conditions, hypertension is the most common comorbidity associated with obesity. The risk of developing hypertension has been found to increase with increasing weight class.[5] Hypertension alone is a cardiovascular risk factor but when combined with obesity, there is a substantially higher cardiovascular risk.[6] A number of studies have shown that weight reduction is associated with significant improvement or remission of many of the obesity-related comorbid conditions and can lead to a decrease in the predicted cardiovascular risk.[7–13] Surgery is currently the most

successful method for sustained weight loss in the morbidly obese.[3,14] There are a number of surgical approaches to weight loss which include both malabsorptive and/or restrictive mechanisms. Currently, in the USA, Roux-en-Y gastric bypass is the most commonly performed bariatric procedure. The aim of this study was to characterize the clinical outcomes, specifically with regard to improvement or resolution of hypertension, of a cohort of morbidly obese hypertensive patients who underwent laparoscopic Roux-en-Y gastric bypass.

Materials and Methods

Patient Identification and Selection

We performed a retrospective analysis of our prospectively collected bariatric database of 95 patients with documented hypertension who underwent laparoscopic gastric bypass with a minimum follow-up of 12 months. This group of patients represented 38% of the cohort of patients who underwent gastric bypass between 2003 and 2006. All patients met the 1991 National Institute of Health Consensus Conference guidelines for bariatric surgery. Our surgical technique consisted of constructing a 15- to 20-ml transected gastric pouch with a 150-cm Roux limb. The gastrojejunal anastomosis was performed in an end-to-side fashion using a circular stapler. Approval for this retrospective study was obtained from the University of California Medical Center Institutional Review Board.

Baseline clinical data including patient characteristics, length of hypertensive condition, weight, antihypertensive medication(s) requirement, and blood pressure readings were obtained at the initial clinic visit. Each patient underwent three blood pressure measurements and the average reading was recorded by one of two medical assistants. All patients with a preexisting diagnosis of hypertension and currently being treated with antihypertensive medication(s) were included in this review. All patients were followed postoperatively in an outpatient clinic at 1 week, 1 month, and then at 3 months interval. Medication adjustments in the postoperative period were made at the discretion of each patient's primary care physician. There was no established protocol for the reduction or discontinuation of antihypertensive medication(s). Improvement of hypertension was defined as a decrease in medication requirement and a normal blood pressure (systolic pressure <140 mmHg and diastolic pressure <80 mmHg). Resolution of hypertension was defined as a normal blood pressure and discontinuation of all antihypertensive medications. The Assessment of Obesity-Related Comorbidity (AORC) scale was used to objectively quantify preoperative and postoperative degrees of hypertension.[15] The scale of 0 was defined as *not present*; a scale of 1 was defined as *borderline/intermittent diagnosis not confirmed*; a scale of 2 was defined as *controlled by diet and exercise*; a scale of 3 was defined as *treatment with a single medication*; and a scale of 4 was defined as *treatment with multiple medications*.

Statistical Analysis

Continuous variables were expressed as mean±standard deviation and were analyzed using two-sample *t* tests. Categorical variables were analyzed using Fisher's exact tests or the Chi-square tests with Yates' correction when appropriate. Statistical analysis was performed using SPSS statistical software, version 12.0 (SPSS Inc., Chicago, IL, USA). A p value of less than 0.05 was considered significant.

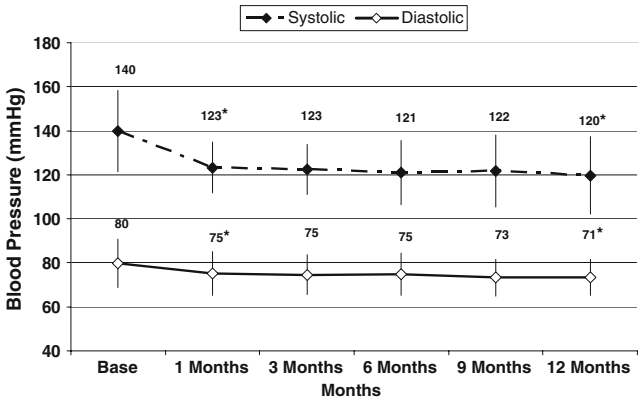
Results

There were 95 morbidly obese patients with documented hypertension who underwent laparoscopic gastric bypass with complete data at 1-year follow-up (Table 1). There were 26 (28%) males and 69 (72%) females with a mean age of 47±9 years (range 26–64 years). The mean body mass index was 47±8 kg/m^2. The mean excess body weight loss was 23% at 1 month, 38% at 3 months, 55% at 6 months, 62% at 9 months, and 66% at 1 year. There were no in-hospital or 30-day mortalities. The mean duration of hypertension prior to gastric bypass was 73±70 months. Preoperatively, all patients were on at least a single antihypertensive medication; 57 patients (60%) have a hypertension AORC scale of 3 and 38 patients (40%) have a hypertension AORC Scale of 4.

Table 1 Characteristics and Outcomes of Hypertensive Morbidly Obese Patients who Underwent Laparoscopic Gastric Bypass

No. of hypertension patients (*N*)	95
No. of females (%)	69 (72)
Mean age (years)	47±9
Baseline body mass index (kg/m^2)	47±8
Mean duration of disease (months)	73±70
No. of patients with preoperative hypertension AORC scale=3[a] (%)	57 (60)
No. of patients with preoperative hypertension AORC scale=4[b] (%)	38 (40)
30-day or in-hospital mortality (%)	0 (0)
Mean excess body weight loss at 1 month (%)	23±9
Mean excess body weight loss at 12 months (%)	66±16

AORC scale Assessment of Obesity-Related Comorbidity scale
[a] Treatment of hypertension with a single medication
[b] Treatment of hypertension with multiple medications



*p<0.05, compared to baseline value; Base=Preoperative blood pressure

Figure 1 Mean change in systolic and diastolic blood pressure in morbidly obese patients with documented hypertension who underwent laparoscopic gastric bypass. *$p<0.05$, compared to baseline value. *Base* preoperative blood pressure.

There was a significant reduction in mean systolic blood pressure from 140±17 mmHg preoperatively to 123±18 mmHg at 1 month and ultimately to 120±18 mmHg at 12 months postoperatively, $p<0.01$ (Fig. 1). There was also a significant reduction in the mean diastolic blood pressure from 80±11 mmHg preoperatively to 75±10 mmHg at 1 month and 71±8 mmHg at 12 months postoperatively, $p<0.01$. At 1 month postoperatively, 24 (25%) patients had complete resolution of hypertension while 34 (36%) had improvement (Fig. 2). At 12 months postoperatively, 44 (46%) patients had complete resolution while 18 (19%) patients had improvement of hypertension. Patients with complete resolution of hypertension at 1 month postoperatively had a shorter duration of disease as compared to those without resolution (38±45 months vs. 87±74 months, $p<0.01$). At 12 months postoperatively, the mean duration of preexisting hypertension was also lower for patients with resolution of hypertension compared to patients who did not have resolution, 53±52 months vs. 95±81 months, respectively, $p=0.03$ (Table 2). The median percent excess

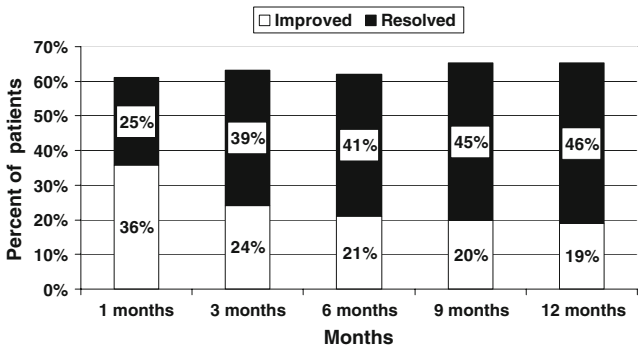


Figure 2 Improvement or resolution of hypertension in morbidly obese patients with documented hypertension who underwent laparoscopic gastric bypass.

Table 2 Comparisons of Patient with Complete Resolution of Hypertension vs. Patients without Resolution at 12 Months Postoperatively

	Resolution (N=44)	No resolution (N=51)
Mean age (years)	46±9	49±8
No of females (%)	33 (75)	34 (67)
No. of Hispanics (%)	8 (18)	6 (12)
No. of African Americans (%)	3 (7)	5 (10)
Mean preoperative no. of antihypertensive medications	2±1	2±1
Mean duration of hypertensive disease (months)	55±52*	93±81
Preoperative systolic blood pressure (mmHg)	136±16	142±17
Systolic blood pressure at 12 months (mmHg)	114±17*	128±12
Preoperative diastolic blood pressure (mmHg)	78±10	81±12
Diastolic blood pressure at 12 months (mmHg)	70±10*	80±11

*$p<0.05$, compared to patients without resolution of hypertension

body weight loss was 57% at 12 months. Of the patients who achieved excess body weight loss above the median value, 72% had resolution of hypertension as compared to 19% had resolution for patients who did not achieve the median weight loss ($p<0.01$). The 12 months, mean systolic blood pressure was lower in patients who had resolution of hypertension when compared to those without resolution, 114±17 mmHg vs. 128±12 mmHg ($p=0.02$) and the diastolic blood pressure was also lower in patients who had resolution of condition, 70±10 mmHg vs. 80±11 mmHg, respectively, $p<0.01$. At 12 months, 46% of patients have a hypertension AORC scale of 0 while 7% and 46% have an AORC scale of 3 and 4, respectively. Age, gender, race, preoperative BMI, preoperative blood pressure, preoperative AORC scale, and preoperative medication requirements were similar between those with resolution of hypertension and those without.

Discussion

The main finding of this study is that morbidly obese patients with hypertension who underwent laparoscopic gastric bypass had a significant improvement in both systolic and diastolic blood pressure at 12 months after surgery and reduction in the need for anti-hypertensive medications. Improvement in blood pressure was seen as early as 1 month postoperatively. At 1 month after gastric bypass, there was 25% complete resolution of hypertension and at 12 months postoperatively, 44% of individuals had

complete resolution. Individuals with complete resolution of hypertension had shorter duration of disease compared to those without resolution.

Hypertension is the most common comorbidity associated with obesity. Numerous mechanisms have been proposed as to how obesity contributes to the development of hypertension. Some of the proposed mechanisms include alteration in the renin–angiotensin–aldosterone system, increased sympathetic nervous system activity, development of insulin resistance, hyperleptinemia and leptin resistance, altered coagulation factors, inflammation, and endothelial dysfunction.[16] Most likely, the mechanism for hypertension in the obese is multifactorial. The incidence of hypertension in patients who undergo bariatric surgery ranges from 40% and up to 70% depending on the definition for hypertension.[10,12,16–19] For example, Fernstrom et al., in their evaluation of 285 gastric bypass patients, included patients with stage 1 hypertension (systolic blood pressure >140 mmHg and diastolic >90 mmHg) without antihypertensive medications and thus found a 57% incidence of hypertension within their study group.[20]

The combination of obesity and hypertension places patients at a higher cardiovascular risk than those patients without hypertension. This risk can be markedly reduced after resolution of hypertension following weight loss.[19] In a large population-based study of 197 patients, Batsis et al. found a significant improvement in hypertension, diabetes, and dyslipidemia, leading to a decrease in the estimated 10-year risk of cardiovascular events in morbidly obese patients after gastric bypass.[13] In our study, the weight loss following laparoscopic gastric bypass led to significant decrease in both systolic and diastolic blood pressure. At 12 months postoperatively, our cohort had a 14% reduction (by 20 mmHg) in the systolic blood pressure and an 11% reduction (by 9 mmHg) in the diastolic blood pressure. Fernstrom et al., in a retrospective review of 347 patients who underwent either gastric bypass or vertical band gastroplasty, reported only a modest reduction in systolic (3 mmHg) and diastolic (4 mmHg) blood pressure.[20] Outcome data from the Swedish Obese Subjects (SOS) study, which compared 1,157 obese patients who underwent bariatric surgery to 1,031 obese-matched medically treated patients, revealed marked reductions in both weight and blood pressure in the surgical group when compared to the medically treated group.[21] The surgically treated group had an improvement of 11 mmHg for systolic blood pressure and 7 mmHg for diastolic blood pressure. However, by year 8, there was no difference between the blood pressures of the surgical group vs. the medically treated group.[21] However, in a small subset of patients who underwent gastric bypass in the SOS study, weight loss and improvement of hypertension persisted. Other studies have also reported similar results with continual improvement/resolution of hypertension after 1 year.[20]

Multiple studies have shown that weight loss after gastric bypass will lead to the resolution of multiple comorbidities. In our study, 46% of patients had complete resolution of hypertension with 65% of patients showed improvement or resolution at 12 months. Sugerman et al. reported a 69% resolution of hypertension in their analysis of 1,025 gastric bypass patients, which was maintained out to 5 to 7 years.[18] Similarly, Fernstrom et al. found 50% resolution of hypertension after surgery with no relapse at 12 to 18 months follow-up. In a large meta-analysis that included 136 studies and 2,115 gastric bypass patients, Buchwald et al. found that 75% of patients had resolution and 87% had resolution or improvement of hypertension.[3] In a retrospective analysis of 55 veterans who underwent gastric bypass, Huerta et al. found 89% resolution of hypertension following the gastric bypass.[22] Maggard and colleagues reviewed 19 studies that reported changes in hypertension after bariatric surgery and found that resolution or improvement of hypertension occurred in 25% to 75% of patients while improvement was seen in 95% to 100% of patients following bariatric surgery.[14]

Our study also showed a relationship between the length of preexisting hypertension and the likelihood for resolution of the disease. The mean length of condition was significantly lower in patients who had complete resolution of hypertension when compared to those without resolution. At 1 month after gastric bypass, patients who experienced resolution of hypertension had a shorter mean length of hypertension at 38 months compared to 87 months in patients without resolution. The same was true at 12 months; patients with resolution of hypertension had a significantly shorter length of hypertension when compared to those without resolution. These findings suggest that a length of preexisting hypertension of less than 4 years may be predictive for those patients who will not only have resolution of hypertension following gastric bypass but those who will resolve sooner. These findings also suggest that the longer hypertension persists, the more functional and structural changes accompany the disease and the more difficult for the disease to resolve.[23,24] This was previously proposed by Sugerman et al.[18] Given this finding, perhaps bariatric surgery should be offered much sooner to morbidly obese patients with hypertension, as length of preexisting condition is an important factor predicting its resolution.

Conclusion

In conclusion, weight loss associated with laparoscopic gastric bypass significantly improves systolic and diastolic blood pressure and is effective in leading to discontinuation or a marked reduction of hypertensive medication

requirements in a large proportion of morbidly obese hypertensive patients. These findings occur as early as 1 month postoperatively and seem to be associated with the duration of preexisting disease. Moreover, patients with a length of preexisting hypertension of less than 4 years are more likely to have resolution of hypertension. This suggests that perhaps patients with morbid obesity and hypertension should be offered surgical weight loss earlier in their disease process.

References

1. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999–2004. JAMA 2006;295(13):1549–1555. doi:10.1001/jama.295.13.1549.
2. Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999–2002. JAMA 2004;291(23):2847–2850. doi:10.1001/jama.291.23.2847.
3. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, Schoelles K. Bariatric surgery: a systematic review and meta-analysis. JAMA 2004;292(14):1724–1737. doi:10.1001/jama.292.14.1724.
4. Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, Lang CC, Rumboldt Z, Onen CL, Lisheng L, Tanomsup S, Wangai P, Razak F, Sharma AM, Anand SS. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case–control study. Lancet 2005;366(9497):1640–1649. doi:10.1016/S0140-6736(05)67663-5.
5. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. JAMA 1999;282(16):1523–1529. doi:10.1001/jama.282.16.1523.
6. Thomas F, Bean K, Pannier B, Oppert JM, Guize L, Benetos A. Cardiovascular mortality in overweight subjects: The key role of associated risk factors. Hypertension 2005;46(4):654–659. doi:10.1161/01.HYP.0000184282.51550.00.
7. Nguyen NT, Varela E, Sabio A, Tran CL, Stamos M, Wilson SE. Resolution of hyperlipidemia after laparoscopic Roux-en-Y gastric bypass. J Am Coll Surg 2006;203(1):24–29. doi:10.1016/j.jamcollsurg.2006.03.019.
8. Nguyen NT, Varela JE, Sabio A, Naim J, Stamos M, Wilson SE. Reduction in prescription medication costs after laparoscopic gastric bypass. Am Surg 2006;72(10):853–856.
9. Varela JE, Hinojosa MW, Nguyen NT. Resolution of obstructive sleep apnea after laparoscopic gastric bypass. Obes Surg 2007;17(10):1279–1282. doi:10.1007/s11695-007-9228-6.
10. Pajecki D, Dalcanalle L, Souza de Oliveira CP, Zilberstein B, Halpern A, Garrido AB, Cecconello I. Follow-up of Roux-en-Y gastric bypass patients at 5 or more years postoperatively. Obes Surg 2007;17(5):601–607. doi:10.1007/s11695-007-9104-4.
11. Sjostrom CD, Lissner L, Wedel H, Sjostrom L. Reduction in incidence of diabetes, hypertension and lipid disturbances after intentional weight loss induced by bariatric surgery: the SOS Intervention Study. Obes Res 1999;7(5):477–484.
12. Yan E, Ko E, Luong V, Wang HJ, Romanova M, Li Z. Long-term changes in weight loss and obesity-related comorbidities after Roux-en-Y gastric bypass: a primary care experience. Am J Surg 2008;195(1):94–98. doi:10.1016/j.amjsurg.2007.01.036.
13. Batsis JA, Romero-Corral A, Collazo-Clavell ML, Sarr MG, Somers VK, Brekke L, Lopez-Jimenez F. Effect of weight loss on predicted cardiovascular risk: change in cardiac risk after bariatric surgery. Obesity (Silver Spring) 2007;15(3):772–784. doi:10.1038/oby.2007.589.
14. Maggard MA, Shugarman LR, Suttorp M, Maglione M, Sugerman HJ, Livingston EH, Nguyen NT, Li Z, Mojica WA, Hilton L, Rhodes S, Morton SC, Shekelle PG. Meta-analysis: surgical treatment of obesity. Ann Intern Med 2005;142(7):547–559.
15. Ali MR, Maguire MB, Wolfe BM. Assessment of obesity-related comorbidities: a novel scheme for evaluating bariatric surgical patients. J Am Coll Surg 2006;202(1):70–77. doi:10.1016/j.jamcollsurg.2005.09.014.
16. Ruano M, Silvestre V, Castro R, Garcia-Lescun MC, Rodriguez A, Marco A, Garcia-Blanch G. Morbid obesity, hypertensive disease and the renin–angiotensin–aldosterone axis. Obes Surg 2005;15(5):670–676. doi:10.1381/0960892053923734.
17. Sjostrom CD. Surgery as an intervention for obesity. Results from the Swedish Obese Subjects study. Growth Horm IGF Res 2003;13(Suppl A):S22–S26.
18. Sugerman HJ, Wolfe LG, Sica DA, Clore JN. Diabetes and hypertension in severe obesity and effects of gastric bypass-induced weight loss. Ann Surg 2003;237(6):751–756. discussion 757–758. doi:10.1097/00000658-200306000-00002.
19. Vogel JA, Franklin BA, Zalesin KC, Trivax JE, Krause KR, Chengelis DL, McCullough PA. Reduction in predicted coronary heart disease risk after substantial weight reduction after bariatric surgery. Am J Cardiol 2007;99(2):222–226. doi:10.1016/j.amjcard.2006.08.017.
20. Fernstrom JD, Courcoulas AP, Houck PR, Fernstrom MH. Long-term changes in blood pressure in extremely obese patients who have undergone bariatric surgery. Arch Surg 2006;141(3):276–283. doi:10.1001/archsurg.141.3.276.
21. Sjostrom CD, Peltonen M, Wedel H, Sjostrom L. Differentiated long-term effects of intentional weight loss on diabetes and hypertension. Hypertension 2000;36(1):20–25.
22. Huerta S, Kohan D, Siddiqui A, Anthony T, Livingston EH. Assessment of comorbid conditions in veteran patients after Roux-en-Y gastric bypass. Am J Surg 2007;194(1):48–52. doi:10.1016/j.amjsurg.2006.11.017.
23. Campese VM, Mitra N, Sandee D. Hypertension in renal parenchymal disease: why is it so resistant to treatment. Kidney Int 2006;69(6):967–973. doi:10.1038/sj.ki.5000177.
24. Hall JE. The kidney, hypertension, and obesity. Hypertension 2003;41(3):625–633. doi:10.1161/01.HYP.0000052314.95497.78.

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ORIGINAL ARTICLE

Does Low Molecular Weight Heparin Impair Anastomotic Wound Healing?

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Abstract
Background Enoxaparin is an important molecule which had been using in prophylaxis and treatment of deep venous thrombosis. Also, it is showed that it prevents postsurgical peritoneal adhesions in rats. It is aimed to evaluate its effects on gastrointestinal wound healing.
Methods Thirty Wistar albino rats were divided into three groups as control, subcutan, and intraperitoneal enoxaparin groups. Left colon anastomoses were performed. On postoperative seventh day, anastomotic healing was evaluated by measuring anastomotic bursting pressure, tissue hydroxyproline levels, and histopathological examination.
Results The anastomotic bursting pressure was highest in subcutan enoxaparin group ($p<0.001$), intraperitoneal enoxaparin group ($p<0.01$) came the second, and the control group has the worst value. The hydroxyproline results were found nearly similar to the bursting pressure values (subcutan ($p<0.001$)>intraperitoneal ($p<0.05$)>control). Neovascularization in subcutan group ($p<0.001$) has a statistically significant difference to other groups.
Conclusion Enoxaparin did not interfere with colonic anastomotic resistance but improved the intestinal wound healing.

Keywords Bursting pressure · Enoxaparin · Gastrointestinal · Hydroxyproline · Wound healing

Introduction

Strategies to reduce adhesion formation include improving surgical techniques, optimizing laparoscopy conditions, using pharmacologic interventions targeted at the inflammatory response and/or fibrin deposition and using agents that provide a physical barrier to adhesion formation. Most of them are expensive or have limited success.[1]

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Low molecular weight heparin (LMWH) is an important and cheap molecule which had been using in prophylaxis of deep venous thrombosis (DVT) in human. Thus, many authors studied this molecule at animal models and they suggested that LMWH prevents postsurgical intraperitoneal adhesions when administered either subcutaneous or intraperitoneally.[1,2] Also, they found that LMWH prevents peritoneal adhesion by increasing the fibrinolysis due to serine esterase activity.[1]

Formation of adhesions occurs as a consequence of the normal physiological wound healing process.[1] Following any trauma to the peritoneal surface, peritoneal mesothelial cells cover connective tissue containing blood vessels, collagen, lymphocytes, fibroblasts, macrophages, plasma cells, and mast cells.[1] Considering the physiological similarities between the healing process of intestinal anastomosis and the formation of adhesions, it is likely that agents affecting adhesion formation may also modulate the wound healing process. In this study, it is aimed to investigate the effects of enoxaparin on anastomotic wound healing and to answer the question: Does LMWH impair the anastomotic wound healing?

Material and Methods

The procedures followed in this study were in accordance with the *Guide for the care and use of laboratory animals* of the National Institutes of Health (Bethesda, MD, USA) and were approved by the Animal Ethics Committee.

Groups

Group 1 is the control group with the same surgical procedure and intraperitoneal 2 mL saline application and daily 2 mL subcutan (SC) saline treatment until killed. Group 2 is the SC LMWH group with the same surgical procedure and intraperitoneal 2 mL saline application. Also, additional SC 100 IU/kg enoxaparin (Clexane®, Aventis Pharma, France) application at 12 h before surgery, 6 h after surgery, and everyday in postoperative period until killed (as routine peroperative DVT prophylaxis).

Group 3 is the intraperitoneal LMWH group with the same surgical procedure and intraperitoneal 100 IU/kg enoxaparin (Clexane®, Aventis Pharma, France) application with no additional SC LMWH (as peritoneal adhesion prevention).[2] Also, daily 2 mL SC saline treatment was administered until killed.

Animals

A total of 30 Wistar albino rats (*Rattus norvegicus*) weighing 180 to 220 g were housed on a 12-h light/dark cycle and at a temperature of 21°C. The rats were accustomed to laboratory conditions 1 week before experimental use. They were housed two per cage under specified pathogen-free conditions with free access to water and standard rodent chow (Medas, Ankara, Turkey) except 12 h before the surgery. Also, ten rats were selected randomly as subcutan LMWH group and they were applied SC 100 IU/kg enoxaparin (Clexane®, Aventis Pharma, France) 12 h before the surgery.

Sterile surgical protocols were maintained throughout the experiment. The rats were anesthetized with IM ketamine (Ketalar, Parke Davis) 40 mg/kg and xylazine (Rompun, Bayer AG, Leverkusen, Germany) 5 mg/kg.

Anastomotic Bursting Pressure Measurements

A 4-cm median laparotomy was performed under anesthesia. The left colon was transected (without any resection) 4 cm proximally to the peritoneal reflection. The bowel was restored by an end-to-end anastomosis with six interrupted inverting sutures of 6/0 polypropylene (Prolene, Ethicon, UK). Before closure of the abdominal wall, animals were assigned randomly to intraperitoneal application of 2 mL saline in the control group (n=10) or 2 mL 100 IU/kg LMWH (Clexane®, Aventis Pharma, France). Also, an intraperitoneal application of 2 mL saline was performed in the animals which have been assigned as SC LMWH group before. The abdominal wall was closed by continuous 3/0 polypropylene sutures (Prolene, Ethicon, UK).

On postoperative seventh day, healing of anastomotic wounds was evaluated by measuring anastomotic bursting pressure, which is reported to be preferable to other methods, such as busting wall tension or tensile strength.[3–5] Postoperative seventh day was the final time point for bursting pressure measurements, since beyond this, most colon segments rupture outside the anastomosis.[3–5] Briefly, 6 cm of colon segment centered by the anastomoses were resected and rats were killed.

Measurements of anastomotic bursting pressures were performed by another researcher except the surgeon in blind fashion to the groups. Distal parts of the segments were closed with 2/0 silk sutures. The proximal parts of the segments were adapted to an intraluminal pressure manometer (monitoring kit L978-A07 Abott, Slingo, Ireland) and filled with isotonic NaCl solution with continuous infusion (4 mL/min). The bursting pressure (peek pressure before anastomotic disruption) was measured with a pressure transducer (peta, K 450, Ankara, Turkey). Since the evaluation of the bursting pressure might have caused damage along the anastomotic line, the anastomotic site was resected and divided into two parts vertically. One used for hydroxyproline measurement and the other placed in 10% formaline for histopathological examination.

Measurements of Hydroxyproline Levels

Hydroxyproline levels are shown to indicate the amount of collagen in tissues, and a direct relation between anastomotic healing and tissue hydroxyproline levels has been reported.[6,7] Hydroxyproline measurements were performed by another researcher in blind fashion to the groups. The tissues (30–50 mg) were placed into hydrolysis tubes. Fifty-millimolar potassium phosphate buffer pH 7.0 and an equal volume of concentrated HCl were added to each tube, and the samples were hydrolyzed at 110°C for 16 h. The samples were oxidized with chloramine-T solution (pH 8.5), and the Ehrlich's reagent was added. The color was allowed to develop at 60°C for 25 min, and the absorbency at 560 μm was determined with Bergman and Loxley's method.[8] Total protein on tissue homogenates was determined by the addition of trichloroacetic acid (10% final concentration) to precipitate proteins, and the sample was centrifuged at 2,500×g for 10 min. The amount of protein in sediment was determined with a protein assay kit based on the Lowry method (Bio-Rad, Hercules, CA, USA). The hydroxyproline concentration was calculated as mg/g wet weight tissue.

Table 1 Histological Grading Scale (Modified from Hunt and Mueller[9])

0	No evidence
1+	Occasional evidence
2+	Light scattering
3+	Abundant evidence
4+	Confluent cells or fibers

The following parameters were each assessed individually: inflammatory cell infiltration, blood vessel and fibroblast in growth, and collagen deposition

Histological Evaluation

After being embedded in paraffin, sections were obtained at 4-μm intervals and stained with hematoxylin and eosin, colonic tissues and anastomosis were examined under light microscopy with a magnification of ×40 and were graded in a blind fashion, using a modified 0 to 4 numerical scale by Ehrlich and Hunt (Table 1).[9,10] The evaluated parameters were inflammatory cell infiltration, fibroblast ingrowth, neovascularization, and collagen deposition. Each parameter was assessed individually using the numerical scale.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 11.5 software (SPSS Inc, Chicago, IL, USA). Descriptive statistics included the mean±standard deviation or the median plus the 25th and 75th percentiles. Prior to implementation of specific statistical tests, all assumptions were assessed. To compare anastomotic bursting pressure and tissue hydroxyproline levels between the three treatment groups, the appropriateness of the assumptions of normality (using the Shapiro–Wilk test) and homogeneity of variance (using Levene's test) were examined. For outcome variables that did not meet the required assumptions, the Kruskal–Wallis test was used to compare outcomes between treatment groups, and for outcomes that met the underlying assumptions, the one-way analysis of variance (ANOVA) was used to compare outcomes between the three treatment groups. When the overall p value from the one-way ANOVA was statistically significant ($p<0.05$), Tukey's HSD procedure was used for pairwise treatment comparisons. When the overall p value from the Kruskal–Wallis test was statistically significant ($p<0.05$), pairwise comparisons between treatment groups were make with the Wilcoxon rank sum test. Histologic variables (Table 1) graded using an ordinal scale (0 to 4) were compared between treatment groups with the Kruskal–Wallis test followed by pairwise Wilcoxon rank-sum tests only if the overall p value from the Kruskal–Wallis test was <0.05.

Results

During the course of experimental protocols, no animal in any of the treatment groups died. There were no wound infections or intra-abdominal abscesses as assessed by clinical inspection. All results were summarized at Table 2.

Anastomotic Bursting Pressure Measurements

Compared with the control group, enoxaparin treatment resulted in statistically significant increase in the medians of anastomotic bursting pressure measurements. There was a statistically significant difference when control group 175 mmHg (170–177.7) comparing by SC group 185 mmHg (182–195; $p<0.001$). Also, there was a statistically significant difference between control group and IP group 180 mmHg (176.5–182.7; $p<0.01$). Nevertheless, there was a statistically significant difference when IP group comparing by SC group ($p<0.01$; Fig. 1).

Measurements of Hydroxyproline Levels

There was a statistically significant difference when control group (5.7±0.33 mg/g wet tissue) comparing by SC group

Table 2 Summary of the Results

Variables	Control	SC	IP	p value
Bursting pressure (mmHg)	175 (170–177.7)*	185 (182–195)	180 (176.5–182.7)*,**	<0.001[b]
Hydroxyproline (mg/g wet tissue)	5.7±0.33*	6.4±0.38	5.9±0.33***	<0.001[c]
Inflammatory cell infiltration[a]	3 (2.7–3.25)	3 (3–4)	3 (3–3)	0.379[b]
Fibroblast ingrowth[a]	2.5 (2–3)	3 (3–3)	3 (2–3)	0.152[b]
Neovascularization[a]	2 (2–2.25)*	3 (2–3)	2 (2–2.25)*	0.031[b]
Collagen deposition[a]	2.5 (2–3)	3 (2–3.25)	3 (2–3.25)	0.629[b]

*$p<0.001$ (statistically significant difference when comparing by SC group); **$p<0.01$ (statistically significant difference when comparing by control group); ***$p<0.05$ (statistically significant difference when comparing by SC group)

[a] According to the histological grading scale

[b] Kruskal–Wallis test; the median and 25th and 75th percentiles are reported

[c] One-way ANOVA; mean±standard deviation are reported

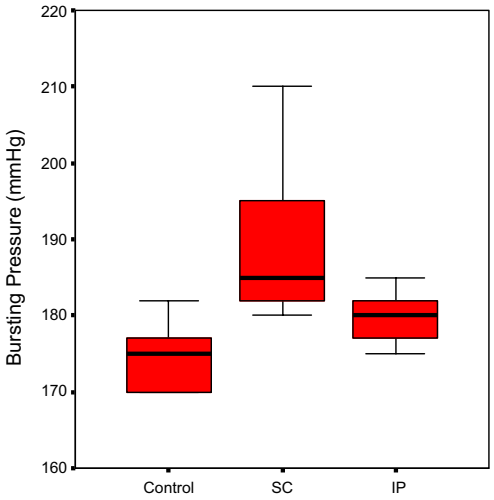

Figure 1 Anastomotic bursting pressures (mmHg) of the control (175 (170–177.7)), subcutan enoxaparin (*SC*; 185 (182–195)) and intraperitoneal enoxaparin (*IP*) (180 (176.5–182.7)) groups. The *box plot* for each treatment group includes the median represented by the *dark line near the center of the box*. The two ends of each box represent the 75th percentile and the 25th percentile. The other two values are the maximum and minimum value for anastomotic bursting pressure (the *vertical lines above and below the box*). There was a statistically significant difference between control and SC ($p<0.001$), control and IP ($p<0.01$), and IP and SC ($p<0.01$) groups. Median values were shown as *black lines*.

(6.4±0.38 mg/g wet tissue; $p<0.001$). Also, there was a statistically significant difference between IP group (5.9± 0.33 mg/g wet tissue) and SC group ($p<0.05$; Fig. 2). But there was no statistically significant difference was found between control group and IP group in the means of tissue hydroxyproline levels ($p>0.05$).

Histological Evaluation

There were no statistically significant differences between groups in the means of inflammatory cell infiltration, fibroblast ingrowth, and collagen deposition ($p>0.05$). Nevertheless, statistically significant differences were calculated when control group comparing by SC group ($p<0.001$) and IP group comparing by SC group ($p<0.001$) in the means of neovascularization. But no statistically significant difference was calculated between control group and IP group ($p>0.05$) in the means of neovascularization (Table 2).

Discussion

Anastomotic dehiscence remains a serious complication in gastrointestinal surgery, resulting in high morbidity and mortality. Furthermore, anastomotic leakage has a large negative impact, reducing over all survival after esophagogastrectomy for cancer and colorectal cancer resection. Therefore, many experiments and trials have been performed in an attempt to find out how to avoid anastomotic leakage after gastrointestinal surgery. The progress of collagen synthesis plays a central role in gastrointestinal healing sequence: Disturbance of its regulation will affect anastomotic strength and might enhance the risk of dehiscence.[11] Hydroxyproline and vitamin C are the main substance in collagen synthesis. Hydroxyproline levels are shown to indicate the amount of collagen in tissues, and a direct relation between anastomotic healing and tissue hydroxyproline levels has been reported.[6,7] Collagen is the most essential basal, skeletal protein employed in the healing cycle. It is synthesized dynamically by proliferating fibroblasts and fills wounds to create a stable scar. Production of collagen in the fibroplasia phase and remodeling phase is initiated days after occurrence of a wound while inflammation and formation of granulated tissue occur immediately and continue for several weeks. Heparin has been shown to inhibit production of collagen in fibroblast culture and it appears likely that it would also delay wound maturation and, consequently, also delay the healing process.[12]

LMWHs are fragments of unfractioned heparin produced by controlled enzymatic or chemical depolymerization. Not only is there a lower hemorrhagic risk for an equivalent antithrombotic effect but their application also is easier than unfractioned heparin.[13] Enoxaparin (enoxaparin sodium) is a low molecular weight heparin that binds to and increases the activity of antithrombin III. The resulting complex inhibits prothrombinase-mediated thrombin generation and direct thrombin generation by binding to factor Xa and thrombin factor IIa. Enoxaparin, used as prophylaxis in medically ill patients at increased risk for thromboembolism, has shown significantly increased efficacy compared with placebo in reducing the incidence of deep vein thrombosis and pulmonary embolism. Okutan et al. suggested that there was no statistically significant difference between enoxaparin and unfractioned heparin or other

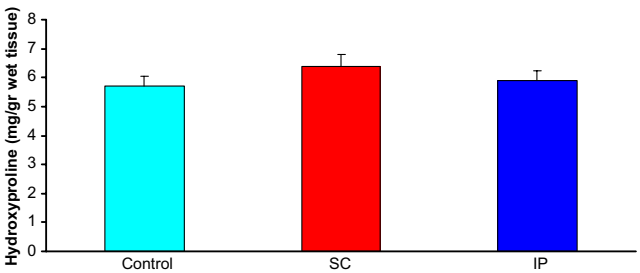

Figure 2 Hydroxyproline levels (mg/g wet tissue) of the control (5.7±0.33), subcutan enoxaparin (*SC*; 6.4±0.38) and intraperitoneal enoxaparin (*IP*; 5.9±0.33) groups. There was a statistically significant difference between control and SC groups ($p<0.05$).

fractionated low molecular weight forms in terms of diminishing acute inflammation after venous thrombosis.[14] Further studies are needed to evaluate the effects of unfractioned heparin or other fractionated low molecular weight heparins on anastomotic wound healing. Also, Lynd et al. concluded that enoxaparin was superior to unfractioned heparin in the terms of cost-effectiveness for the prophylaxis of deep vein thrombosis following major trauma.[15]

LMWH reduces peritoneal adhesion by increasing the fibrinolysis due to serine esterase activity.[2] All LMWHs block the transformation of fibrinogen to fibrin by inhibiting thrombin. Enoxaparin inhibits not only thrombin but also prothrombinase. Many authors suggested that LMWH as well as enoxaparin prevents postsurgical intraperitoneal adhesions when administered either subcutaneous or intraperitoneally.[1,2,16,17]

However, there is no report about the effects of enoxaparin on gastrointestinal wound healing neither applications to prevent intra-abdominal adhesions nor usages in prophylaxis or treatment of deep venous thrombosis. In this study, the same dosing in DVT treatment in human was applied for the rats. Also, this dosing regimen was reported as preventing postoperative intraperitoneal adhesion formation.[1,2,16]

In this study, we found that the anastomotic bursting pressure was higher in both the subcutan enoxaparin (SC) group (median=185 mmHg) and the intraperitoneal enoxaparin (IP) group (median=180 mmHg) when compared to the control group (median=175 mmHg; $p<0.001$ for SC versus control and $p<0.01$ for IP versus control)). Arikan et al. also found the hydroxyproline levels higher in the enoxaparin received group, in their experimental study that they have studied cutaneous wound healing and peritoneal adhesions.[17] They have found only fibrosis formation was significantly different only in the group that received both hyperbaric oxygen treatment and enoxaparin. In histopathological examination of our anastomotic specimens, it is found that only neovascularization in SC group has a statistically significant difference to other groups. Thus, we thought that it might be the pathogenetical mechanism of how enoxaparin effects the wound healing. Since we investigated only the effect of enoxaparin on intestinal anastomotic wound healing in rats, not the mechanism of this effect, we did not evaluate it. These parameters should be analyzed in further studies that investigate the mechanism of this effect of enoxaparin.

Positive effects of enoxaparin on circulation were shown in previous studies.[18] Sifil et al. suggested that intraperitoneal enoxaparin administration did not cause as the same effect as SC application.[19] We thought that the lesser effect of the intraperitoneal administration of enoxaparin on wound healing and neovascularization in our study might due to a dose effect. These parameters should be analyzed in further studies.

There is no doubt that heparin usage in abdominal surgery is indispensable. However in parallel to their demonstrated anticoagulant ability, LMWHs have effects on viability, proliferation, and apoptosis of various cells. Based on reports that have been published over the last decade, Basson suggested that collaboration of cells in the mucosal and submucosal (below the basement membrane) layers appear to be a necessary condition for the proper healing of the gut.[20] In our study, SC enoxaparin group has the best bursting pressure value and tissue hydroxyproline level. In light microscopic evaluation of the tissues, neovascularization in SC group ($p<0.001$) has a statistically significant difference to other groups. This fact could be explained by a better angiogenesis of rats treated with enoxaparin, once heparin is associated with the activation of fibroblasts growth factors, epidermal growth, and especially vascular endothelial growth.[21–24] This latter one would be the main factor for the vascular neoformation stimulus.[24–27] There are experimental studies reporting faster healing as a result of the better granulation tissue formation and collagen fibers in rats with second degree burns treated with subcutaneous heparin and improvement on angiogenesis and decrease on the healing time in patients with diabetic ulcer, ulcerative colitis and burns.[23,24,28,29]

Conclusion

Enoxaparin, especially in the DVT prophylaxis dose with SC application daily, did not only interfere with colonic anastomotic resistance but also improved the intestinal wound healing in rats. In the light of our findings, we suggest the usage of SC enoxaparin (in DVT prophylaxis dose) for the patients not only in the group under DVT risk but also those who had undergone bowel anastomoses at least until the postoperative seventh day.

References

1. Ergul E, Korukluoglu B. Peritoneal adhesions: facing the enemy. Int J Surg. 2008;6(3):253–260. doi:10.1016/j.ijsu.2007.05.010.
2. Celik A, Ucar AE, Ergul E, Bekar ME, Kusdemir A. Which is most effective in prevention of postoperative intraperitoneal adhesions—Methylene blue, low molecular weight heparin or vitamin E: an experimental study in rats. Internet J Surg 2008;15 (1).
3. Christensen H, Langfelt S, Laurberg S. Bursting strength of experimental colonic anastomoses. A methodological study. Eur Surg Res 1993;25:38–45. doi:10.1159/000129255.
4. Uzunkoy A, Akinci OF, Coskun A, Aslan O, Kocyigit A. Effects of antiadhesive agents on the healing of intestinal anastomosis. Dis Colon Rectum 2000;43:370–375. doi:10.1007/BF02258304.
5. Mansson P, Zhang XW, Jeppsson B, Thorlacius H. Anastomotic healing in the rat colon: comparison between a radiological

method, breaking strength and bursting pressure. Int J Colorectal Dis 2002;17:420–425. doi:10.1007/s00384-002-0392-9.
6. Hendriks T, Mastboom WJ. Healing of experimental intestinal anastomoses. Parameters for repair. Dis Colon Rectum 1990;33:891–901. doi:10.1007/BF02051930.
7. Jonsson K, Jiborn H, Zederfeldt B. Mechanical and biochemical alterations in the intestinal wall adjacent to an anastomosis. Am J Surg 1986;151:387–90. doi:10.1016/0002-9610(86)90474-5.
8. Bergman I, Loxley R. Two improved and simplified methods for the spectrophotometric determination of hydroxyproline. Anal Chem 1963;35:1961–1965. doi:10.1021/ac60205a053.
9. Hunt TK, Mueller RV. Wound healing. In Way LW, ed. Current surgical diagnosis and treatment, 10th ed. New Jersey: Appleton and Lange, 1994, pp 80–93.
10. Ehrlich HP, Tarver H, Hunt TK. Effects of vitamin A and glucocorticoids upon inflammation and collagen synthesis. Ann Surg 1973;177:222–227. doi:10.1097/00000658-197302000-00017.
11. Martens MF, Hendriks T, de Koning HJ. Postoperative changes in collagen synthesis in intestinal anastomoses of the rat: differences between small and large bowel. Gut 1991;32:1482–1487. doi:10.1136/gut.32.12.1482.
12. Ferrao AV, Mason RM. The effect of heparin on cell proliferation and type-I collagen synthesis by adult human dermal fibroblasts. Biochim Biophys Acta 1993;1180:225–230.
13. Andriuoli G, Mastacchi R, Barbanti M, et al. Comparison of the antithrombotic and hemorrhagic effects of heparin and a new low molecular weigh heparin in the rat. Haemostasis 1985;15:324.
14. Okutan H, Eroglu E, Karahan N, Aydin A, Tunc B, Candir O, Kutsal A. Comparison of different low-molecular-weight heparins (dalteparin, enoxaparin, nadroparine) and standard heparin in rat venous thrombosis model. Turk J Vasc Surg 2004;13:17–22.
15. Lynd LD, Goeree R, Crowther MA, O'Brien BJ. A probabilistic cost-effectiveness analysis of enoxaparin versus unfractionated heparin for the prophylaxis of deep-vein thrombosis following major trauma. Can J Clin Pharmacol 2007;14:215–226.
16. Sahin Y, Saglam A. Synergistic effects of carboxymethylcellulose a low molecular weight heparin in reducing adhesion formation in the rat uterine horn model. Acta Obstet Gynecol Scand 1994;73:70–73. doi:10.3109/00016349409013399.
17. Arikan S, Adas G, Barut G, Toklu AS, Kocakusak A, Uzun H, Kemik O, Daduk Y, Aydin S, Purisa S. An evaluation of low molecular weight heparin and hyperbaric oxygen treatment in the prevention of intra-abdominal adhesions and wound healing. Am J Surg 2005;189:155–160. doi:10.1016/j.amjsurg.2004.11.002.
18. Jorneskog G, Brismar K, Fagrell B. Low molecular weight heparin seems to improve local capillary circulation and healing of chronic foot ulcers in diabetic patients. Vasa 1993;22:137–142.
19. Sifil A, Mermut C, Yenicerioglu Y, Cavdar C, Gumustekin M, Celik A, Yuksel F, Camsari T. Intraperitoneal and subcutaneous pharmacokinetics of low molecular weight heparin in continuous ambulatory peritoneal dialysis patients. Adv Perit Dial 2003;19:28–30.
20. Basson MD. Invited research review: cell–matrix interactions in the gut epithelium. Surgery 2003;133:63–67. doi:10.1067/msy.2003.24.
21. Levine A, Kenet G, Bruck R, Avni Y, Avinoach I, Aeed H, Matas Z, David M, Yayon A. Effect of heparin on tissue binding activity of fibroblast growth factor and heparin binding epidermal growth factor in experimental colitis in rats. Pediatr Res 2002;5:635–640. doi:10.1203/00006450-200205000-00015.
22. Street JT, McGrath M, O'Regan K, Wakai A, Mc Ginness A, Redmond HPR. Thromboprophylaxis using a low molecular weight heparin delays fracture repair. Clin Orthop Relat Res 2000;381:278–289. doi:10.1097/00003086-200012000-00032.
23. Michell NP, Lalor P, Langman MJ. Heparin therapy for ulcerative colitis? Effects and mechanisms. Eur J Gastroenterol Hepatol 2001;13:449–456. doi:10.1097/00042737-200104000-00026.
24. Galvan L. Effects of heparin on wound healing. J Wound Ostomy Continence Nurs 1996;23:224–226. doi:10.1016/S1071-5754(96)90095-9.
25. Folkman J. Regulation of angiogenesis: a new function of heparin. Biochem Pharmacol 1985;34:905–909. doi:10.1016/0006-2952(85)90588-X.
26. Terranova VP, Diflorio R, Lyall RM, Hic S, Friesel R, Maciag T. Human endothelial cells are chemotactic to endothelial cell growth factor and heparin. J Cell Biol 1985;101:2330–2334. doi:10.1083/jcb.101.6.2330.
27. Piazuelo E, Jiemenez P, Lanas A, Garcia A, Esteva F, Sainz R. Platelet-derived growth factor and epidermal growth factor play a role in human colonic fibroblastic repair. Eur Surg Res 2000;32:191–196. doi:10.1159/000008762.
28. Jorneskog G, Brismar K, Fagrell B. Low molecular weight heparin seems to improve local capillary circulation and healing of chronic foot ulcers in diabetic patients. Vasa 1993;22:137–142.
29. Saliba MJ. The effects and uses of heparin in the care of burns that improves treatment and enhances the quality of life. Acta Chir Plast 1997;39:13–16.

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MULTIMEDIA ARTICLE

Laparoscopic Rectosigmoid Resection for Acute Sigmoid Diverticulitis

Marty Zdichavsky · Alfred Königsrainer · Frank A. Granderath

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Abstract Laparoscopic sigmoid colectomy has been widely accepted as elective approach but is, however, still discussed controversially for acute cases. Patients receiving a laparoscopic early single-stage procedure benefit from an early postoperative convalescence with a minimum of disability. As more surgeons gain expertise in minimally invasive surgery of the rectosigmoid, this video highlights the main steps of a rectosigmoid resection for acute complicated diverticulitis.

Keywords Laparoscopic · Diverticulitis · Acute · Sigmoid resection

Introduction

The laparoscopic surgical approach for complicated diverticulitis is challenging ranging from a multistage procedure to a single-stage resection with primary anastomosis. We present a laparoscopic rectosigmoid resection for acute sigmoid diverticulitis as a technically demanding procedure resulting from an acute inflammatory process.

Method

A 61-year-old male was hospitalized with abdominal pain in the left lower quadrant. A computed tomography (CT) scan revealed inflammation of the sigmoid mesocolon together with pneumoperitoneum (grade IIb according to Hansen and Stock). Despite liquid diet and antibiotic therapy, symptoms did not disappear. A laparoscopic rectosigmoid resection was performed as an early elective procedure. Trocars were placed in the upper left abdominal quadrant (11 mm), the right side (11 mm) and the lower right (12 mm) quadrant. Adhesions of the small bowel to the sigmoid colon were transected. The inflamed sigmoid mesentery was separated from the lateral abdominal wall with preservation of the genital vessels and the left ureter. The mesorectum was dissected circularly. The sigmoid branches were dissected and the rectosigmoid junction was divided using two 45-mm endoscopic linear cutting staplers. The colon was exteriorized through a 5-cm Pfannenstiel incision and the anastomosis was performed laparoscopically using a double-stapling technique. A non-suction drainage was inserted into the Douglas pouch.

Results

The video presents a patient with an acute episode of a recurrent sigmoid diverticulitis with extraluminal air in the CT scan suggesting the side of colon perforation. No intraoperative or postoperative complication occurred. Operation time was 125 min. A primary anastomosis without diverting ileostomy was performed because peritonitis was localized. The size of the Pfannenstiel incision line depended on the diameter of the inflammatory conglomerate process and can usually be kept as small as possible. Bowel movement was restored on the first day after surgery and the patient was discharged from hospital after complete nutritional build up.

Electronic supplementary material The online version of this article (doi:10.1007/s11605-008-0675-8) contains supplementary material, which is available to authorized users.

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Conclusion

This case indicates that laparoscopic rectosigmoid resection in patients with acute sigmoid diverticulitis might serve as a feasible one-stage procedure with fast recovery. This demanding operative approach should be performed in high volume centres by surgeons with expertise. However, prospective randomized trials are necessary to evaluate this procedure as surgical alternative and as attractive approach for the patients.

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CASE REPORT

Rosai–Dorfman Disease (Sinus Histiocytosis with Massive Lymphadenopathy) of the Pancreas: Second Case Report

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Abstract
Introduction Rosai–Dorfman disease (RDD), originally described as sinus histiocytosis with massive lymphadenopathy, is a rare histiocytic proliferative disorder with a distinctive microscopic appearance. It formerly was thought to be a process limited to lymph nodes, yet RDD has been documented to occur in many organ systems, notably the bone, skin, soft tissue, central nervous system, eye and orbit, and upper respiratory tract. The digestive system, however, is affected only exceptionally, with this being only the second documented case involving the pancreas.
Case Description In this case report, we present a case of a 63-year-old African-American female who was found to have a pancreatic head mass and right middle lobe pleural nodule during evaluation for obstructive jaundice.
Discussion and Conclusion She underwent a Whipple procedure. Her pathology of both the pancreatic mass and RML lung wedge resection showed sinus histiocytosis with massive lymphadenopathy, along with extensive fibrosis intertwined with nodular mixed inflammatory infiltrate. The histiocytes characteristically showed "emperipolesis," in which lymphocytes had penetrated the cytoplasm and remained viable within the histiocytes (lymphocytes continued to have free movement in the histiocyte). In addition, the histiocytic cells were positive with S-100 protein and CD68, hallmarks of RDD. Although rare, Rosai–Dorfman disease should be considered in the differential diagnosis of patients presenting with pancreatic and/or lung nodules, especially when biopsy or cytology results report atypical inflammatory findings.

Keywords Obstructive jaundice · Rosai–Dorfman disease · Sinus histiocytosis with massive lymphadenopathy · Emperipolesis · Pancreatic mass · Whipple procedure

Case Description

A 63-year-old African-American woman with hypertension and diabetes mellitus type-II presented to a community hospital with progressive painless jaundice, pruritis, and darkening urine. She denied nausea, vomiting, abdominal pain, pulmonary symptoms, hematochezia, or appetite changes. Also found was a 5-lb weight gain over a few months. Her physical exam was notable for scleral icterus and multiple papular erythematous non-tender lesions on the chest, with the rest of the exam negative. Laboratory examination demonstrated a normal complete blood count, metabolic profile, and CA-19–9. Further workup included a chest/abdomen CT scan showing a pancreatic mass as well as a right pleural nodular mass within the right middle lobe. An endoscopic retrograde cholangiopancreatography (ERCP) was performed in order to relieve the obstructive jaundice with stent placement. Brush cytology of the common bile duct showed significant reactive ductal epithelium in the background of acute and chronic inflammatory cells.

Further evaluation continued after transfer to our hospital for the recently discovered pancreatic mass and pleural-based lung nodule. A chest/abdomen CT scan with contrast was repeated showing an isodense nodule (2.5 cm) in the

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head of the pancreas, adjacent to the bile duct stent (Fig. 1a) and a pleural-based nodule within the right middle lobe (Fig. 1b). A PET scan was then performed, showing increased metabolic activity in the head of the pancreas and right middle lobe nodule.

VATS was performed (video-assisted thoracoscopic surgery) with wedge biopsy showing a 1.2-cm-sized nodule. Histology showed a mixed inflammatory infiltrate with numerous histiocytes and fibroblasts. Further histological analysis (pathologically reviewed further by consultation of an outside physician) revealed prominent large pale histiocytes, some of which showing "emperipolesis," and S100 positive immunohistochemistry. The pathology thus showed no metastatic pancreatic carcinoma.

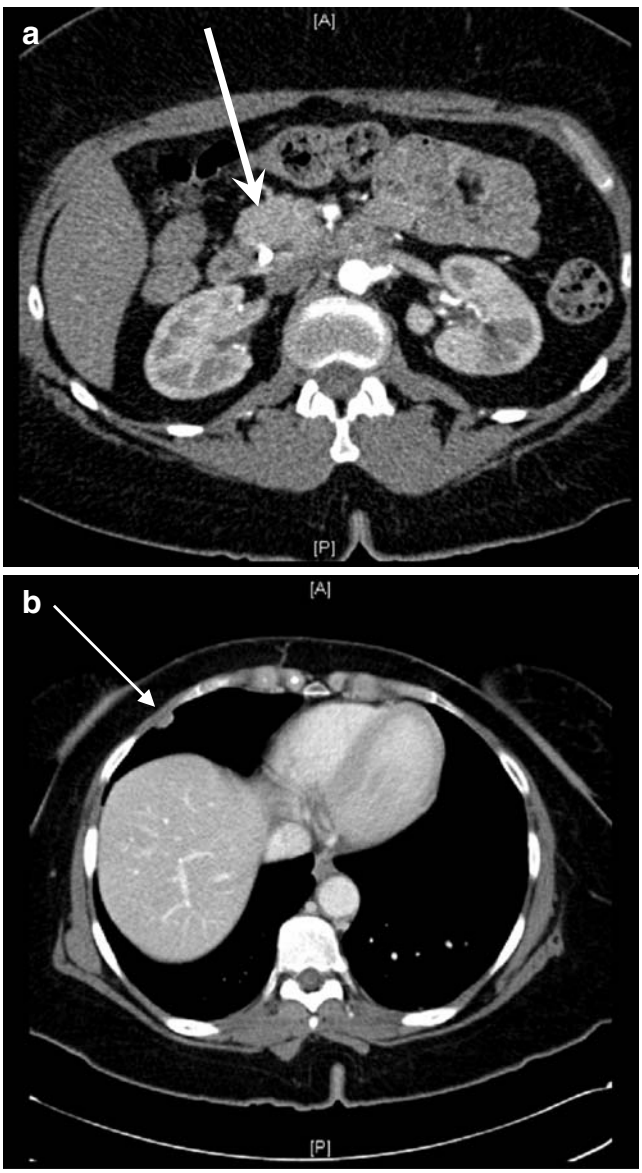

Figure 1 **a** CT scan image of the pancreatic head mass (*white arrow*). **b** CT scan image of the pleural nodule in the right middle lobe (*white arrow*).

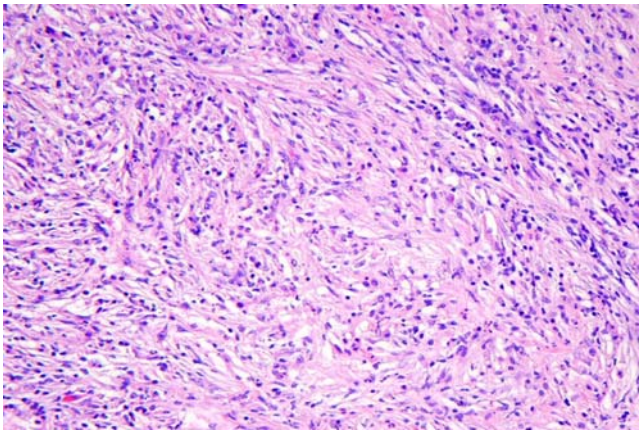

Figure 2 Low power view of the pancreatic mass histology showing histiocytic infiltrates, spindle cells, mixed inflammatory infiltrates, and mild fibrosis.

Next, an endoscopic ultrasound was performed, reconfirming the presence of a 2.3-cm mass at the head of the pancreas and several lymph nodes involved in the area. Fine needle aspiration (FNA) of the pancreas showed rare atypical cells that included aggregates of crushed lymphocytes in a background of fibrosis. It was stated to be negative for malignancy based on cytology.

The assessment following this full diagnostic workup was obstructive jaundice and a pancreatic head mass that was suspicious for pancreatic malignancy. It was further planned for a Whipple procedure based on appearance on CT image (Fig. 1a), the inconclusiveness of the FNA, and the potentially poor prognosis of pancreatic cancer. The patient had the procedure with an uneventful post-op course and continues to do well 8 months after surgery.

The patient's pancreatic pathology was consistent with extranodal Rosai–Dorfman disease (RDD). Histology showed predominantly histiocytic infiltrates, spindle cells, mixed inflammatory infiltrates, and mild fibrosis (Fig. 2). The peri-pancreatic lymph nodes had expanded sinuses with histiocytosis. Within the histiocytes was "emperipolesis" or "lymphophagocytosis," which is lymphocytic penetration and movement within a histiocyte (Fig. 3). The immunohistochemical staining highlighted the dense histiocytic infiltrates with diffuse S100 and CD68 positivity, a hallmark of RDD.[1] Markers for Langerhan's and dendritic cells (CD1a, CD23), AFB, and calcium deposit stains were all negative.

Discussion

Ultimately, this patient's lung nodule and pancreatic mass were consistent with extranodal Rosai–Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy (SHML). This case report marks the

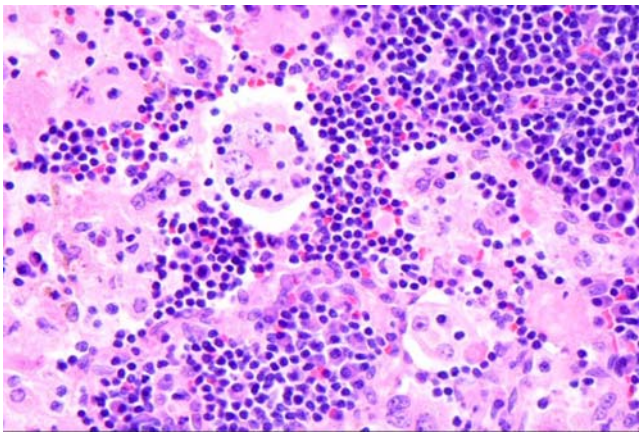

Figure 3 High power view of the pancreatic mass histology showing "emperipolesis" or "lymphophagocytosis" within the histiocytes.

second recording of RDD involving the pancreas. Esquivel et al. described the first case involving the pancreas of a 48-year-old African-American female with hypertension. She presented with abdominal pain and was found to have a mass in the tail of the pancreas with focal involvement of the spleen and peripancreatic lymph nodes. She underwent surgical resection with no recurrence.[2]

RDD, first described in 1965, is a histiocytic proliferative disorder which primarily affects superficial and deep lymph nodes. Extranodal involvement occurs in about half of the patients, and the head and neck area represents the regions most commonly involved. SHML has been described in almost every organ in the body, including the CNS, heart, thyroid, breast, skin, soft tissues, digestive tract, liver, and ocular system.[2] It is a rare disorder of unknown etiology, primarily in children and young adults, and typically with a prolonged clinical course. This benign disease rarely causes visceral damage, with pathological and immunohistochemical analysis required to make the diagnosis.[3]

For this case of a 63-year-old African-American, the pathological report from the Whipple procedure showed hallmarks of RDD, including sinus histiocytosis, emperipolesis, and positive S100 and CD68 staining. As for the right middle lobe wedge resection, the pathology showed nonspecific findings of nodular mixed inflammatory infiltrate, fibrosis, and focal necrosis. In retrospect, it showed characteristics of RDD. Biopsy slides from the lung lesion were not sent for outside consultation until after the pathological findings of the Whipple procedure was reported.

Another aspect of this patient's presentation was the skin manifestations of papular erythematous non-tender lesions on the chest. There are many case reports of Rosai–Dorfman disease expressing itself with cutaneous lesions, yet do not typically present as pruritic.[4,5,6] For this case, we concluded the skin lesions were a result of the patient's pruritis and excessive scratching. And thus, biopsy of the skin lesions was not considered.

While the etiology of RDD is still unknown, there have been several theories as to its cause. Parvovirus B19 infection has been suggested from four cases of RDD analyzed by immunohistochemistry to detect B19 capsid proteins VP1/VP2. All four cases were shown to be positive, and identified within either lymphocytes or, in one extranodal case, respiratory epithelial cells.[7] Parvovirus B19 had not been tested in this patient due to the limit of this finding to only one published article. Expression of the Human Herpes Virus-6 (HHV-6) antigens in benign and malignant lymphoproliferative disease has also been investigated, with one case of HHV-6 being found within skin lesions,[8] while in three other cases an absence of detection of HHV-8 and HHV-6 had resulted from skin lesions.[9] For this case, HHV-6 by PCR quantification was negative.

A similar presentation has been documented in another disease known as lymphoplasmacytic sclerosing pancreatitis (LP), also known as autoimmune pancreatitis. Patients present typically with abdominal pain or jaundice and are found to have a pancreatic mass resembling adenocarcinoma on clinical and radiological review. Classic histological characteristics of LP include lymphoplasmacytic infiltration, interstitial fibrosis, periductal inflammation, and periphlebitis, all similar to the pathology found in RDD. Two differentiating factors are one, many patients with LP have elevated IGG-4 serum levels, and two, ultimately respond to steroids.[10] In this case report, our patient was found to have normal levels of IGG-4.

The clinical course of RDD is varied. While expectant management is most often appropriate, treatment has typically been reserved for forms that are directly threatening or progressive.[1] A literature review of 80 cases over 30 years found that spontaneous resolution was most frequently observed, chemotherapy and immunotherapy (α-interferon) were ineffective, and radiotherapy had limited efficacy. Surgical debulking, when required, showed complete resolution.[1] In our case with obstructive jaundice and pancreatic head mass, our concern was for pancreatic adenocarcinoma and thus the Whipple procedure was performed.

In conclusion, this case report reflects a rare cause for obstructive jaundice that mimics malignancy, both clinically and radiologically. Had the diagnosis of RDD from the lung biopsy been made earlier, the patient still would have needed palliation because of obstructive jaundice. Since the patient had no major co-morbidities, it was felt she could tolerate a pacreaticoduodenectomy without a major complication. If left alone or simply bypassed with hepaticojejunostomy, it is unknown whether the disease would have progressed. With only one previous case report of RDD presenting in the pancreas, one cannot make a definite

statement upon long-term outcome. What can be said is both this patient and the previous case-reported patient have remained stable without complications for many months after surgical resection (Whipple and distal pancreatectomy), suggesting that surgical debulking may be an important treatment option for extranodal RDD involving the pancreas.

References

1. Galicier L, Fieschi C, Meignin V. Histiocytose sinusale de Rosai–Dorfman. Presse Med 2007;36(11):1669–1675. doi:10.1016/j.lpm.2007.06.008.
2. Esquivel J, Krishnan J, Jundi M. Rosai–Dorfman disease (sinus histiocytosis with massive lymphadenopathy) of the pancreas: first case report. Hepatogastroenterology 1999;46(26):1202–1205.
3. Alessandro P, Gabriel A, Falucucci P. Treatment of sinus histiocytosis with massive lymphadenopathy (Rosai–Dorfman disease): report of a case and literature review. Am J Hematol. 2002;69:67–71. doi:10.1002/ajh.10008.
4. Lauwers G, Perez-Atayde A, Dorfman R, Rosai J. The digestive system manifestations of Rosai–Dorfman disease (sinus histiocytosis with massive lymphadenopathy): review of 11 cases. Hum Pathol 2000;31:380–385. doi:10.1016/S0046-8177(00)80254-3.
5. Brenn T, Calonje E, Granter SR. Cutaneous Rosai–Dorfman disease is a distinct clinical entity. Am J Dermatopathol. 2002;24:385–391. doi:10.1097/00000372-200210000-00001.
6. Frater JL, Maddox JS, Obadiah JM. Cutaneous Rosai–Dorfman disease: comprehensive review of cases reported in the medical literature since 1990 and presentation of an illustrative case. J Cutan Med Surg. 2006;10(6):281–290.
7. Mehraein Y, Wagner M. Parvovirus B19 detected in Rosai–Dorfman disease in nodal and extranodal manifestations. J Clin Pathol 2006;59:1320–1326. doi:10.1136/jcp.2005.029850.
8. Scheel M, Rady P, Tyring S. Sinus histiocytosis with massive lymphadenopathy: presentation as giant granuloma annulare and detection of human herpesvirus 6. J Am Acad Dermatol 1997;37(4):643–646. doi:10.1016/S0190-9622(97)70186-5.
9. Ortonne N, Fillet AM, Kosuge H. Cutaneous destombes–Rosai–Dorfman disease: absence of detection of HHV-6 and HHV-8 in skin. J Cutan Pathol 2002;29:113–118. doi:10.1034/j.1600-0560.2002.290209.x.
10. Weber S, Olcay CD, Palesty JA. Lymphoplasmacytic sclerosing pancreatitis: inflammatory mimic of pancreatic carcinoma. J Gastrointest Surg 2003;7:129–138. doi:10.1016/S1091-255X(02)00148-8.

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HOW I DO IT

Choledocho-Choledochostomy in Deceased Donor Liver Transplantation

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Abstract Biliary complications following deceased donor liver transplantation occur with an incidence of approximately 5–10%. The most common type of biliary reconstruction in whole-organ deceased donor liver transplantation remains the choledocho-choledochostomy, which creates an anastomosis between the donor and recipient common bile ducts or common hepatic ducts. Key elements in performing a successful choledocho-choledochostomy include ensuring that bile ducts have adequate blood supply and avoiding mechanical trauma or tension on the anastomosis. Techniques including ductoplasty and spatulation can be used to fashion an anastomosis even in the face of significant size mismatch between donor and recipient bile ducts. This article describes the technique of choledocho-choledochostomy in deceased donor liver transplantation.

Keywords Choledocho-choledochostomy · Liver transplantation · Biliary anastomosis · Deceased donor

The biliary anastomosis has often been referred to as the "Achilles' heel" of liver transplantation due to the importance of biliary drainage and to the incidence of biliary complications, which ranges from 5–10%.[2,3] The critical aspects of performing the biliary anastomosis, as in most other GI surgery, include ensuring that the tissues have adequate blood supply, are free of tension, and can be approximated with minimal mechanical trauma. Options for biliary reconstruction include creating an anastomosis between donor and recipient bile ducts (choledocho-choledochostomy) and creating an anastomosis between donor bile duct and recipient jejunum (hepaticojejunostomy). This report describes the technical aspects of choledocho-choledochostomy.

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Biliary reconstruction is performed after reperfusion has been completed and hemostasis is adequate. Occasionally, this requires a staged procedure, as in patients with hemodynamic instability or profound coagulopathy. In these patients, the biliary anastomosis can be safely completed at a planned re-exploration 24–48 hours later. As a general principle, it is best to wait until hemostasis is assured before performing the biliary anastomosis, as placing excess traction on the liver to search for bleeding can lead to tension on the biliary anastomosis and subsequent bile leak.

The donor gallbladder is removed to the level of the cystic duct, which is ligated and divided. It is not necessary to carry the dissection of the cystic duct back to its confluence with the common hepatic duct, as this maneuver risks devascularizing the distal-most common hepatic duct. Earlier concerns that leaving a long cystic duct remnant would increase the risk of biliary complications have not been realized. Donor and recipient bile duct ends are trimmed sharply to remove cauterized or devascularized tissue. Vigorous bleeding should be evident from both donor and recipient ducts, which may in turn be controlled with fine sutures placed so as to avoid narrowing the bile duct lumen. Use of cautery should be avoided. Lack of bleeding suggests the duct has been devascularized and may need to be trimmed shorter. If the point of transection of the donor duct reveals both cystic and common hepatic

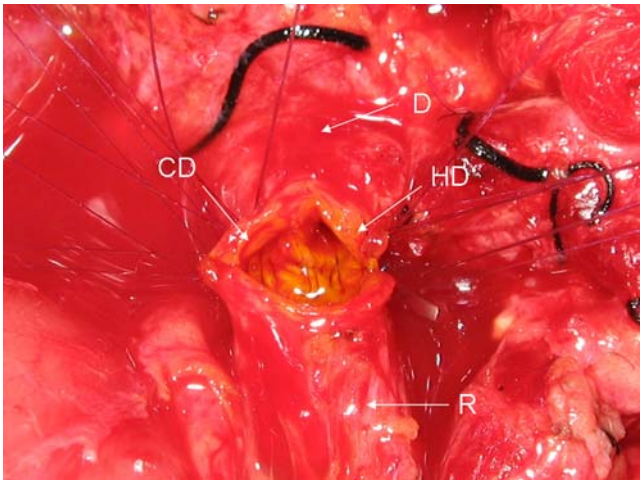

Figure 1 Partially completed choledocho-choledochostomy during deceased-donor liver transplant. Donor (*D*) duct and recipient (*R*) ducts are indicated. Note the donor duct lumen includes both hepatic duct (HD) and cystic duct (CD) lumens, which have been joined to create a common lumen, which nearly matches the size of the recipient duct.

duct lumens, the anastomosis can be fashioned using this shared lumen by creating a common septum (Fig. 1). The level of the biliary anastomosis is typically between common hepatic duct of the recipient (i.e., proximal to cystic duct) and either the common hepatic duct or the common bile duct of the donor. The recipient duct should be probed with a #3 Baakes dilator to confirm that there is easy passage through the ampulla into the duodenum. It should be noted that the complication of post-transplant cholangitis and biliary obstruction due to pre-existing common duct stones is well described in the literature.

An end-to-end anastomosis is created between donor and recipient bile ducts using interrupted absorbable monofilament suture. Our preference is 5-0 or 6-0 polydiazone suture (PDS; Ethicon, Somerville, NJ), depending on the thickness of the bile duct. Sutures are placed with knots outside the bile duct to avoid leaving a nidus for stone or sludge formation (Figs. 1 and 2). Suture placement must account for mild to moderate donor and recipient bile duct size mismatch. Ducts in which the larger duct is less than 50% greater in diameter than the smaller duct can usually be handled without altering the size of the larger duct, whereas those with greater size discrepancy should be handled with ductoplasty to narrow the larger duct (see below). In some cases, the cystic duct lumen of either donor or recipient duct can be incorporated into the anastomosis to increase the circumference of the surgical lumen (Fig. 1). While this obviously does not increase the functional diameter of the bile duct, it may obviate the need for ductoplasty and can make the anastomosis easier to perform. In performing the anastomosis, great care is taken to pass sutures perpendicular to the duct wall and to avoid excess needle trauma, as ducts are typically thin-walled and non-dilated.

Two basic suture placement techniques can be utilized for the choledocho-choledochostomy. The first is a corner-stitch technique common in vascular surgery, in which corner stitches are placed laterally 180° apart in both ducts for alignment, followed by placement of the back row of sutures and then the front row. A typical back row requires four to five sutures for an 8- to 10-mm duct. We typically place the entire back row prior to tying any of the sutures to allow for maximal duct mobility and visualization during this portion. Once the back row is secured placement of the front row of sutures is straightforward because the duct is less mobile and the needle and suture placement is anterior in the

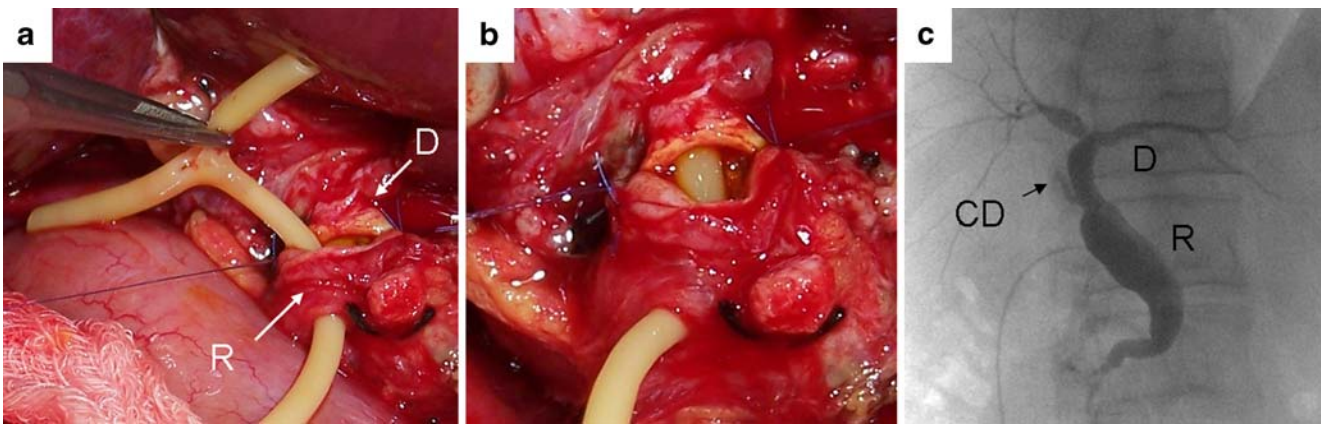

Figure 2 Choledocho-choledochostomy involving ducts of moderate size discrepancy. In this case, the recipient duct (*R*) has a diameter roughly 30% greater than the donor duct (*D*) but is still suitable for anastomosis without need for ductoplasty: (**a**) T-tube entering recipient duct; posterior row of sutures has been tied with knots placed externally; (**b**) T-tube across anastomosis after completion of the posterior wall; (**c**) T-tube cholangiogram 6 months after transplant demonstrated persistent size discrepancy between donor (*D*) and recipient (*R*) ducts without evidence of anastomotic compromise. Donor cystic duct remnant (*CD*) is also evident.

operating field (Fig. 2). This technique is useful when there is a significant size discrepancy between donor and recipient ducts since the corner stitches create visual cues for the surgeon to "divide and conquer" the posterior and anterior duct segments. The second technique is one of sequential posterior-to-anterior fixation. In this technique, a few posterior stitches are initially placed and tied to provide fixation and orientation after which the surgeon places and ties sutures individually from back to front (posterior to anterior). This technique avoids the distortion sometimes caused by corner stitches and is useful with very small ducts, but can be more difficult if there is a size mismatch between ducts since the surgeon lacks the visual aid of corner stitches in dividing the duct into smaller segments. The recent description of routine spatulation of both donor and recipient bile duct lumens prior to end-to-end anastomosis to create a longer suture line represents a novel biliary option and may also be useful in dealing with discrepancies in bile duct diameter.[1] This technique is intriguing but has not been widely reported and has not been utilized by the authors.

Ductoplasty

In cases of significant donor and recipient size discrepancy, options include hepaticojejunostomy or performing ductoplasty (Fig. 3). If the donor duct is large, consideration should be given to hepaticojejunostomy, as the chance of stricture later is relatively low. However, if the donor duct is small, performing a ductoplasty of the recipient duct to facilitate a duct-to-duct anastomosis has the advantage of leaving intact the option for trans-ampullary biliary access in the event of anastomotic stricture. Ductoplasty is performed by closing a portion of the lumen of the larger duct with monofilament suture. Anastomosis then proceeds similar to an unaltered duct, taking great care to place a suture close to each side of the ductoplasty suture line to avoid leak. Alternatively, the anastomosis can precede the ductoplasty by first connecting the smaller duct to as much of the larger duct as is needed, after which the excess portion of the larger duct is closed (Fig. 3). Our preference is to leave a T-tube in place after ductoplasty for the possibility of bile leak.

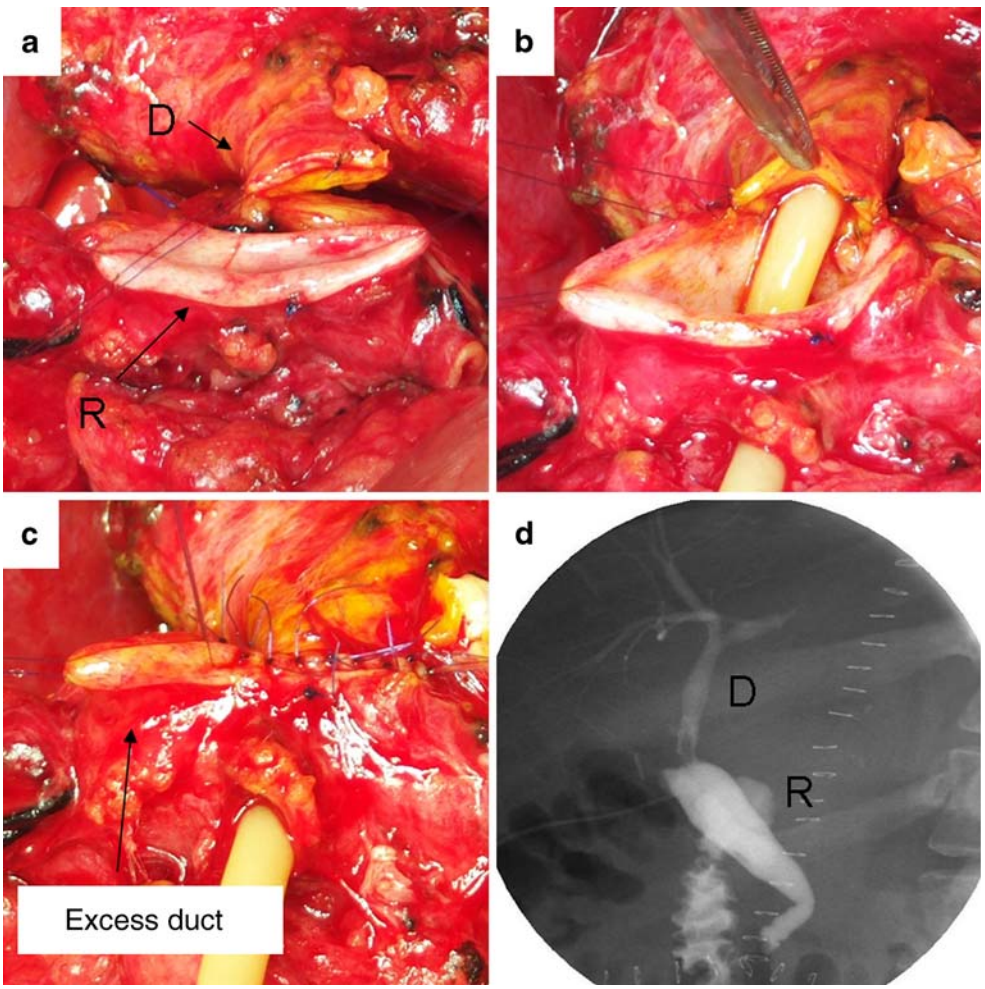

Figure 3 Choledocho-choledochostomy utilizing ductoplasty of recipient bile duct: (**a**) Donor (*D*) and recipient (*R*) ducts demonstrating > 2:1 diameter discrepancy; (**b**) back row of anastomosis is completed and T-tube placed; (**c**) anastomosis is completed over a T-tube and excess portion of recipient duct can now be closed with non-absorbable suture; (**d**) T-tube cholangiogram 1 week after transplant shows size discrepancy of donor and recipient ducts and filling artifact in duct due to T-tube.

Use of T-tube or Biliary Stent

T-tubes should be used judiciously due to concerns over increased biliary complications in patients undergoing routine T-tube placement. In a prospective clinical trial performed by Scatton et al., in which recipients of deceased donor orthotopic liver transplants were randomized to either receive or not receive placement of a T-tube after choledochocholedochostomy, the T-tube group had a significantly higher incidence of biliary complications.[4] We typically limit T-tube placement to patients at increased risk for bile leak due to: (1) use of ductoplasty; (2) large duct size discrepancy; (3) split liver graft; (4) concern over tight ampulla. Our preference, when they are required, is to place a small-diameter (5 or 8 French) T-tube through the recipient (distal) bile duct, as this tissue is typically well vascularized and not compromised by tube placement. The T-tube is placed so as to exit the bile duct 1–1.5 cm distal to the anastomosis and the proximal limb is positioned to traverse the anastomosis (Fig. 2). The T-tube exit site should be secured with absorbable monofilament suture placed either adjacent to the tube or as a purse-string around the tube. The T-tube itself is not secured to the duct in any way, as inadvertent removal could then create a large rent in the bile duct and variation in suture absorption rate would make the timing of removal somewhat speculative.

At our institution T-tubes are removed after steroid taper is completed, which typically occurs 6 months post-transplant. While earlier removal is probably safe, we prefer waiting until the potential detrimental effects of steroids on wound repair and infection are minimized, as T-tube removal by necessity creates a temporary leak in the biliary tree. At the time of removal, antibiotics are administered intravenously and a T-tube cholangiogram is performed to ensure biliary integrity and drainage. If the cholangiogram is normal, the T-tube is removed over a wire and replaced with a temporary external drain, which is removed over 12–24 hours. This practice essentially creates a controlled external fistula between the bile duct defect and the skin until the bile duct seals. When performed in this manner, bile leak or biliary peritonitis following T-tube removal is uncommon. Endoscopic retrograde cholangiopancreatography should be performed quickly if a significant bile leak is suspected, as trans-ampullary drainage provides rapid and definitive resolution.

An alternative to the T-tube is to place an internal biliary stent across the anastomosis and across the ampulla using either one-half of a ureteral double J-stent or a similar material. Advantages of an internal stent include less risk of leak with removal and possibly less injury to the bile duct wall. Disadvantages include the possible future need for endoscopic removal and the learning curve associated with placing a trans-ampullary stent.

References

1. Buczkowski AK, Schaeffer DF, Kim PW, Ho SG, Yoshida EM, Steinbrecher UP, et al. Spatulated end-to-end bile duct reconstruction in orthotopic liver transplantation. Clin Transplant 2007;21(7):7–12.
2. Klein AS, Savader S, Burdick JF, Fair JH, Mitchell M, Colombani P, et al. Reduction of morbidity and mortality from biliary complications following liver transplantation. Hepatology 1991;14(5):818–823.
3. Park JS, Kim MH, Lee SK, Seo DW, Lee SS, Han J, et al. Efficacy of endoscopic and percutaneous treatments for biliary complications after cadaveric and living donor liver transplantation. Gastrointest Endosc 2003;57(1):78–85.
4. Scatton O, Meunier B, Cherqui D, Boillot O, Sauvanet A, Boudjema K, et al. Randomized trial of choledochocholedochostomy with or without a T tube in orthotopic liver transplantation. Ann Surg 2001;233(3):432–437. Mar.

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REVIEW ARTICLE

Preoperative Biliary Drainage in Patients with Obstructive Jaundice: History and Current Status

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Abstract
Rationale Preoperative biliary drainage (PBD) has been introduced to improve outcome after surgery in patients suffering from obstructive jaundice due to a potentially resectable proximal or distal bile duct/pancreatic head lesion. In experimental models, PBD is almost exclusively associated with beneficial results: improved liver function and nutritional status; reduction of systemic endotoxemia; cytokine release; and, as a result, an improved immune response. Mortality was significantly reduced in these animal models. Human studies show conflicting results.
Findings For distal obstruction, currently the "best-evidence" available clearly shows that routine PBD does not yield the appreciated improvement in postoperative morbidity and mortality in patients undergoing resection. Moreover, PBD harbors its own complications. However, most of the available data are outdated or suffer from methodological deficits.
Conclusion The highest level of evidence for PBD to be performed in proximal obstruction, as well as over the preferred mode, is lacking but, nevertheless, assimilated in the treatment algorithm for many centers. Logistics and waiting lists, although sometimes inevitable, could be factors that might influence the decision to opt for PBD, as well as an extended diagnostic workup with laparoscopy (on indication) or scheduled preoperative chemotherapy.

Keywords Obstructive jaundice · Biliary drainage · Proximal bile duct tumor · Pancreatic head tumor

Obstructive Jaundice

Malignant disease of the extrahepatic distal (pancreatic head area) or proximal biliary tract is the most prevalent cause of obstructive jaundice, clinically evident by jaundiced skin, nausea, pruritus, dark urine and discoloration of stool, and the first presenting symptom in up to 90% of the patients. The hazardous consequence of prolonged and progressive obstructive jaundice is hepatic dysfunction due to bile stasis and cholangitis, eventually leading to hepatic failure.

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In western countries, pancreatic cancer currently is the fourth cancer type for death, with an incidence of 10–15 per 100,000, whereas the reported incidence of extrahepatic cholangiocarcinoma (CCA) is approximately 1 per 100,000.[1] Radical resection of the tumor is the only possible treatment for cure. Pancreatic head tumors and distal CCA are managed by pancreatoduodenectomy (PD), while for proximal or hilar (Klatskin) extrahepatic CCA affecting the CBD, hilar resection with partial hepatectomy is indicated. Unfortunately, locoregional irresectability and/or metastatic disease, which may become apparent during preoperative work-up, preclude resection in the majority of patients.

Although the postoperative mortality after extensive hepatopancreatobiliary surgery has decreased from 20% to less than 5% in experienced centers, the overall morbidity remains high at approximately 40–60%, depending on applied definitions.[2–6] Frequently encountered surgical complications are anastomotic leakage, in particular, pancreaticojejunostomy leakage, hemorrhage, delayed gastric emptying, and impaired wound healing. Nowadays, complications are generally managed nonoperatively, mainly

due to an emerging role of the interventional radiologist.[7] Nonsurgical complications consist primarily of sepsis, pneumonia, and renal disorders.

Already in 1935, this increased risk of surgery in jaundiced patients was acknowledged by A.O. Whipple, and he was the first to introduce the concept of preoperative biliary drainage (PBD) by performing a staged PD: application of a cholecystogastrostomy to reduce jaundice was followed by resection at a later stage, depending on the severity of jaundice.[8] In the mid 1960s, a nonoperative, external drainage procedure was devised: percutaneous transhepatic cholangiography (PTC) was performed using the CIBA needle.[9] Internal drainage came up in the seventies when the concept of endoscopic retrograde cholangiopancreatography (ERCP) was introduced. In one procedure, a diagnostic investigation was combined with a therapeutic intervention by inserting an endoprosthesis. Up to now, most patients with distal obstruction (pancreatic head/distal bile duct) are treated with ERCP, whereas in patients with proximal biliary obstruction, PTC is generally the preferred method.

The present article will focus on the role of PBD to reduce septic complications following surgery for distal and proximal biliary obstruction by considering the best evidence available in literature.

Experimental Studies

Obstructive Jaundice

Obstructive jaundice is associated with a proinflammatory state, resulting from portal and systemic endotoxemia, and experimental studies have extensively reported on the processes that are implicated in the underlying pathophysiological mechanisms; the most elucidated are discussed hereafter.[10–12]

The endotoxin concentration in the portal circulation is increased, as a result of lack of bile salts in the gut lumen with, consequently, an unbalanced bacterial intestinal microflora and increased permeability of the intestinal mucosal barrier, promoting translocation of bacteria.[13,14] Inadequate clearance of endotoxins in obstructive jaundice has been attributed to an altered reticuloendothelial system (RES) function of Kuppfer cells in the liver.[14,15] Recently, it has been demonstrated that, in isolated liver Kuppfer cells from cholestatic mice, increased numbers of viable intracellular bacteria after infection were present, suggesting an impaired intracellular bacterial killing.[16] The exact consequence with respect to development of infectious complications remains to be elucidated.

The exposure to endotoxemia and bacterial translocation due to obstructive jaundice leads to an uncontrolled induction of the inflammatory cascade: animal experiments have shown increased concentrations of proinflammatory cytokines, such as tumor necrosis factor (TNF), IL-6, GRO/KC (IL-8), and IL-10.[17–22] Increased concentrations of TNF, mainly produced by liver Kuppfer cells, or rather, the imbalance with its soluble receptors, as antagonists and released from the cell membrane by endotoxemia, are suggested to contribute to development of complications.[18,23] After endotoxin administration to cholestatic rats, Kennedy et al. demonstrated that blockade of Kuppfer cells with gadolinium chloride leads to a lower systemic TNF activity and subsequently resulted in an improved survival.[17] On the other hand, the enhanced IL-6 release, as found in jaundiced mice exposed to endotoxin, might actually play an important role in protecting the cholestatic host against hypersensitivity to endotoxin and was found to abrogate cholestatic liver injury.[22,24] In the perspective of these results found in animal models of biliary obstruction, it appears that the generalized inflammatory state in patients with obstructive jaundice was profoundly different.[25] Although obstructive jaundice caused alterations in circulating concentrations of endotoxin-binding proteins, neutrophil activation and increased concentrations of IL-8, the concentrations of many of the investigated mediators in animals, such as TNF and its receptors, were not as high in patients.[25] Although biliary drainage did reduce IL-8 and endotoxin binding proteins, it did not change many of the mediators suggested to correlate with mortality in animal experiments.

It was demonstrated that cellular immunity, measured by the lymphocyte response to mitogens (concanavalin-A and phytohemagglutinin), was significantly lower in bile duct ligated rats but did not occur in jaundiced germ-free rats.[26] This would imply that hyperbilirubinemia itself does not contribute to immunosuppression, but rather, increased levels of gut-derived endotoxins due to obstructive jaundice are responsible because bilirubin levels in both conventional and germ-free bile duct ligated rats were not different. Obstructive jaundice also leads to deeply suppressed natural killer (NK) activity of nonparenchymal liver cells in rats, which can be reversed by biliary drainage of an adequate duration.[27,28] Furthermore, the decrease in NK cell activity resulted in an enhanced growth of liver metastases, and supposedly, PBD might help to prevent liver metastases after surgery.[27]

Next to an increased risk for development of infectious complications, obstructive jaundice has been associated with renal dysfunction, with its extent depending on the intensity of biliary obstruction.[10,29,30] In the pathogenesis of renal failure, extracellular volume depletion may be an important factor, and while the observed increases in plasma renin and aldosterone are logical endocrine responses to a reduced extracellular water compartment, there also is a paradoxical rise in plasma atrial natriuretic

peptide (ANP) in response to biliary obstruction.[31] The raised plasma ANP level might be the result of the passage of bile components to the blood and is reversed to basal levels after biliary drainage, thereby improving renal dysfunction.[31,32] Furthermore, myocardial dysfunction in obstructive jaundice has been suggested to be the consequence of hemodynamic disturbances due to altering ANP concentrations, while after biliary drainage, a correlation was found between decreasing ANP concentrations and increasing cardiac output.[33]

Biliary Drainage

Biliary drainage as a therapeutic method to reduce postoperative septic complications has been shown in multiple experimental models to improve liver function, nutritional status, and cell-mediated immune function; to reduce systemic endotoxemia and cytokine release; and, subsequently, to improve overall immune response.[20,26,34–38] Mortality was significantly reduced in these animal models. With respect to the preferred route of drainage, internal PBD was found to be superior to external PBD in terms of reduction in endotoxemia and mortality by some, whereas others demonstrated external drainage, although in the short-term, to lead to a better recovery of cellular immunity than internal drainage.[34,39,40] In jaundiced rats undergoing hepatectomy, both external and internal PBD improved serum liver function tests; however, a better liver regeneration and function after hepatectomy was observed after internal drainage.[41]

A negative side-effect of biliary drainage is the associated complications of the procedure itself. In dogs, insertion of biliary endoprostheses resulted in bile contamination and severe chronic inflammation of the bile duct.[42] This inflammatory process led to considerable thickening of the wall in both normal and obstructed bile duct, with transmural, fibrosing inflammation and, occasionally, ulceration. Two months after removal of the endoprosthesis, bacterobilia persisted and the bile duct remained inflamed and dilated, albeit less severe. To put an endoprosthesis in the bile duct before surgery resulted in higher postoperative infectious complications, an increased risk of anastomotic dehiscence, more frequent leakage of infected bile, and increased abscess formation. It is likely that the infected bile and the condition of the bile duct wall, as a consequence of the preoperative stenting, were responsible for these complications.

Concerning the duration of PBD, it has been suggested that adequate recovery of hepatic function depends on the duration of biliary decompression and duration of obstructive jaundice before decompression.[43] A minimum of 4–6 weeks of preoperative drainage was advised, with even longer periods proposed for patients with a prolonged biliary obstruction before decompression. A more recent study showed that preoperative decompression is necessary for at least 3 weeks before coagulation and hepatic and RES function start improving.[44]

PBD for Distal Obstruction

Patients suspected to have a tumor in the pancreatic head area (pancreas, distal bile duct, papilla of Vater), without radiological evidence of irresectability, will undergo an exploration with the intention of resection of the tumor. In the preoperative course, a majority of these patients suffer from symptomatic obstructive jaundice.

For many decades, diagnostic strategies comprised the performance of an ERCP in patients with obstructive jaundice, accompanied in most cases with stent placement for PBD as a therapeutic measure for relief of symptoms. Nowadays, state-of-the-art radiological techniques offer a higher diagnostic accuracy than ERCP, require a minimum amount of time, are noninvasive, and have the advantage of assessing local tumor extension, as well as distant metastases.[45–47] Therefore, ERCP as a diagnostic tool is considered obsolete in many countries, although geographical differences do exist. Implementation of a strategy without diagnostic ERCP is not generally adapted yet in The Netherlands; a survey revealed that, prior to referral for further assessment and (surgical) treatment at the tertiary center, almost 40% of patients already had ERCP performed, primarily as a diagnostic procedure.[48]

The therapeutic effect of PBD, either by means of ERCP or PTC, has been extensively debated throughout the past few decades. One of the largest prospective randomized trials performed in the USA by Pitt et al. concluded that PBD does not reduce operative risk; however, it increases hospital cost and, therefore, should not be performed routinely.[49] A systematic review from our institution summarized all retrospective and prospective studies, published between 1966 and 2001, with the aim to evaluate the efficacy of drainage in jaundiced patients, compared to patients that underwent direct surgical treatment.[50] Outcome measures of the meta-analysis were in-hospital death rate, overall complications resulting from the treatment modality (PBD- and surgery-related complications), and hospital stay. Five randomized controlled studies comprising 302 patients (level I evidence) and 18 cohort studies comprising 2,853 patients (level II evidence) met inclusion criteria and were analyzed. Meta-analysis for both level I and level II studies showed no difference in mortality between patients who had PBD and those who had surgery without PBD. However, overall complication rate was significantly adversely affected by PBD compared with surgery without PBD; for level I, they were 57% and 42%,

respectively, indicating a relative risk reduction of 15% and an absolute risk reduction of 27% in case surgery would be performed without PBD. Analysis of level II studies showed equal numbers. If PBD had been without complications, the complication rate would be in favor of PBD based on level I studies, and without difference based on level II studies. Further, overall hospital stay was prolonged after PBD. In all it, was concluded that the potential benefit of PBD, in terms of postoperative rates of death and complications, does not outweigh the disadvantage of the drainage procedure and therefore should not be performed routinely, unless further improved PBD techniques would become available.

The inverse relationship between the institutional volume of major oncological surgery and the resulting morbidity and mortality rates is well recognized and the key reason for a plea for centralization of complex surgical procedures.[4,51] Pisters et al. brought this argument up to justify PBD to create time for referral of patients to high-volume tertiary surgical centers, their (retrospective) study did not demonstrate an increase in the risk of major postoperative complications associated with PBD and stent placement.[52,53] Logistics in terms of (local) referral patterns, waiting lists, extended diagnostic workup with laparoscopy (on indication), or scheduled preoperative chemotherapy could be other plausible factors that might influence the decision to opt for PBD. Possibly, these factors are region-specific for, at least in the USA, in the eastern part of the country, early surgery without drainage is strongly advocated, whereas in the southern part, PBD is favored.[53] However, ideally, such logistic arguments should never be decisive in treatment consideration. Furthermore, even in high case-load centers, a hospital volume-outcome effect for ERCP and stenting exists, which should be taken into account in the discussion of whether or not to start with ERCP and drainage before referral.[54,55]

It should be mentioned that the prospective studies included in our meta-analysis largely consisted of a suboptimal design, while they were not carried out according to the basic principles of clinical trial reporting (the CONSORT statement).[56] Various (outdated) forms of internal and external drainage procedures for both proximal and distal obstruction were included, different durations of drainage were used, and different surgical procedures were followed. These possible methodological and reporting deficiencies might hamper drawing conclusions. Furthermore, due to the time span of included studies, outmoded PBD techniques and materials inevitably add significantly to the negative outcome of drainage.

Therefore, we have conceived a large randomized controlled multicenter trial (in patients needing a PD, distal obstruction) to obtain the highest level of evidence by comparing a "PBD strategy" (standard strategy) with that of an "early-surgery" strategy: the drainage vs. operation (DROP) trial.[57] Primary outcome measure is the incidence of overall severe complications; secondary outcome measure includes hospital stay, number of invasive diagnostic tests, costs, and quality of life.

PBD for Proximal Obstruction

Hilar CCA remains one of the most difficult tumors in terms of staging and radical treatment.[58] Furthermore, the correct mode of preoperative management is still under debate.[59,60] Most patients with hilar CCA show liver dysfunction caused by obstructive jaundice, which has proven to be a significant risk factor in major liver resection.[61–63]

As mentioned earlier, animal studies concerning PBD are convincing in terms of complication reduction; clinical studies report conflicting results.[64–67] Two randomized controlled trials, in which a PBD strategy was compared to early-surgery strategy in jaundiced patients, including patients with proximal lesions, did not display a difference in perioperative mortality; however, they encountered a high rate of PBD-procedure-related complications.[68,69] Cautious interpretation is warranted as these studies used outdated techniques; included a variety of causes of biliary obstruction; and, moreover, comprised only a limited number of patients with proximal CCA. A prospective cohort study found a significantly higher rate of infectious complications if PBD was applied, whereas another study concluded that routine use of PBD was not justified since mortality was not significantly different and recovery of hepatic synthetic function was identical to that of non-jaundiced patients.[70,71]

In contrast, Japanese literature is unanimous in advising and emphasizing the benefit of PBD.[72–74] The postoperative mortality rates after major liver resections performed for hilar CCA in Japan are low, currently between 0% and 9%, for which many consider PBD to be an essential element in preoperative management.[73–76] Most centers agree that, for tumors requiring extensive liver resection, biliary drainage of at least the future remnant liver is necessary to prevent hepatic failure.[77] With the introduction of preoperative portal embolization, to induce hypertrophy of the future remnant liver, the application of wider resection margins and the development of new endoscopic techniques are other factors that have led to a favorable attitude for a preoperative drainage strategy.[78]

The technique of PBD for proximal obstruction, as well as which part of the liver should be drained, is an ongoing controversy. External drainage by PTC is traditionally the preferred method for relief of obstructive jaundice due to proximal obstruction. Endoscopic biliary drainage, al-

though a less invasive technique, carries the increased risk of developing cholangitis due to bacterial contamination from the duodenum.[78] Moreover, endoscopic biliary drainage implicates total biliary drainage (TBD) (entire liver), or at best, hemihepatic drainage by left or right hepatic duct drainage, whereas drainage via PTC offers the possibility to perform more selectively segmental drainage. An argument for selective biliary drainage (SBD) is the subsequent induction of hypertrophy of the future remnant liver and atrophy of the future resected part of the liver.[79,80] A retrospective cohort study investigated 42 consecutive patients who underwent SBD or TBD before hepatectomy.[81] SBD was found not to increase the risk for cholangitis, compared with TBD. In association with portal vein embolization, SBD was superior to TBD in promoting hypertrophy of the future remnant liver, whereby extended hemihepatectomy could be performed more safely. Although not in the perspective of PBD, the only existing prospective randomized controlled trial comparing TBD vs. SBD appointed patients with unresectable hilar bile duct tumors to undergo either unilateral or bilateral endoscopic hepatic duct drainage.[82] Unilateral drainage resulted in a higher technical success rate of stent insertion and a significantly lower incidence of complications, mainly early cholangitis.

In spite of the presumed advantages of PTC drainage over endoscopic drainage, it should be noted that no clinical randomized controlled trials exist regarding the most optimal route of drainage in terms of complication reduction and patient burden. Currently, the preferred technique of biliary drainage prior to surgery for a proximal bile duct tumor depends mainly on local expertise.

Summary and Conclusion

Obstructive jaundice is the most prevalent symptom in potentially resectable distal and proximal lesions of the extrahepatic biliary tract/pancreatic head area. The presence of toxic substances such as bilirubin and bile salts, impaired liver function, and altered nutritional status due to obstructive jaundice have been characterized as factors for the development of complications. Whereas PBD was to yield beneficial effects in experimental models, conflicting results have been observed in human studies. For distal obstruction, currently, the "best evidence" available clearly shows that PBD should not be performed routinely. Unfortunately, most of the available data are outdated, and hopefully, the large prospective randomized controlled DROP trial will solve the dilemma of whether or not PBD, as an additional procedure, improves surgical outcome to such an extent that postponement to resection of progressive malignant disease is justified.[57] The highest level of evidence for PBD to be performed in proximal obstruction, as well as over the preferred mode, is lacking but, nevertheless, assimilated in the preferred treatment algorithm for many centers. Logistics pose an undesirable, although sometimes inevitable, argument to perform PBD.

References

1. Jemal A, Siegel R, Ward E et al. Cancer statistics, 2006. CA Cancer J Clin 2006;56:106–130.
2. Wente MN, Bassi C, Dervenis C et al. Delayed gastric emptying (DGE) after pancreatic surgery: A suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 2007;142:761–768. doi:10.1016/j.surg.2007.05.005.
3. Wente MN, Veit JA, Bassi C et al. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery 2007;142:20–25. doi:10.1016/j.surg.2007.02.001.
4. Gouma DJ, van Geenen RC, van Gulik TM et al. Rates of complications and death after pancreaticoduodenectomy: risk factors and the impact of hospital volume. Ann Surg 2000;232:786–795. doi:10.1097/00000658-200012000-00007.
5. Bassi C, Dervenis C, Butturini G et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005;138:8–13. doi:10.1016/j.surg.2005.05.001.
6. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–213. doi:10.1097/01.sla.0000133083.54934.ae.
7. Sohn TA, Yeo CJ, Cameron JL et al. Pancreaticoduodenectomy: role of interventional radiologists in managing patients and complications. J Gastrointest Surg 2003;7:209–219. doi:10.1016/S1091-255X(02)00193-2.
8. Whipple AO, Parsons WB, Mullins CR. Treatment of carcinoma of the ampulla of Vater. Ann Surg 1935;102:763–779. doi:10.1097/00000658-193510000-00023.
9. Glenn F, Evans JA, Mujahed Z, Thorbjarnsarson B. Percutaneous transhepatic cholangiography. Ann Surg 1962;156:451–462. doi:10.1097/00000658-196209000-00012.
10. Greve JW, Gouma DJ, Buurman WA. Complications in obstructive jaundice: role of endotoxins. Scand J Gastroenterol Suppl 1992;194:8–12. doi:10.3109/00365529209096019.
11. Clements WD, Erwin P, McCaigue MD et al. Conclusive evidence of endotoxaemia in biliary obstruction. Gut 1998;42:293–299.
12. Kimmings AN, Van Deventer SJ, Obertop H et al. Inflammatory and immunologic effects of obstructive jaundice: pathogenesis and treatment. J Am Coll Surg 1995;181:567–581.
13. Parks RW, Clements WD, Smye MG et al. Intestinal barrier dysfunction in clinical and experimental obstructive jaundice and its reversal by internal biliary drainage. Br J Surg 1996;83:1345–1349. doi:10.1002/bjs.1800831007.
14. Clements WD, McCaigue M, Erwin P et al. Biliary decompression promotes Kupffer cell recovery in obstructive jaundice. Gut 1996;38:925–931. doi:10.1136/gut.38.6.925.
15. Tanaka N, Ryden S, Bergqvist L et al. Reticulo-endothelial function in rats with obstructive jaundice. Br J Surg 1985;72:946–949. doi:10.1002/bjs.1800721204.

16. Minter RM, Fan MH, Sun J et al. Altered Kupffer cell function in biliary obstruction. Surgery 2005;138:236–245. doi:10.1016/j.surg.2005.04.001.
17. Kennedy JA, Clements WD, Kirk SJ et al. Characterization of the Kupffer cell response to exogenous endotoxin in a rodent model of obstructive jaundice. Br J Surg 1999;86:628–633. doi:10.1046/j.1365-2168.1999.01114.x.
18. Nehez L, Andersson R. Compromise of immune function in obstructive jaundice. Eur J Surg 2002;168:315–328. doi:10.1080/11024150260284815.
19. Ohtsuka M, Miyazaki M, Kondo Y, Nakajima N. Neutrophil-mediated sinusoidal endothelial cell injury after extensive hepatectomy in cholestatic rats. Hepatology 1997;25:636–641. doi:10.1002/hep.510250324.
20. Bemelmans MH, Gouma DJ, Greve JW, Buurman WA. Cytokines tumor necrosis factor and interleukin-6 in experimental biliary obstruction in mice. Hepatology 1992;15:1132–1136. doi:10.1002/hep.1840150626.
21. Abe T, Arai T, Ogawa A et al. Kupffer cell-derived interleukin 10 is responsible for impaired bacterial clearance in bile duct-ligated mice. Hepatology 2004;40:414–423. doi:10.1002/hep.20301.
22. Sewnath ME, van der PT, van Noorden CJ et al. Cholestatic interleukin-6-deficient mice succumb to endotoxin-induced liver injury and pulmonary inflammation. Am J Respir Crit Care Med 2004;169:413–420. doi:10.1164/rccm.200303-311OC.
23. Bemelmans MH, Greve JW, Gouma DJ, Buurman WA. Increased concentrations of tumour necrosis factor (TNF) and soluble TNF receptors in biliary obstruction in mice; soluble TNF receptors as prognostic factors for mortality. Gut 1996;38:447–453. doi:10.1136/gut.38.3.447.
24. Gehring S, Dickson EM, San Martin ME et al. Kupffer cells abrogate cholestatic liver injury in mice. Gastroenterology 2006;130:810–822. doi:10.1053/j.gastro.2005.11.015.
25. Kimmings AN, Van Deventer SJ, Obertop H et al. Endotoxin, cytokines, and endotoxin binding proteins in obstructive jaundice and after preoperative biliary drainage. Gut 2000;46:725–731. doi:10.1136/gut.46.5.725.
26. Greve JW, Gouma DJ, Soeters PB, Buurman WA. Suppression of cellular immunity in obstructive jaundice is caused by endotoxins: a study with germ-free rats. Gastroenterology 1990;98:478–485.
27. Hirazawa K, Hazama S, Oka M. Depressed cytotoxic activity of hepatic nonparenchymal cells in rats with obstructive jaundice. Surgery 1999;126:900–907.
28. Lane DR, Joshi P, Grogan JB et al. Suppression of natural killer cell activity in biliary obstruction. Am Surg 1996;62:259–262.
29. Wait RB, Kahng KU. Renal failure complicating obstructive jaundice. Am J Surg 1989;157:256–263. doi:10.1016/0002-9610(89)90540-0.
30. Padillo FJ, Cruz A, Briceno J et al. Multivariate analysis of factors associated with renal dysfunction in patients with obstructive jaundice. Br J Surg 2005;92:1388–1392. doi:10.1002/bjs.5091.
31. Martinez-Rodenas F, Pereira JA, Jimenez W et al. Circulating bile is the main factor responsible for atrial natriuretic peptide release in experimental obstructive jaundice. Br J Surg 1998;85:480–484. doi:10.1046/j.1365-2168.1998.00661.x.
32. Padillo FJ, Briceno J, Cruz A et al. Randomized clinical trial of the effect of intravenous fluid administration on hormonal and renal dysfunction in patients with obstructive jaundice undergoing endoscopic drainage. Br J Surg 2005;92:39–43. doi:10.1002/bjs.4790.
33. Padillo J, Puente J, Gomez M et al. Improved cardiac function in patients with obstructive jaundice after internal biliary drainage: hemodynamic and hormonal assessment. Ann Surg 2001;234:652–656. doi:10.1097/00000658-200111000-00010.
34. Gouma DJ, Coelho JC, Fisher JD et al. Endotoxemia after relief of biliary obstruction by internal and external drainage in rats. Am J Surg 1986;151:476–479. doi:10.1016/0002-9610(86)90107-8.
35. Roughneen PT, Gouma DJ, Kulkarni AD et al. Impaired specific cell-mediated immunity in experimental biliary obstruction and its reversibility by internal biliary drainage. J Surg Res 1986;41:113–125. doi:10.1016/0022-4804(86)90016-8.
36. Gouma DJ, Roughneen PT, Kumar S et al. Changes in nutritional status associated with obstructive jaundice and biliary drainage in rats. Am J Clin Nutr 1986;44:362–369.
37. Bemelmans MH, Gouma DJ, Greve JW, Buurman WA. Effect of antitumour necrosis factor treatment on circulating tumour necrosis factor levels and mortality after surgery in jaundiced mice. Br J Surg 1993;80:1055–1058. doi:10.1002/bjs.1800800845.
38. Megison SM, Dunn CW, Horton JW, Chao H. Effects of relief of biliary obstruction on mononuclear phagocyte system function and cell mediated immunity. Br J Surg 1991;78:568–571. doi:10.1002/bjs.1800780516.
39. Gouma DJ, Coelho JC, Schlegel JF et al. The effect of preoperative internal and external biliary drainage on mortality of jaundiced rats. Arch Surg 1987;122:731–734.
40. Mizuguchi K, Ajiki T, Onoyama H et al. Short-term effects of external and internal biliary drainage on liver and cellular immunity in experimental obstructive jaundice. J Hepatobiliary Pancreat Surg 2004;11:176–180. doi:10.1007/s00534-003-0886-z.
41. Saiki S, Chijiiwa K, Komura M et al. Preoperative internal biliary drainage is superior to external biliary drainage in liver regeneration and function after hepatectomy in obstructive jaundiced rats. Ann Surg 1999;230:655–662. doi:10.1097/00000658-199911000-00007.
42. Karsten TM, Davids PH, van Gulik TM et al. Effects of biliary endoprostheses on the extrahepatic bile ducts in relation to subsequent operation of the biliary tract. J Am Coll Surg 1994;178:343–352.
43. Koyama K, Takagi Y, Ito K, Sato T. Experimental and clinical studies on the effect of biliary drainage in obstructive jaundice. Am J Surg 1981;142:293–299. doi:10.1016/0002-9610(81)90296-8.
44. Kawarada Y, Higashiguchi T, Yokoi H et al. Preoperative biliary drainage in obstructive jaundice. Hepatogastroenterology 1995;42:300–307.
45. Johnson CD. Guidelines for the management of patients with pancreatic cancer periampullary and ampullary carcinomas. Gut 2005;54(Suppl 5):v1–16. doi:10.1136/gut.2004.057059.
46. de Groen PC, Gores GJ, LaRusso NF et al. Biliary tract cancers. N Engl J Med 1999;341:1368–1378. doi:10.1056/NEJM199910283411807.
47. Phoa SS, Reeders JW, Rauws EA et al. Spiral computed tomography for preoperative staging of potentially resectable carcinoma of the pancreatic head. Br J Surg 1999;86:789–794. doi:10.1046/j.1365-2168.1999.01138.x.
48. Tilleman EH, Benraadt J, Bossuyt PM et al. Diagnosis and treatment of pancreatic carcinoma in the region of Amsterdam Comprehensive Cancer Care Center in 1997. Ned Tijdschr Geneeskd 2001;145:1358–1362.
49. Pitt HA, Gomes AS, Lois JF et al. Does preoperative percutaneous biliary drainage reduce operative risk or increase hospital cost? Ann Surg 1985;201:545–553. doi:10.1097/00000658-198505000-00002.
50. Sewnath ME, Karsten TM, Prins MH et al. A meta-analysis on the efficacy of preoperative biliary drainage for tumors causing obstructive jaundice. Ann Surg 2002;236:17–27. doi:10.1097/00000658-200207000-00005.
51. van Heek NT, Kuhlmann KF, Scholten RJ et al. Hospital volume and mortality after pancreatic resection: a systematic review and an evaluation of intervention in the Netherlands. Ann Surg 2005;242:781–788. discussion doi:10.1097/01.sla.0000188462.00249.36.
52. Pisters PW, Hudec WA, Hess KR et al. Effect of preoperative biliary decompression on pancreaticoduodenectomy-associated morbidity in 300 consecutive patients. Ann Surg 2001;234:47–55. doi:10.1097/00000658-200107000-00008.

53. Pisters PW, Lee JE, Vauthey JN, Evans DB. Comment and perspective on Sewnath and colleagues' recent meta-analysis of the efficacy of preoperative biliary drainage for tumors causing obstructive jaundice. Ann Surg 2003;237:594–595. doi:10.1097/00000658-200304000-00024.
54. Sewnath ME, Birjmohun RS, Rauws EA et al. The effect of preoperative biliary drainage on postoperative complications after pancreaticoduodenectomy. J Am Coll Surg 2001;192:726–734. doi:10.1016/S1072-7515(01)00819-5.
55. Isenberg G, Gouma DJ, Pisters PW. The on-going debate about perioperative biliary drainage in jaundiced patients undergoing pancreaticoduodenectomy. Gastrointest Endosc 2002;56:310–315.
56. Moher D, Jones A, Lepage L. Use of the CONSORT statement and quality of reports of randomized trials: a comparative before-and-after evaluation. JAMA 2001;285:1992–1995. doi:10.1001/jama.285.15.1992.
57. van der Gaag NA, de Castro SM, Rauws EA et al. Preoperative biliary drainage for periampullary tumors causing obstructive jaundice; DRainage vs. (direct) OPeration (DROP-trial). BMC Surg 2007;7:3. doi:10.1186/1471-2482-7-3.
58. Lazaridis KN, Gores GJ. Cholangiocarcinoma. Gastroenterology 2005;128:1655–1667. doi:10.1053/j.gastro.2005.03.040.
59. Clavien PA, Emond J, Vauthey JN et al. Protection of the liver during hepatic surgery. J Gastrointest Surg 2004;8:313–327. doi:10.1016/j.gassur.2003.12.006.
60. Clavien PA, Petrowsky H, DeOliveira ML, Graf R. Strategies for safer liver surgery and partial liver transplantation. N Engl J Med 2007;356:1545–1559. doi:10.1056/NEJMra065156.
61. Blamey SL, Fearon KC, Gilmour WH et al. Prediction of risk in biliary surgery. Br J Surg 1983;70:535–538. doi:10.1002/bjs.1800700910.
62. Dixon JM, Armstrong CP, Duffy SW, Davies GC. Factors affecting morbidity and mortality after surgery for obstructive jaundice: a review of 373 patients. Gut 1983;24:845–852. doi:10.1136/gut.24.9.845.
63. Shigeta H, Nagino M, Kamiya J et al. Bacteremia after hepatectomy: an analysis of a single-center, 10-year experience with 407 patients. Langenbecks Arch Surg 2002;387:117–124. doi:10.1007/s00423-002-0301-2.
64. Suzuki H, Iyomasa S, Nimura Y, Yoshida S. Internal biliary drainage, unlike external drainage, does not suppress the regeneration of cholestatic rat liver after partial hepatectomy. Hepatology 1994;20:1318–1322.
65. Aronson DC, Chamuleau RA, Frederiks WM et al. The effect of extrahepatic cholestasis on liver regeneration after partial hepatectomy in the rat. Liver 1995;15:242–246.
66. Ohtsuka M, Miyazaki M, Kondo Y, Nakajima N. Neutrophil-mediated sinusoidal endothelial cell injury after extensive hepatectomy in cholestatic rats. Hepatology 1997;25:636–641. doi:10.1002/hep.510250324.
67. Saiki S, Chijiiwa K, Komura M et al. Preoperative internal biliary drainage is superior to external biliary drainage in liver regeneration and function after hepatectomy in obstructive jaundiced rats. Ann Surg 1999;230:655–662. doi:10.1097/00000658-199911000-00007.
68. Hatfield AR, Tobias R, Terblanche J et al. Preoperative external biliary drainage in obstructive jaundice. A prospective controlled clinical trial. Lancet 1982;2:896–899. doi:10.1016/S0140-6736(82)90866-2.
69. McPherson GA, Benjamin IS, Hodgson HJ et al. Pre-operative percutaneous transhepatic biliary drainage: the results of a controlled trial. Br J Surg 1984;71:371–375. doi:10.1002/bjs.1800710522.
70. Hochwald SN, Burke EC, Jarnagin WR et al. Association of preoperative biliary stenting with increased postoperative infectious complications in proximal cholangiocarcinoma. Arch Surg 1999;134:261–266. doi:10.1001/archsurg.134.3.261.
71. Cherqui D, Benoist S, Malassagne B et al. Major liver resection for carcinoma in jaundiced patients without preoperative biliary drainage. Arch Surg 2000;135:302–308. doi:10.1001/archsurg.135.3.302.
72. Nimura Y, Kamiya J, Kondo S et al. Aggressive preoperative management and extended surgery for hilar cholangiocarcinoma: Nagoya experience. J Hepatobiliary Pancreat Surg 2000;7:155–162. doi:10.1007/s005340050170.
73. Seyama Y, Kubota K, Sano K et al. Long-term outcome of extended hemihepatectomy for hilar bile duct cancer with no mortality and high survival rate. Ann Surg 2003;238:73–83. doi:10.1097/00000658-200307000-00010.
74. Kawasaki S, Imamura H, Kobayashi A et al. Results of surgical resection for patients with hilar bile duct cancer: application of extended hepatectomy after biliary drainage and hemihepatic portal vein embolization. Ann Surg 2003;238:84–92. doi:10.1097/00000658-200307000-00011.
75. Kosuge T, Yamamoto J, Shimada K et al. Improved surgical results for hilar cholangiocarcinoma with procedures including major hepatic resection. Ann Surg 1999;230:663–671. doi:10.1097/00000658-199911000-00008.
76. Nagino M, Kamiya J, Nishio H et al. Two hundred forty consecutive portal vein embolizations before extended hepatectomy for biliary cancer: surgical outcome and long-term follow-up. Ann Surg 2006;243:364–372. doi:10.1097/01.sla.0000201482.11876.14.
77. Belghiti J, Ogata S. Preoperative optimization of the liver for resection in patients with hilar cholangiocarcinoma. HPB 2005;7:252–253.
78. Maguchi H, Takahashi K, Katanuma A et al. Preoperative biliary drainage for hilar cholangiocarcinoma. J Hepatobiliary Pancreat Surg 2007;14:441–446. doi:10.1007/s00534-006-1192-3.
79. Miyagawa S, Makuuchi M, Kawasaki S. Outcome of extended right hepatectomy after biliary drainage in hilar bile duct cancer. Arch Surg 1995;130:759–763.
80. Hadjis NS, Adam A, Gibson R et al. Nonoperative approach to hilar cancer determined by the atrophy-hypertrophy complex. Am J Surg 1989;157:395–399. doi:10.1016/0002-9610(89)90583-7.
81. Ishizawa T, Hasegawa K, Sano K et al. Selective versus total biliary drainage for obstructive jaundice caused by a hepatobiliary malignancy. Am J Surg 2007;193:149–154. doi:10.1016/j.amjsurg.2006.07.015.
82. De Palma GD, Galloro G, Siciliano S et al. Unilateral versus bilateral endoscopic hepatic duct drainage in patients with malignant hilar biliary obstruction: results of a prospective, randomized, and controlled study. Gastrointest Endosc 2001;53:547–553. doi:10.1067/mge.2001.113381.

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GI IMAGE

Jejunal Gallstone Ileus: An Unusual Site of Gallstone Impaction

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Abstract
Introduction Gallstone ileus is a life-threatening surgical emergency where characteristic imaging can be diagnostic. Jejunum is the one of the rare sites of gallstone impaction.
Materials and Methods We hereby emphasize the role of multidetector computed tomography (MDCT) by describing a case of jejunal gallstone ileus with cholecystoduodenal fistula in a 59-year-old lady who presented with symptoms and signs of proximal small bowel obstruction.
Conclusion MDCT of the abdomen established the diagnosis, and the patient managed surgically.

Keywords Gallstone ileus · Jejunal · Impaction

Introduction

Gallstone ileus is a rare clinical entity responsible for 1–4% of all cases of mechanical bowel obstruction.[1] Multidetector computed tomography (MDCT) has revolutionized the diagnostic approach with improved diagnostic accuracy in gallstone ileus. It not only detects the presence, number, and exact location of gallstones in the bowel but can also depict the biliary-enteric fistula, thus helping the surgeons to plan prompt and appropriate treatment.

Case Report

A 59-year-old woman came to the emergency of our hospital with chief complaints of acute pain abdomen, vomiting, and constipation for 2 days. Pain was of colicky nature and localized in the left lumbar region. There was no previous history of any surgery or tuberculosis. Physical examination demonstrated mild abdominal distension with tenderness in the right upper quadrant and left lumbar region. No evidence of any flank dullness or shifting dullness noticed. Relevant laboratory investigations revealed only moderate leukocytosis (WBC count of 13×10^6/L). Plain abdominal radiograph was done, which suggested proximal small bowel mechanical obstruction with no evidence of air under the domes of diaphragm. A contrast enhanced computed tomography (CECT) of the abdomen was performed after oral administration of diluted (2%) ionic iodinated contrast and intravenous injection of nonionic iodinated contrast. CECT revealed pneumobilia with air-contrast level in gallbladder lumen, suggesting the presence of cholecystoenteric fistula (Fig. 1a,b). The proximal jejunal loops were dilated with presence of approximately $2.8 \times 3 \times 3.5$ cm sized calcific focus giving lamellated appearance seen intraluminally in one of the jejunal loops [Fig. 2a,b]. However, there was no evidence of bowel perforation/ischemia. Based on these imaging findings, a diagnosis of gallstone ileus was suggested. Patient underwent emergency enterolithotomy with extraction of the gallstone, which was seen impacted in one of the proximal jejunal loops. Cholecystectomy was also performed with repair of cholecystoduodenal fistula. The patient had an uneventful postoperative hospital stay and was discharged after 10 days in good health.

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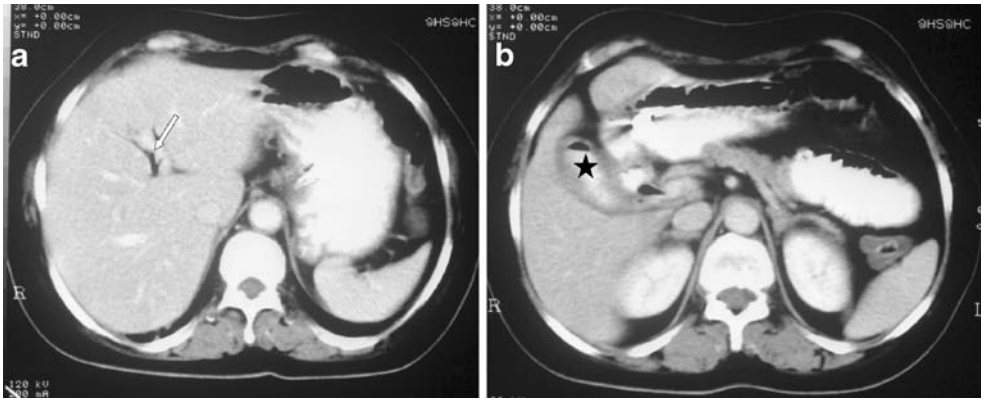

Figure 1 (**a**, **b**): Axial contrast enhanced CT images shows pneumobilia (arrow) and air contrast level in gall bladder (asterisk) suggesting presence of cholecystoenteric fistula.

Discussion

Gallstone causing mechanical small bowel obstruction, known as gallstone ileus, is one of the rare causes of small bowel obstruction accounting 1–4% of all cases.[1] The peak incidence of gallstone ileus lies between 65 to 75 years and it is 3–16 times more common in females.[2] The advancing age makes the patients further prone to develop gallstone ileus.

A past history of chronic cholecystitis is usually present in such patients responsible for formation of adhesions with adjacent bowel loops and subsequent erosion of gallstones into the bowel lumen.[3] The size of gallstones also determines their fate after these pass into the bowel lumen. Smaller stones (<2–2.5 cm) pass distally into the feces whereas the bigger ones tend to get impacted in the narrow segments of small bowel with terminal ileum or ileocecal valve, being the commonest sites of gallstone impaction.[4] Jejunum is one of the rare sites of the gallstone impaction.

Gallstone ileus has a high mortality rate of 7.5–15%, predominantly because of delayed diagnosis and comorbid conditions of the patients such as cardiorespiratory disease, diabetes, and obesity.[2] Thus, prompt preoperative diagnosis of gallstone ileus is of vital importance.

In the past, plain abdominal radiographs were used to diagnose the gallstone ileus based on the classic Rigler's triad with a sensitivity of less than 50%, consisting of pneumobilia, mechanical intestinal obstruction, and ectopic gallstone.[5] At present, with the advancement in the ultrasound and CT technology, ectopically situated gallstone can be localized with confidence in the abdomen and cholecystoenteric fistula can be demonstrated with high accuracy. CECT shows the ectopically lying gallstone as a rounded mass with curvilinear or homogeneous calcification with its accurate localization thus enabling the clinician to plan appropriate treatment.[6]

Once the diagnosis of gallstone ileus is established, it requires emergent surgery in the form of enterolithotomy with or without cholecystectomy and cholecystoenteric fistula repair. Bowel resection is only required when there is bowel perforation or ischemia.[7]

In conclusion, one should be familiar with the characteristic imaging findings of the gallstone ileus on MDCT, which is utilized more frequently in the diagnosis of such emergency conditions.

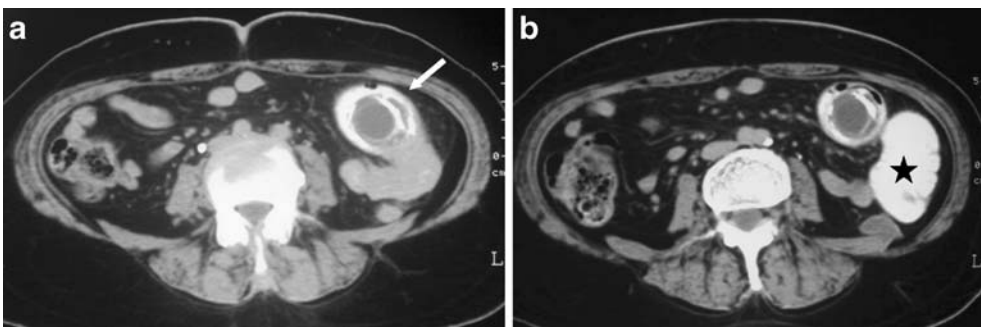

Figure 2 (**a**, **b**): Axial contrast enhanced CT images shows a large gallstone impacted in the proximal jejunum (arrow) and proximal dilatation of jejunum (asterisk).

References

1. Chou JW, Hsu Ch, Liao KF, Cheng KS, Peng CY, Yang MD, Chen YF. Gallstone ileus: Report of two cases and review of literature. World J Gastroenterol 2007;13(8):1295–1298.
2. Reisner RM, Cohen JR. Gallstone ileus: A review of 1001 reported cases. Am Surg 1994;60:441–446.
3. Abou-Saif A, Al-Kawas FH. Complications of gallstone disease: Mirrizi syndrome, cholecystocholedochal fistula, and gallstone ileus. Am J gastroenterol 2002;97(2):249–254.
4. Day EA, Marks CM. Gallstone ileus: Review of the literature and presentation of thirty-four new cases. Am J Surg 1975;129:552–558.
5. Clavien PA, Richon J, Burgan S, Rohner A. Gallstone ileus. Br J Surg 1990;77:737–742.
6. Lassandro F, Romano S, Ragozzino A, Rossi G, Valente T, Ferrara I, Romano L, Grassi R. Role of helical CT in diagnosis of gallstone ileus and related conditions. AJR Am J Roentgenol 2005;185:1159–1165.
7. Tam YM, Wong WK, Ooi LL. A comparison of two surgical strategies for the emergency treatment of gallstone ileus. Singapore Med J 2004; 45: 69–72.