Mesenteric Lymph Collected During Peritonitis or Sepsis Potently Inhibits Gastric Motility in Rats

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Gastrointestinal motility is strongly inhibited during peritonitis or sepsis and proinflammatory cytokines released into mesenteric lymph during an acute gastrointestinal insult mediate systemic responses. We investigated whether mesenteric lymph collected during peritonitis or sepsis inhibits gastric motility and gastric emptying. Mesenteric lymph was collected for 12 hours from three experimental groups: vehicle (saline, 1 ml, intraperitoneally [ip], control lymph), peritonitis (0.5% acetic acid, 1ml, ip, peritonitis lymph), and sepsis (lipopolysaccharide [LPS], 5 mg/kg, 1 ml, ip, sepsis lymph). Gastric motility and gastric emptying were measured in recipient rats in response to lymph injections into the jugular vein. Quantitative polymerase chain reaction (PCR) for tumor necrosis factor α (TNFα) gene expression in the jejunum and in lymph cells were measured during sepsis. Mesenteric lymph flow significantly increased during peritonitis or sepsis (lymph flow [ml] per 60 minutes; control 2.45 ± 0.04; peritonitis 2.67 ± 0.07; sepsis 3.25 ± 0.1, $p < 0.01$ vs. control). Injection of peritonitis or sepsis lymph (1 ml) produced a significant and prolonged inhibition of gastric motility in recipient rats (decrease in intragastric pressure and duration: control lymph −0.14 ± 0.05 cm H_2O, 1.89 ± 1.31 minutes; peritonitis lymph: −0.56 ± 0.06 cm H_2O, 9.9 ± 0.9 minutes; sepsis lymph: −0.51 ± 0.05 cm H_2O, 6.9 ± 0.6 minutes; $p < 0.001$ vs. control for all comparisons). Gastric emptying was significantly inhibited by continuous infusion of sepsis lymph (3 ml per 60 minutes; gastric emptying: saline 81% ± 4%; control lymph: 80% ± 6%; sepsis lymph: 44% ± 10%; $p < 0.001$ vs. control). TNFα gene expression in the gut wall of the jejunum increased during sepsis over 90-fold within the first 2 hours and decreased continuously thereafter (relative TNFα mRNA transcription: basal 1.0 ± 0.05; LPS 2 hours: 91.9 ± 2.6, $p < 0.001$ vs. basal; 12 hours: 24.7 ± 16.8, not significant [NS]; 24 hours: 7.0 ± 3.4, NS). In conclusion, mediators in mesenteric lymph, possibly cytokines, may be responsible for the inhibition of gastric motility during peritonitis or sepsis. Because the composition of mesenteric lymph probably reflects the interstitial fluid of the gut wall, monitoring visceral lymph might be an extremely beneficial tool to determine mediators released during impaired gut wall function. (J GASTROINTEST SURG 2004;8:645–652)

KEY WORDS: Mesenteric lymph, gastric motility, sepsis, peritonitis, cytokines

Gastrointestinal motility and gastrointestinal transit are strongly inhibited after an acute insult to the GI tract, such as abdominal surgery, peritonitis, or sepsis.[1] Recently, it has been illustrated that during the occurrence of peritonitis, hemorrhagic shock, or surgical trauma, intestinal derived inflammatory mediators like cytokines are predominantly released into mesenteric lymph rather than into the portal blood.

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These intestinal derived inflammatory mediators contribute to distant organ injury, such as to the lung,[2–4] and hemorrhagic shock-induced lung injury seems to be activated through mediators in the mesenteric lymph. Mesenteric lymph drains the interstitial fluid of the gastrointestinal tract, which contains the largest lymphatic system of the body, into the systemic circulation via the thoracic duct. The lung is the first organ exposed to the mesenteric lymph, and, accordingly, it has been illustrated that ligation of the mesenteric lymph duct prevented hemorrhagic shock-induced lung injury.[4] These results support the hypothesis that gut-derived inflammatory mediators released during an acute gastrointestinal insult alter distant organ function. However, it is unknown whether mediators in mesenteric lymph, released from the gut wall during peritonitis or sepsis, alter gastric motility and gastric emptying. We therefore investigated the effects of mesenteric lymph, collected during peritonitis or sepsis, on gastric motility and emptying in recipient rats.

MATERIAL AND METHODS

Animals

Male Sprague–Dawley rats (Harlan Industries, San Diego, CA), maintained on regular laboratory chow, were housed under controlled conditions of illumination (12:12 hours light/dark cycle starting at 07:00 hours p.m.), humidity, and temperature (21°C). Rats were fasted overnight but allowed water ad libitum before all surgical and experimental procedures. The institutional guidelines for the care and use of laboratory animals were followed throughout the study.

Mesenteric Lymph Collection

The method of mesenteric lymph duct cannulation has been previously published by the authors.[5] In brief, rats (260–300 g) were anesthetized with methohexital sodium (60 mg/kg intraperitoneally [ip]; Brevital, Jones Pharma Inc., St. Louis, MO) and the mesenteric lymph duct, draining the area of the superior mesenteric artery, was cannulated with a polyvinyl tube (Medical Grade, 0.50 mm inner diameter [ID], 0.80 mm outer diameter [OD], Dural Plastics, Sydney, Australia) fixed in place with a drop of ethyl cyanoacrylate glue (Krazy Glue, Elmers Products Inc., Columbus, OH) and externalized through a surgical incision in the right flank. A second cannula (silicone elastomer, 1 mm ID, 2.15 mm OD) was passed through the fundus of the stomach, extended 3 cm into the duodenum, secured in place with a silk suture, and additionally fixed with a drop of ethyl cyanoacrylate glue. After surgery, rats were placed in Bollman cages and a glucose-saline solution (glucose 0.2 mol/L, NaCl 145 mmol/L, and KCL 4 mmol/L) was infused continuously through the duodenal cannula at a rate of 3 ml/hour to equalize volume and energy losses via the lymph, which was draining freely. A steady condition of lymph flow of 2.5 ± 0.5 ml/hour after a 22-hour recovery period confirmed a nonobstructive lymph flow and confirmed that the cannula was appropriately positioned.

After 22 hours of recovery, abdominal lymph was collected for 2 hours during infusion of the glucose-saline solution, followed by a 12-hour collection period after an ip injection of either saline (1 ml, ip, n = 7, control lymph), acetic acid (0,5%, 1 ml, ip, n = 7, peritonitis lymph), or lipopolysaccharide (LPS; Sigma, St. Louis, MO; 5 mg/kg in 1ml, ip, n = 7, sepsis lymph). Lymph was collected in ice-chilled tubes, centrifuged, pooled for the animals within one group, and frozen and stored at −80°C for further experimental use. In each animal, only one attempt was initiated to place the lymph cannula in the superior mesenteric lymph duct. A total of four animals failed to reach nonobstructive lymph flow of 2.5 ± 0.5 ml/hour and were accordingly excluded from the experiments.

Recording of Gastric Motility

These methods have been published previously.[5] In brief, rats (200–250 g) were anesthetized with urethane (1.25 g/kg ip; Sigma, St. Louis, MO) and a catheter was placed into the trachea to ensure a clear airway (PE 240, 1.67 mm ID, 2.42 mm OD). After an upper abdominal laparatomy, the pylorus was ligated and the gastric contents were gently flushed out with warm saline 0.9% through an incision in the forestomach. A catheter (silicone elastomer, 2 mm ID, 3.2 mm OD) was introduced in the forestomach and secured with a purse-string suture to measure intraluminal gastric pressure (IGP). After a recovery period of approximately 45–60 minutes, the stomach was filled with warm saline (0.9%, 1 ml) and kept under a continuous pressure of 5–6 cm H_2O for 60 minutes to normalize baseline IGP. A catheter was placed in the jugular vein (PE 50, 0.58 mm ID, 0.965 mm OD) for administration of lymph. IGP was displayed online on a monitor and data were collected continuously on a computer. The maximal decrease of IGP was measured as maximal pressure decrease in cm H_2O from baseline IGP pressure. The duration (minutes) of decreased IGP was measured from the onset of decreased IGP until baseline IGP was reached again (Fig. 1, *A*). Changes of IGP are given as maximal decrease of IGP and duration (minutes).

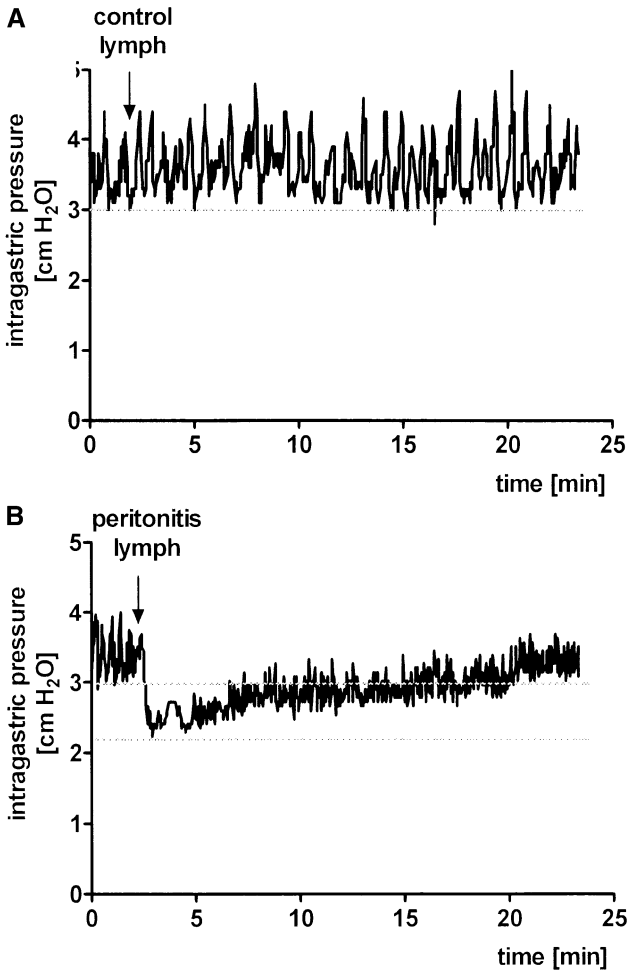

Fig. 1. Recording trace of intragastric pressure before and after control lymph injection (**A**) or peritonitis lymph injection (**B**). The baseline intragastric pressure is marked with a *dotted line* and is approximately 3 cm H_2O. After injection of peritonitis, lymph intragastric pressure rapidly decreases to approximately 2.2 cm H_2O (*lower dotted line*) and thereafter intragastric pressure increases slowly and reaches baseline activity at approximately 20 minutes.

Gastric motility was measured in four groups of urethane-anesthetized recipient rats in response to intravenous saline or lymph injections into the jugular vein (1 ml as bolus). Lymph samples were defrosted, stirred, centrifuged at 1000 g to eliminate cells and clots, and injected intravenously (iv). Group 1 animals (n = 6) received an injection with saline, group 2 animals (n = 10) received an injection with control lymph, group 3 animals (n = 10) received an injection with peritonitis lymph, and group 4 animals (n = 10) received an injection with sepsis lymph. IGP was recorded for 60 minutes after the lymph injection; thereafter in each experiment, sulfated CCK-8 (Sigma) (10 pmol in 0.1 ml intra-arterially) was injected, which served as a positive control to ensure the integrity of the preparation.

In a separate set of experiments, sepsis lymph or control lymph diluted 1:2, 1:4, and 1:8 in physiological saline (total volume 1 ml) was injected in a randomized order into recipient rats (n = 8, each group) and IGP was monitored for 20 minutes after each injection.

Recording of Gastric Emptying

Rats (260–300 g) were anesthetized with ketamine hydrochloride (Ketanest, 1 mg/kg, Parke Davis, Berlin, Germany) and xylasine (Rompun, 15 mg/kg, Bayer, Leverkusen, Germany). Polyethylene (PE) tubing (PE 50, 0.58 mm ID, 0.965 mm OD) was placed in the jugular vein and externalized through a skin incision in the neck. The tubing was blocked with heparin-sodium solution to prevent blood clotting and then closed. Three days later, gastric emptying was measured in response to continuous intravenous lymph infusion for 1 hour at a rate equal to the average lymph flow rate of the donor rats (3 ml/hour). In enflurane anesthesia, a semisolid test meal, marked with Cr^{51}-ethylenediaminetetraacetic acid (EDTA) (gum arabic 0.25 g, charcoal 0.005 g; Cr^{51}-EDTA, approximately 180 000 μCi, in 0.5ml) was given as a bolus into the stomach by gavage. Rats recovered from enflurane anesthesia within 2 minutes and were kept in their home cages for another 20 minutes. The stomach and the small intestine were then dissected out and radioactivity was measured in the stomach and in the small intestine using a gamma counter. Gastric emptying was calculated as the percentage of radioactivity emptied into the small intestine.

Group 1 animals (n = 8) received an infusion with physiological saline, group 2 animals received control lymph (n = 8), group 3 animals (n = 8) received an infusion with peritonitis lymph, and group 4 animals (n = 8) received sepsis lymph. The test meal was given at the end of the mesenteric lymph infusion and gastric emptying was measured 20 minutes later.

Real-time TaqMan PCR

TNFα gene expression was measured in the gut wall of the jejunum in untreated rats (basal TNFα gene expression) and in rats 2, 12, and 24 hours after LPS injection (n = 4 for each time point). Additionally, TNFα gene expression was measured in cellular components of the mesenteric lymph after saline or LPS injection (pooled samples 0–12 hours after saline or LPS injection).

The primers and TaqMan probes were designed over an exon–exon junction to discriminate between genomic DNA and complementary DNA as described

previously.[6] Primer and TaqMan probe oligonucleotides were as follows (all 5' to 3'): glyceraldehyde-3-phosphate dehydrogenase (GAPDH; endogenous control) forward primer rGAPHD.170f: AAGCTGGTCATCAATGGGAAAC; reverse primer rGAPDH.280r: GAAGACGCCAGTAGACTCCACG; TaqMan probe rGAPDH.200p: 6FAM-ATCTTCCAGGAGCGCGATCCCG-TAMRA; forward primer TNFα-198f: TGGGCTCCCTCTCATCAGTT; reverse primer TNFα-281r: TGGGCTACGGGCTTGTCA; TaqMan probe TNFα-224p: 6FAM-CCCAGACCCTCACACTCAGATCATCTTCT-TAMRA. GenBank accession numbers were GAPDH: AB017801; TNFα: M38296. Every TaqMan PCR product was sequenced once to verify analytical specificity. Amplification efficiency was obtained on twofold diluted cDNA and the slope of the standard curve was compared with the one of GAPDH; the two TaqMan systems were within the 10% tolerance as defined by Applied Biosystems (Applied Biosystems, Foster City, CA).

RNA Extraction, cDNA Synthesis, and TaqMan PCR Analysis

Total RNA was extracted using silica-based spin columns (RNeasy; Qiagen, Valencia, CA) according to the manufacturer's recommendations. Reverse transcription was performed in a 20 ml final volume containing 50 U SuperScript II (Life Technologies, Gaithersburg, MD) reverse transcriptase, 5 mM $MgCl_2$, 10 mM Tris-HCl (pH 8.3), 50 mM KCl, 1.25 mM random hexadeoxyribonucleotide ($pd(N)_6$) primers (random hexamer primer, Amersham Pharmacia Biotech, Piscataway, NJ), 0.5 U/ml RNase inhibitor (RnaseOut; Life Technologies, Gaithersburg, MD), and 1 mM dNTPs (Amersham Pharmacia Biotech, Piscataway, NJ). The mixture was subjected to 42°C for 50 minutes, inactivated at 95°C for 5 minutes, and diluted 1:5 using PCR-grade water. The cDNA was analyzed immediately or stored at −20°C until use. Real-time TaqMan PCR systems for rat GAPDH and the target genes were run in separate wells. The PCR reactions contained 400 nM of each primer, 80 nM of the TaqMan probe and commercially available PCR mastermix (TaqMan Universal PCR Mastermix; Applied Biosystems), containing 10 mM Tris-HCl (pH 8.3), 50 mM KCl, 5 mM $MgCl_2$, 2.5 mM deoxynucleotide triphosphates, 0.625 U AmpliTaq Gold DNA polymerase per reaction, 0.25 U AmpErase UNG per reaction, and 10 ml of the diluted cDNA sample in a final volume of 25 ml. The samples were placed in 96 well plates and amplified in an automated fluorometer (ABI PRISM 7700 Sequence Detection System; Applied Biosystems). Amplification conditions were 2 minutes at 50°C, 10 minutes at 95°C, 40 cycles of 15 seconds at 95°C, and 60 seconds at 60°C.

Final Quantification of Gene Transcription

Final quantification was calculated with the comparative CT method (ABI User Bulletin No. 2): Target gene signals were normalized with the GAPDH signal (dCT) and calibrated with signals from carrier-treated animals (ddCT). The normalized and calibrated values were transformed into linear values according to the formula 2_{ddCT}. Thus, all experimental samples are expressed as an n-fold difference relative to the calibrator.

TNFα Detection in Mesenteric Lymph

TNFα was measured in control lymph (NaCl ip, n = 7), peritonitis lymph (acetic acid ip, n = 7), and sepsis lymph (LPS ip, n = 7) and was collected 12 hours after treatment by a specific enzyme-linked immunosorbent assay (ELISA) test (KRC 3011; Biosource, Solingen, Germany).

Statistical Analysis

Data are presented as mean ± standard error of the mean (SEM). Differences between groups were determined by the double-sided Student's *t* test using the software package of GraphPad Prism 3.02 (GraphPad Software, San Diego, CA). A probability of p less than 0.05 was taken as significant.

RESULTS

Effects of Peritonitis or Sepsis on Mesenteric Lymph Flow

After a recovery period of 24 hours, abdominal lymph flow during intestinal glucose-saline infusion reached a steady state of approximately 2.5 ml/hour in all groups. Vehicle injection did not alter the mesenteric lymph flow (average hourly lymph flow: 2.4 ± 0.04 ml/hour). However, induction of peritonitis or sepsis increased the mesenteric lymph flow significantly (average hourly lymph flow, peritonitis: 2.67 ± 0.07 ml/hour; sepsis: 3.25 ± 0.1 ml/hour; both $p < 0.01$ vs. vehicle). Lymph flow increased maximally by 72% approximately 4 hours after LPS treatment (4.2 ml/hour, Fig. 2).

Effects of Peritonitis or Sepsis Lymph on Gastric Motility

Gastric motility was significantly decreased after injection of peritonitis or sepsis lymph into recipient

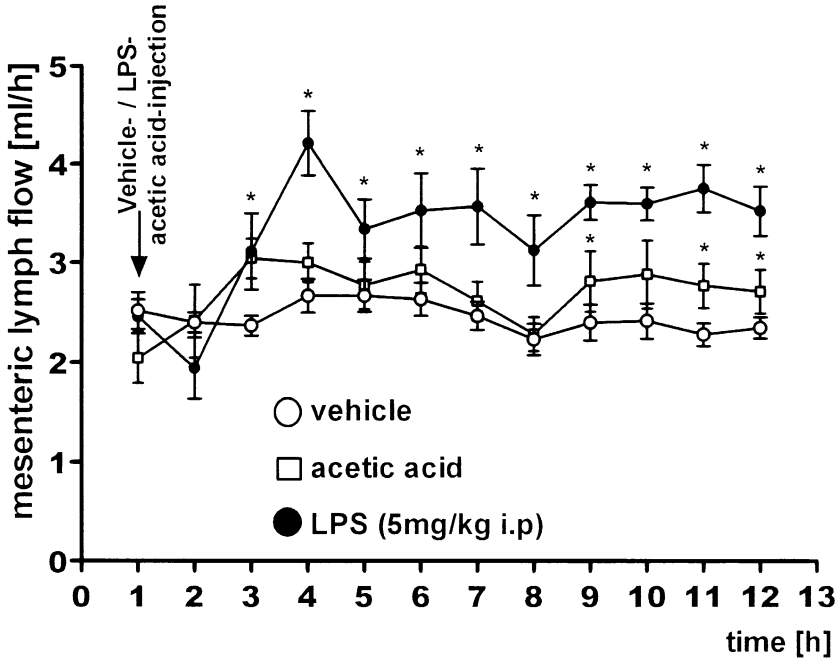

Fig. 2. Induction of sepsis increased the mesenteric lymph flow significantly throughout the recording period, whereas during peritonitis a moderate increase of lymph flow was measured (n = 7 each group). *$p < 0.01$ vs. control.

rats. Injection of control lymph exhibited only minimal effects on gastric motility and did not differ from the injection of saline (Fig. 3). In addition, gastric motility was inhibited for a significantly longer period of time after an injection of peritonitis or sepsis lymph, as compared with an injection of control lymph (inhibition of gastric motility: saline: 1.46 ± 0.87 minutes; control lymph: 1.89 ± 1.31 minutes; peritonitis lymph: 9.9 ± 0.9 minutes*; sepsis lymph: 6.9 ± 0.6 minutes*; *$p < 0.001$ vs. control lymph).

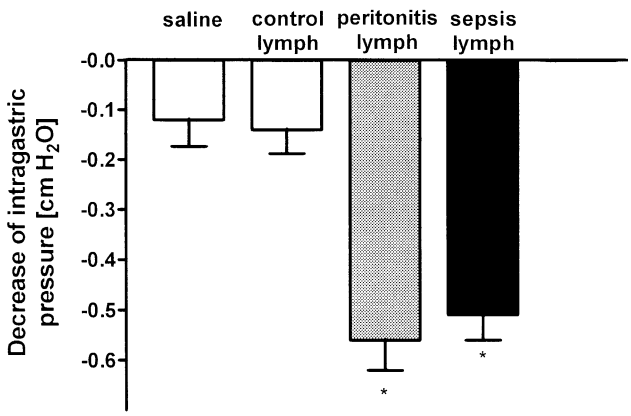

Fig. 3. Gastric motility was significantly inhibited after injection of peritonitis or sepsis lymph (decrease in intragastric pressure; saline (n = 6): 0.12 ± 0.07 cm H_2O; control lymph (n = 10): 0.14 ± 0.05 cm H_2O; peritonitis lymph (n = 10): 0.56 ± 0.06 cm H_2O; sepsis lymph (n = 10): 0.51 ± 0.05 cm H_2O). *$p < 0.001$ vs. control lymph.

Control and sepsis lymph diluted 1:2, 1:4, and 1:8 were significantly less potent in inhibiting gastric motility than undiluted sepsis lymph (decrease in intragastric pressure and duration: control lymph [pure] −0.14 ± 0.05 cm H_2O, 1.89 ± 1.31 minutes; control lymph (1:2) −0.11 ± 0.04 cm H_2O, 1.21 ± 0.91 minutes; control lymph (1:4) −0.13 ± 0.06 cm H_2O, 0.87 ± 0.34 minutes; control lymph (1:8) −0.14 ± 0.05 cm H_2O, 0.9 ± 0.1 minutes; sepsis lymph (pure) −0.51 ± 0.05 cm H_2O, 6.9 ± 0.6 minutes; sepsis lymph (1:2) −0.38 ± 0.06 cm H_2O, 4.2 ± 0.8 minutes; sepsis lymph (1:4) −0.23 ± 0.06 cm H_2O, 2.1 ± 0.72 minutes; sepsis lymph (1:8) −0.16 ± 0.05 cm H_2O, 1.3 ± 0.5 minutes; $p < 0.05$ vs. sepsis lymph (pure) for all comparisons).

Effects of Sepsis Lymph on Gastric Emptying

Gastric emptying was significantly inhibited by continuous infusion of sepsis lymph into awake recipient rats. Approximately 80% ± 6% and 65% ± 9% of the semisolid test meal was emptied into the small intestine after control lymph and peritonitis lymph infusion, respectively, not being different from saline infusion (81% ± 4%). Gastric emptying was significantly decreased to 44% ± 10% during continuous infusion of sepsis lymph (Fig. 4).

Effects of Sepsis on TNFα Gene-Expression in the Gut Wall and in Mesenteric Lymph Cells

LPS treatment significantly increased TNFα gene-expression in the gut wall of the jejunum to

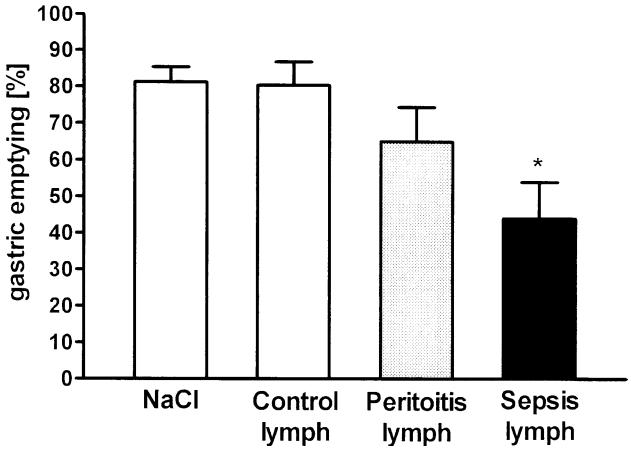

Fig. 4. Gastric emptying was significantly reduced after continuous infusion of sepsis lymph (n = 8 each group). *$p < 0.001$ vs. control or saline.

greater than 80-fold within the first 2 hours, as compared with basal gene expression, but continuously decreased thereafter (Fig. 5, relative TNFα mRNA transcription: basal 1.0 ± 0.05; LPS 2 hours: 91.9 ± 2.6, $p < 0.001$ vs. basal; 12 hours: 24.7 ± 16.8, NS; 24 hours: 7.0 ± 3.4, NS). TNFα gene-expression increased greater than 60-fold in cellular components of sepsis lymph compared with control lymph (relative TNFα gene expression: control lymph 1.0 ± 0.04; sepsis lymph 61 ± 10.35; $p < 0.001$ vs. control lymph).

Effect of Peritonitis and Sepsis on TNFα Release into Mesenteric Lymph

TNFα was significantly increased by approximately 2.8-fold and 19-fold, respectively, in mesenteric lymph during peritonitis or sepsis (control lymph 83 ± 24 pg/ml, peritonitis lymph 233 ± 39 pg/ml*, sepsis lymph 1583 ± 197 pg/ml**, *$p < 0.05$ vs. control lymph, **$p < 0.001$ vs. control lymph).

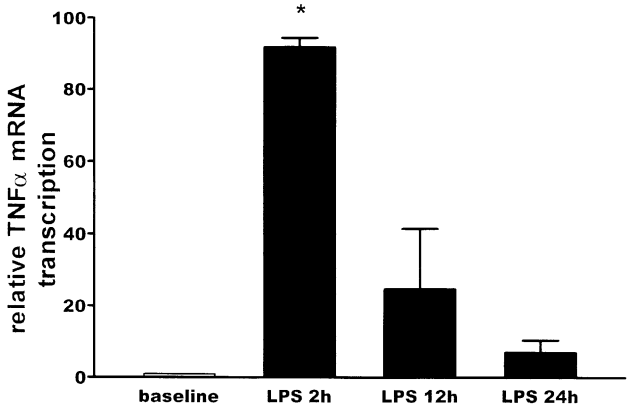

Fig. 5. TNFα gene expression in the gut wall of the jejunum significantly increased after LPS treatment by greater than 80-fold within 2 hours compared with baseline TNFα gene expression, but continuously decreased thereafter (n = 4 each time point). *$p < 0.001$ vs. control.

DISCUSSION

The present study demonstrates that mesenteric lymph collected from donor rats during peritonitis or sepsis potently inhibits gastric motility and gastric emptying when injected into recipient rats. The mesenteric lymph flow was significantly increased after peritonitis or sepsis, TNFα gene-expression was significantly increased in the gut wall and in lymph cells during sepsis, and, accordingly, TNFα in mesenteric lymph was significantly increased during sepsis. Our data suggest that gut-derived mediators, possibly released from neuronal sources or inflammatory cells in the gut wall that are drained into the mesenteric lymph and reach the systemic circulation via the thoracic duct, are involved in peritonitis-derived and sepsis-derived inhibition of gastrointestinal motility and transit. Because the composition of lymph reflects the interstitial fluid, mediators released into the interstitium during gut injury may be transported via lymph to distant sites to alter gastrointestinal and other visceral functions.

Acute insults to the gut, such as abdominal surgery, peritonitis, or sepsis are known to result in inhibition of gastrointestinal motility.[7,8] This can cause a variety of problems to develop in surgically ill patients, such as nausea, vomiting, aspiration pneumonia, and bacterial translocation from the gut lumen to the blood. Total enterale nutrition is delayed and the recovery period can be considerably prolonged in these patients. The pathways and mechanisms mediating insult-associated inhibition of gastrointestinal motility are largely unknown, but likely involve effects at the level of enteric neurons, the pacemaker cells of the intestine (interstitial cells of Cajal [ICC]), vagal, and spinal afferents, the brain stem, and the central nervous system.[9,10]

Abdominal surgery leads to activation and invasion of immune cells into the gut followed by mediator release.[11,12] Histologically similar responses are observed during peritonitis[13] and during sepsis.[14,15] Recently, it has been demonstrated that the gut can produce and release a variety of mediators including proinflammatory cytokines after an acute insult induced by peritonitis or hemorrhagic shock.[2,3] Further, it has been demonstrated that these gut-derived mediators are contained in mesenteric lymph in concentrations up to sevenfold higher than in peripheral or portal blood.[2,16] It is plausible that these mediators

enter the lymphatic system, because they are primarily released by activated immune cells into the interstitium, which is drained by the mesenteric lymphatic system. Other studies have indicated that mesenteric lymph, but not portal blood, was able to increase endothelial cell permeability and contributed to lung injury after hemorrhagic shock, whereas drainage of the mesenteric lymph prevented hemorrhagic shock associated with lung injury.[4,16,17] Also, when TNFα (1000 pg) was injected iv in healthy recipient rats, a concentration according to sepsis lymph, the motility index (MI) for the stomach (MI: area under the curve treatment/area under curve baseline × 100) measured with strain gauge transducers was reduced by 31% compared with saline injection (MI: saline vs. TNFα 103 ± 12 vs. 71 ± 11).[18] These results indicate that the mesenteric lymphatic route is important in draining gut-derived mediators into the systemic circulation via the thoracic duct and that these mediators can influence distant organ function.

Several pathways have been identified as being involved in the inhibition of gastrointestinal motility and transit after an acute insult to the gut. It has been illustrated that mediators such as proinflammatory cytokines released from activated immune cells are able to decrease muscle contractility, mediated likely through inhibitory pathways within the gut.[11,19] Additionally, pathways involving visceral afferent nerve fibers have been identified to be essential in mediating inhibition of gastrointestinal motor function after surgery.[1] Signal transduction pathways from the viscera to the central nervous system (e.g., by spinal afferents as well as centers in the brain stem such as the nucleus tractus solitarius and the area postrema that can function as primary central nervous system detectors of blood-borne mediators such as cytokines) are also likely to be involved in regulating gastrointestinal motility after acute insults to the gut.[20,21]

CONCLUSION

The present studies have demonstrated that gut-derived mediators in mesenteric lymph, released during peritonitis or sepsis, potently inhibit gastric motility and emptying. Because the composition of mesenteric lymph probably reflects the interstitial fluid of the gut wall, monitoring visceral lymph might be an extremely beneficial tool to determine mediators released during impaired gut wall function. However, it remains to be determined whether these mediators are released from neuronal sources or from activated immune cells. Further, the pathways involved are yet to be determined.

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Survival and Functional Quality of Life After Resection for Hepatic Carcinoid Metastasis

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Retrospective studies suggest that resection improves 5-year survival for patients with hepatic carcinoid metastasis (HCM). The purpose of our study was to describe clinical outcomes following resection for HCM, including survival and longitudinal functional quality of life (QOL). We reviewed the records of patients undergoing resection for HCM from 1980 to 2001 at our institution. Outcome measures included tumor symptoms, biochemical tumor markers, functional QOL through Karnofsky functional scores, and survival. Thirteen patients underwent a total of 17 resections. Overall 5-year survival was 85%. Eleven patients were symptomatic, including eight with classic carcinoid syndrome. Nine experienced complete relief of symptoms and two had incomplete relief for 30 ± 12 months. Eight patients had elevated tumor markers, and 50% of these had postoperative normalization of all tumor markers that persisted to the close of the study. For the 10 patients with longitudinal follow-up available to 54 months, significant improvement in functional QOL was observed at all follow-up time points compared to preresection functional QOL ($P < 0.05$). Resection of ⩾90% tumor volume was significantly associated with more favorable survival and tumor marker normalization compared to resection of <90% tumor volume ($P < 0.01$ and $P < 0.05$, respectively), but trajectory of functional QOL improvement did not differ between these two groups ($P = 0.24$). We conclude that resection for HCM is associated with significantly improved and sustained functional QOL and prolonged survival. Resection of ⩾90% tumor volume is significantly associated with extended survival and normalization of tumor markers, but is not required for symptomatic or functional QOL improvement. (J GASTROINTEST SURG 2004;8:653–659)

KEY WORDS: Carcinoid, liver, metastatic, neuroendocrine tumor, resection

Carcinoid tumors are of neuroendocrine origin and may produce a wide range of biologically active peptides. They generally follow an indolent course compared to the more malignant neuroendocrine carcinomas, but can be unpredictable and often cause disabling symptoms.[1] The term "karzinoid" was first used by Oberndorfer[2] in 1907 to describe tumors that resembled adenocarcinomas but appeared to be more benign. Carcinoid tumors typically show minimal pleomorphism and low mitotic index, and do not exhibit large areas of necrosis.[3] Seventy-four percent of carcinoid tumors arise in the gastrointestinal tract, the majority of these being in the appendix or ileum.[4]

Regardless of origin, approximately 75% of patients with carcinoid tumors will develop liver metastasis.[5–7] Hepatic carcinoid metastases (HCM) often cause carcinoid syndrome, characterized by flushing, diarrhea, and abdominal cramping.[1] The prognosis for patients with HCM is poor, with 5-year survival

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ranging from 20% to 30%.[6–10] Despite the increasing number of therapeutic modalities available to patients with HCM, surgical resection (RSX) for selected patients remains the best choice for prolonged survival. Although no prospective studies have proved this point, a number of retrospective studies have suggested it.[11–17] Some of these studies have also established decreased symptoms after RSX, but no quantitative analyses of change in functional QOL after RSX alone for HCM have been performed. Because definitive cure for HCM is almost impossible and recurrence rates after RSX approach 100%, treatment of HCM is essentially a question of effective long-term palliation with improved QOL and survival extension. We reviewed the experience at Vanderbilt University Medical Center (VUMC) with patients who underwent hepatic RSX for HCM between 1980 and 2001 to assess outcome measures including biochemical markers, symptomatic response, survival, and functional QOL.

PATIENTS AND METHODS

After obtaining approval from the institutional review board, we reviewed data prospectively gathered by the VUMC Tumor Registry for patients diagnosed with carcinoid tumors between 1980 and 2001. Hospital and clinic charts were reviewed if the patient had confirmed HCM by CT scan, octreotide scan, ultrasonography, and/or confirmed pathologic findings after exploratory laparotomy. Patients with extensive extrahepatic metastases were excluded. Only patients who underwent RSX for treatment of their hepatic metastases at our institution qualified for this study.

Demographic data included sex and age at the time of diagnosis of the metastatic carcinoid and at the time of hepatic RSX. Clinical data included location and treatment of the primary carcinoid tumor, any nonoperative carcinoid treatments, time to tumor recurrence after RSX, number of subsequent resections, and overall length of survival.

Symptoms attributed to the metastatic disease and the duration of symptomatic response (if any) after RSX were also noted. Symptomatic response was judged to be relief from carcinoid syndrome as well as relief from any symptoms directly attributable to the physical or biochemical activity of the HCM. Extent and duration of symptomatic relief from the HCM were used as outcome measures. Response was classified as complete, incomplete, or negative, as reported by other investigators.[12]

Biochemical analysis was used as an objective outcome measure. Tumor markers reviewed included serum levels of neuron-specific enolase, chromogranin-A, and/or urinary 5-hydroxyindoleacetic acid (5-HIAA). Changes in preoperative vs. 3-month postoperative tumor markers were compared. Liver function was assessed by serum levels of albumin, total bilirubin, and alkaline phosphatase. Transaminases were considered to be abnormal if any were one multiple or greater out of the normal range.

Radiographic data included evidence of residual metastatic tumor on postoperative studies (CT, octreotide scan, and/or ultrasonography), overall percentage of tumor excised, and evidence of recurrence after complete excision.

Operative reports were reviewed to determine intent and outcome of each hepatic RSX and percentage of tumor excised. Resections were considered complete if all gross tumor was removed and pathologic margins were negative, and if postoperative imaging revealed no residual tumor. Resections were considered incomplete if any tumor remained either visibly, palpably, or on postoperative imaging.

Histologic characteristics of the disease were assessed by reviewing the pathology specimens. Routinely processed hematoxylin and eosin–stained slides from each case were reviewed by a single pathologist (L.W.L.) to confirm the diagnosis of carcinoid tumor. Attention was given to morphologic pattern, nuclear pleomorphism, mitotic rate, necrosis, and presence or absence of lymphovascular invasion.

Patient functional performance was assessed by means of the method reported by Karnofsky et al.[18] The Karnofsky functional score ranges from 0 to 100 and includes the following ranges: ability to carry out normal work and activity (80–100), inability to work but ability to care for most personal needs with varying amounts of assistance (50–70), and inability to care for one's self and/or the need for chronic hospitalization (0-40). Karnofsky functional scores were assigned preoperatively, 3 and 6 months postoperatively, and annually thereafter.

Preoperative and/or follow-up data from other institutions or by phone calls to patients were obtained, when necessary, to complete the database. Follow-up was 100% at the close of the study. Survival data were analyzed by means of the Kaplan-Meier method. Repeated-measures and mixed-model analysis of variance were used to test the effects of clinical factors such as resection (before vs. after), resection group ($<90\%$ vs. $\geqslant 90\%$), and their interaction on functional QOL. Unless otherwise noted, summary data are reported as means $\pm$ standard error of the mean.

RESULTS

Patients

Through the Tumor Registry review, 184 patients with the diagnosis of carcinoid tumor were identified

between 1980 and 2001 at VUMC. Thirteen of these patients (7%) had isolated, resectable HCM and were included in the analysis. The 13 patients had a mean age at diagnosis of HCM of 47.0 ± 2.3 years (range 33 to 65 years) and four (31%) were male. Seven patients (54%) had received nonoperative treatment for their liver metastases before undergoing RSX: six patients had received octreotide therapy for 25.7 ± 14.4 months, and three patients received a total of four hepatic artery chemoembolizations. Ten patients (77%) underwent resection of their primary carcinoid tumor either in conjunction with (n = 6) or prior to (n = 4) their liver RSX. One patient had previously undergone cryoablation of multiple small liver metastases. Locations of primary tumors included the following: small bowel in five patients, pancreas in one, colon in one, rectum in one, liver in one, and lung in one. Three patients had primary lesions of unknown origin.

Hepatic Resections

Thirteen patients underwent a total of 17 hepatic resections at a mean age of 49 ± 2.6 years (range 35 to 69 years). Types of RSX included hemihepatectomy (n = 2), hemihepatectomy and partial RSX of the remaining lobe (n = 4), and wedge/segmentectomy (n = 11). Nine patients (69%) underwent attempts at complete RSX and four patients underwent RSX for palliation only. Six of the nine patients who underwent an attempt at complete RSX actually had resections that were pathologically and radiographically complete, for a total of seven patients who underwent incomplete RSX. After all 17 resections in the 13 patients, 10 patients had ⩾90% of the liver tumor mass resected (RSX ⩾90%), whereas three patients had <90% resected (RSX <90%). There were no perioperative deaths and a total of four complications for the 17 resections. Mean hospital stay was 10.9 ± 1.9 days (median = 8 days).

Pathologic Findings

Eleven patients (85%) had bilobar liver involvement, and two patients had disease confined to one lobe of the liver. The average size of the largest tumor resected was 7.8 ± 1.1 cm. Five patients had three tumors or less, two had 4 to 10 tumors, and six had more than 10 tumors present in the liver at RSX. All tumors examined fell into the category of regular carcinoid, rather than atypical carcinoid or neuroendocrine carcinoma—that is, no significant nuclear atypia, no increase in mitoses, and no extensive necrosis. They all exhibited foci of lymphovascular invasion away from the tumor nodules in the grossly normal liver parenchyma.

Tumor Recurrence

Among the 13 patients, six had resections that were considered complete and seven patients had variable amounts of residual tumor. Four of the six patients who had initially complete resections had recurrence of HCM that was radiographically verifiable at 9, 9, 56, and 104 months, and in one patient in the adrenal glands at 19 months. The remaining patient has no evidence of recurrence at 93 months.

Symptoms

Of the 13 patients, 11 (85%) had at least some preoperative symptoms associated with their HCM including, but not limited to, flushing, tachycardia, diarrhea, abdominal pain, fatigue, early satiety, nausea, vomiting, and/or weight loss. Eight of these patients exhibited classic carcinoid syndrome. Of the 13 patients, two (15%) were asymptomatic preoperatively and remained so during their postoperative courses. Fig. 1 summarizes the postoperative duration of symptom relief. There was no significant difference in symptomatic responses between RSX ⩾90% and RSX <90% patients (data not shown). Nine (82%) of the 11 symptomatic patients experienced complete relief from all symptoms, and two patients had incomplete relief. Six of the nine patients experiencing complete relief had partial or total recurrence of their symptoms at 4, 8, 12, 20, 30, and 44 months (mean 20.0 ± 6.1 months). Three patients had no recurrent

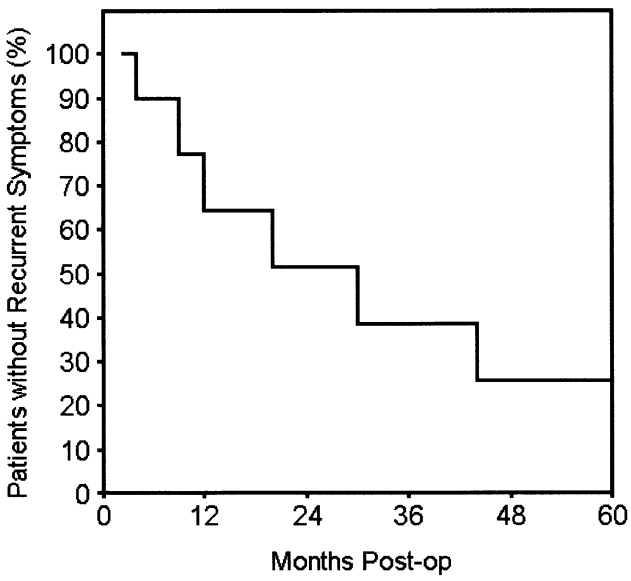

Fig. 1. Kaplan-Meier plot showing duration of symptomatic response (initially complete in 9 patients and incomplete in 2 patients) for patients undergoing resection for hepatic carcinoid metastasis.

symptoms. The average duration of symptomatic response for the 11 patients experiencing both complete and incomplete relief was 30 ± 12 months.

Biochemical Data

All 13 patients had normal biochemical liver function preoperatively and postoperatively. Eight (62%) of the 13 patients had at least one elevated tumor marker before undergoing RSX. Four of these eight patients experienced postoperative normalization of all tumor markers; three patients experienced decreases of two- and four-fold and in one patient values were unchanged. Five of the eight patients underwent RSX ⩾90%; four of the five had postoperative normalization of all tumor markers and the remaining patient showed a four-fold decrease in markers (all persisting at the close of the study). Three of the eight patients underwent RSX of <90% tumor volume, and none had postoperative normalization. Two of the three experienced two- to three-fold decreases in tumor marker values, and values remained unchanged in one. The difference in responses between the two groups (RSX ⩾90% vs. RSX <90%) was significant ($P < 0.05$).

Functional Quality Of Life

Average functional QOL improved by the postoperative month 3 in the 13 patients from a Karnofsky Functional Score of 75 ± 5 to 88 ± 5 ($P < 0.01$). The amount of tumor resected (⩾90% vs. <90%) did not influence the trajectory of this improvement (group by time interaction effect $P = 0.26$) (Fig. 2).

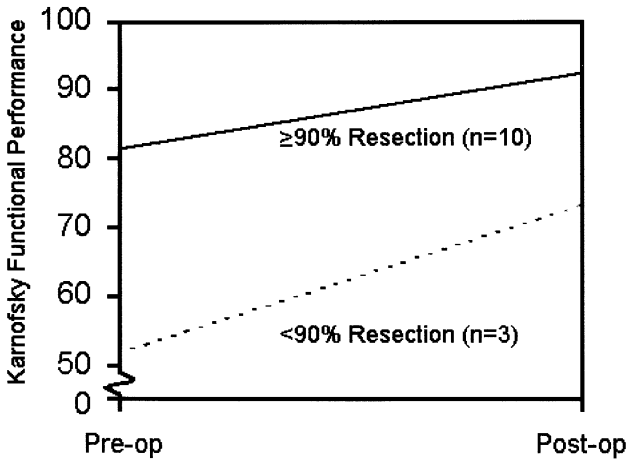

Fig. 2. Three-month postoperative increase in Karnofsky functional performance score in patients undergoing resection of ⩾90% vs. <90% total liver tumor volume. Although the starting points differ, the trajectory of the increase did not differ between the two groups (group by time interaction effect, $P = 0.24$).

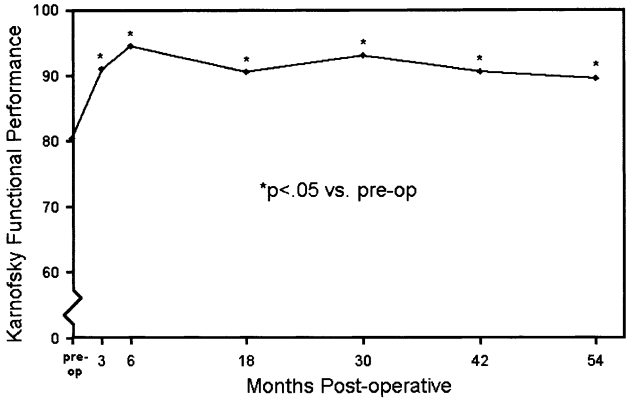

Fig. 3. Longitudinal Karnofsky functional performance score for the 10 patients with follow-up to 54 months. Overall, patients experienced a statistically significant improvement in functional performance after resection (*$P < 0.05$).

Although those with less extensive resections had lower preoperative functional QOL scores in comparison to those with ⩾90% of their tumors resected (Karnofsky Functional Score = 52 ± 8 vs. 82 ± 4, respectively; $P < 0.01$), both groups' average functional QOL improved substantively (by more than 10 points on the Karnofsky scale) by the postoperative month 3 (to Karnofsky Functional Score = 73 ± 9 and 93 ± 3, respectively). The overall longitudinal functional QOL in 10 patients who survived through postoperative month 54 or longer is depicted in Fig. 3. For these 10 patients, a statistically significant improvement ($P < 0.05$) was observed by postoperative

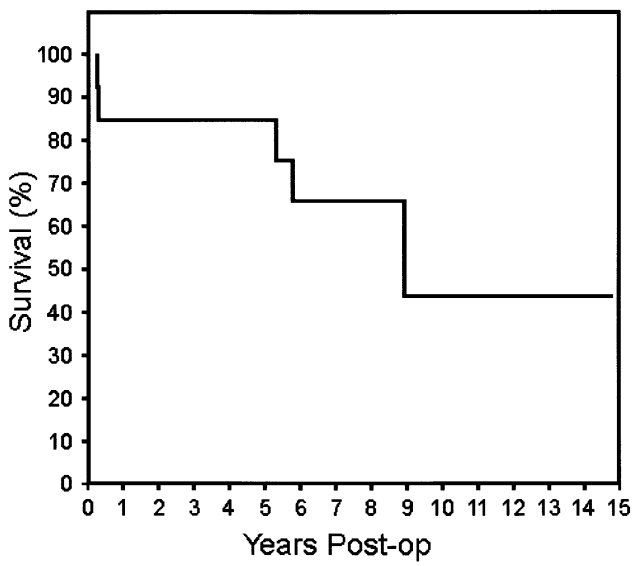

Fig. 4. Kaplan-Meier survival curve for all patients undergoing liver resection for hepatic carcinoid metastasis.

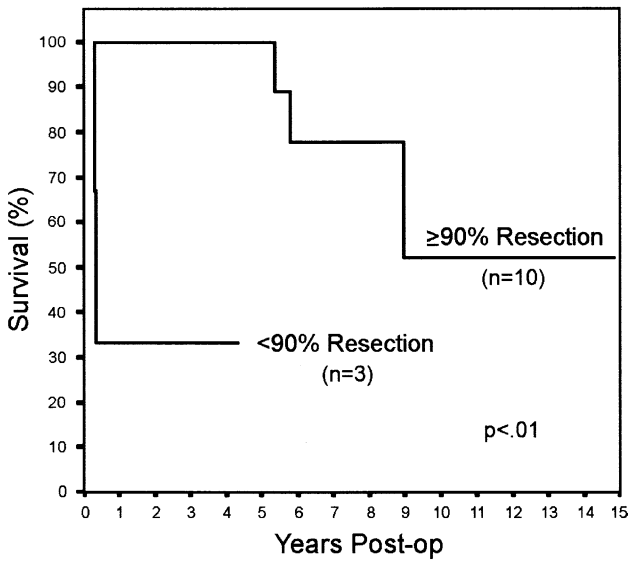

Fig. 5. Kaplan-Meier survival curves for patients undergoing resection of ⩾90% vs. <90% total liver tumor volume. Patients undergoing resection of ⩾90% tumor volume lived significantly longer ($P < 0.01$).

month 3 and was sustained through postoperative month 54.

Survival

Actuarial 1, 5, and 8-year survival was 85%, 85%, and 66%, respectively (Fig. 4). Five patients (38%) died at 4, 4, 64, 70, and 104 months, respectively. Mean survival for RSX ⩾90% vs. RSX <90% patients was 135 ± 19 vs. 19 ± 13 months ($P < 0.01$; Fig. 5). Increased age at diagnosis of liver metastasis, which was classified as being ⩾45.6 years (fiftieth percentile for this sample) or <45.6 years, was significantly associated with reduced survival ($P < 0.01$). However, given the significant correlation ($r = -0.59$, $P < 0.05$) between age group (⩾ vs. < fiftieth percentile) and the extent of resection performed (⩾ vs. < 90%), this finding is likely a spurious effect and a function of disease progression. Sex was not a significant predictor of survival ($P = 0.48$), nor was the presence of carcinoid syndrome ($P = 0.79$), the gross outcome of RSX (complete vs. incomplete, $P = 0.22$), or the type, if any, of preoperative treatment for HCM ($P = 0.99$).

DISCUSSION

There is no single, universal treatment that can be successfully offered to all patients with HCM. Patients present with varying degrees of metastases, tumor growth rates, and symptoms. In decades past, complications caused by hormonal abnormalities were the leading cause of death for patients with HCM, but somatostatin analogs now offer excellent control of these symptoms. Other options include hepatic arterial embolization, hepatic arterial chemoembolization, radiofrequency ablation, radiation therapy, and liver transplantation. There is no available chemotherapy regimen to effectively treat carcinoid tumors.[19] Bulky progression of tumor mass has become the leading cause of death for patients with HCM, making RSX more attractive.[11] As Pascher et al.[20] pointed out, there is an unfortunate lack of prospective studies on the role of RSX for HCM, mostly because of the indolent nature and infrequency of this disease and the wide range of treatment strategies reported in the literature. However, the studies that have reported experiences with RSX show favorable results for these patients.[11–17] With an average 5-year survival for all HCM patients reported to be around 30%,[6,7,10] it is not surprising that surgical RSX, which has reported 10-year survival rates as high as 100%,[13] is aggressively pursued.

Our study showed 5- and 8-year actuarial survival after RSX for HCM to be 85% and 66%, respectively, including incompletely resected patients. This is fairly consistent with other results in the literature. Wangberg et al.[13] reported on 14 patients with HCM who underwent radical RSX with 10-year actuarial survival of 100%, and all had postoperative normalization of tumor markers. Such successful outcomes are likely related to the fact that only patients with unilobar liver metastasis were considered for RSX, and all resections were anatomically curative. Yao et al.[11] reviewed the records of 16 patients with neuroendocrine tumors metastatic to the liver who underwent resection. This study included patients with both unilobar and bilobar metastases, but only patients with apparently completely resectable HCM as well as resectable primary tumors were considered for RSX. All 16 of the RSX patients had normalization of tumor markers, and their 5-year survival was 70%. Chamberlain et al.[15] reviewed 34 patients undergoing RSX and found their 1-, 3-, and 5-year survival rates to be 94%, 83%, and 76%, respectively. Our survival results with a varied group of resected patients is therefore consistent with those reported in the literature.

One of the biggest problems with the retrospective comparisons of HCM patients found in the literature is the extent of their disease. Only 10% of patients with HCM will be surgical candidates, and their tumors will differ anatomically from those in patients who are ineligible for RSX.[6,12] Patients with HCM are generally not candidates for RSX because of the more extensive nature of their hepatic or

extrahepatic disease on evaluation for therapy. Thus, a retrospective comparison between resected and unresected HCM patients is often a comparison between two groups of patients who differ in terms of the initial extent of their liver disease and can be inherently biased in favor of resected patients. McEntee et al.[12] agree that HCM groups can not be meaningfully compared because in most studies only patients with localized or predominantly unilobar disease are considered for RSX.

Chen et al.[17] attempted to avoid this problem by comparing resected and unresected patients who did not differ significantly on the basis of age, pathologic findings, serum alkaline phosphatase levels, primary tumor site, or percentage of liver involved with tumor. Both groups had the same average of 19% liver involvement on evaluation for surgery. Fifteen patients underwent grossly curative RSX with 5-year actuarial survival of 73%, whereas 23 patients did not undergo RSX and had an actuarial 5-year survival of 29%. Of note is that a significant difference in bilobar tumor involvement was seen between the two groups (76% in unresected vs. 27% in resected patients), which again highlights the difficulties inherent in comparing these two groups.[17] Nonetheless, this study used perhaps the least biased retrospective design and demonstrated significantly better prognosis for resected patients. Despite the better comparative groups, however, the 5-year survival in the RSX group was essentially equivalent to that in our study and most others in the literature.

The question therefore becomes one of selection criteria for surgery. Foster and Berman[21] reported as early as the 1970s that 90% resectability should be the cutoff point for RSX for liver metastatic carcinoid. They found that although complete RSX is naturally the preferred outcome, palliative RSX is warranted when at least 90% of the tumor mass can be removed. This finding had been endorsed by others since then.[12,14,15] In our analysis, patients undergoing RSX $\geq$90% lived significantly longer than patients undergoing RSX $<$90%, and they also had a significantly better biochemical response ($P < 0.05$). A number of factors may have contributed to this fact. The three RSX $<$90% patients were above the fiftieth percentile for age at diagnosis of HCM and had primary tumors of unknown origin, both of which have been shown to influence survival after RSX.[15] All three had at least 10 distinct hepatic carcinoid tumors found during surgical exploration, and tumor volume has been correlated with survival.[10] These patients did not experience normalization of their tumor markers postoperatively, which is consistent with the reported correlation between tumor volume and tumor markers. Additionally, the small sample size and duration of the study period must be considered when interpreting these data.

Based on the literature, we expected to find that resection of $\geq$90% of tumor volume would be a significant predictor of survival. However, we were surprised to find that grossly curative resections were not associated with longer survival than incomplete resections. Because carcinoid tumors metastasize to the liver through the lymphovascular system, micrometastases are almost always present within the liver at the time of resection and, in fact, were found in all of our patients. It is, therefore, almost impossible to achieve a definitive cure for HCM, and recurrence should always be expected. Thus, all eligible patients should be resected, provided that at least 90% of the tumor volume can be debulked. One of the larger studies of patients undergoing RSX for liver metastatic neuroendocrine tumors reported that survival was not different for patients undergoing complete versus incomplete RSX.[22] Interestingly, Chamberlain et al.[15] reported intent of resection to be the only significant predictor of survival in a multivariate analysis, but this terminology is likely analogous to RSX $\geq$90%. In our study, all RSX $\geq$90% had curative intent.

Ablative techniques such as cryoablation and radiofrequency ablation (RFA) have also gained interest over the past decade. Our institution does not routinely perform cryoablation for the treatment of liver tumors based on data showing significant risk of complications, including disseminated intravascular coagulation, hepatic failure, renal failure, thrombocytopenia, and multisystem injury.[23–25] These systemic complications generally do not occur with RFA.[26,27] Considering that curative resection does not appear to be necessary for increases in survival and quality of life, RFA seems attractive for patients with an isolated, slow-growing metastasis, for patients with a technically challenging lesion, or for patients who do not wish to undergo liver resection. Although we do employ RFA in selected cases, either alone or in combination with RSX, complete RSX is almost always the preferred treatment for eligible patients. Data regarding the long-term efficacy of RFA in the treatment of carcinoid tumors is lacking.

Eighty-four percent of our patients experienced a functional QOL greater than or equal to their preoperative functional QOL for their entire postoperative course. Although most patients eventually experienced some recurrence of symptoms, recurrent symptoms were rarely as severe as they were prior to RSX and did not greatly affect functional QOL. The patients with more extensive disease who underwent RSX $<$90% had lower functional QOL preoperatively and postoperatively than the patients undergoing RSX $\geq$90%, but the relative increase did not

differ between these two groups. There was no question among our patient group that undergoing resection had been the correct decision. We are not aware of any other quantitative analysis of change in functional QOL for patients treated only with RSX.

Thus, for purposes of prolonging survival, we would agree that RSX should not be considered unless at least 90% of the tumor can be debulked. However, if symptomatic improvement is the goal, our data do not support this rule. Gulec et al.[22] also reported significantly improved QOL in patients undergoing palliative RSX. Que et al.[22] found similar symptomatic responses in patients undergoing curative and palliative intent resections. It is entirely possible that another form of treatment might have offered our RSX <90% patients the same functional QOL improvement as RSX ⩾90% without the risks of surgery, but we do not have data to support this notion.

CONCLUSION

For selected patients, RSX should be performed, especially when RSX ⩾90% is possible. This is associated with significantly improved functional QOL and extended survival. For patients with more advanced disease who are not able to undergo RSX ⩾90%, resection of <90% of tumor volume should be considered as a possible palliative treatment. However, patients with <90% RSX should not expect any benefit in terms of survival by undergoing RSX, and may experience comparable symptomatic relief through RSX or other treatment modalities.[28]

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Real-Time Spectroscopic Assessment of Thermal Damage: Implications for Radiofrequency Ablation

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Radiofrequency ablation (RFA) is an evolving technology used to treat unresectable liver tumors. Currently, there is no accurate method to determine RFA margins in real-time during the procedure. We hypothesized that a fiber-optic based spectroscopic monitoring system could detect thermal damage from RFA in real-time. Fluorescence (F) and diffuse reflectance (Rd) spectra were continuously acquired from within the expected ablation zone during canine hepatic RFA using a fiber-optic microinterrogation probe (MIP). The F and Rd spectral feedback were continuously monitored and ablations were stopped based on changes in spectra alone. After each ablation, the MIP tract was marked with India ink and the ablation zone was excised. The relationship of the MIP to the zone of ablation was examined grossly and microscopically. F and Rd spectral changes occurred in three characteristic phases as the ablation zone progresses past the MIP. Phase 1 indicates minimal deviation from normal lives. Phase 2 occurs as the MIP lies within the hemorrhagic zone of the ablated tissue. Phase 3 correlates with complete tissue coagulation. The absolute magnitude of spectral change correlates with the gross and histologic degree of thermal damage. Optical spectroscopy is a technology that allows real-time detection of thermal tissue damage. In this study, both F and Rd spectroscopy accurately defined the advancing hemorrhagic edge of the zone of ablation and the central coagulation zone. These results suggest that F and Rd spectroscopy can be used to create a real-time feedback system to accurately define RFA margins. (J GASTROINTEST SURG 2004;8:660–669)

KEY WORDS: Diffuse reflectance spectroscopy, fluorescence spectroscopy, liver tumors, radiofrequency ablation, spectroscopy

Radiofrequency ablation (RFA) is an evolving technology used to treat patients with unresectable primary and metastatic liver tumors.[1] Although debate exists concerning the indications for the use of RFA, this technique is becoming an important alternative and a complementary modality with regard to the treatment of primary and metastatic tumors of the liver.[2] It can be performed percutaneously, laparoscopically, or during laparotomy. The RFA electrode-needle, placed under image guidance, produces coagulation necrosis of the tumor through thermal conversion of electrical energy. It is a relatively safe procedure with a complication rate of 5%–13% in most series.[3–6] The efficacy of RFA treatment of hepatic tumors is not clear. Most published reports present short follow-up periods; thus, there is poor data regarding recurrence and disease-free survival after RFA. The largest of the clinical series report local recurrence rates of up to 39% when calculated per lesion.[7–15] Many of the patients in these studies exhibit multiple lesions; therefore, recurrence rates are actually higher when calculated on a per patient basis.

Experience with hepatic resection for colorectal metastases has indicated that microscopically negative margins are required for long-term survival. By inference, achieving adequate margins of tissue ablation

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should be a prerequisite for a successful oncologic RFA treatment. Intraoperative determination of RFA margins is difficult. Currently, there is no effective way to measure ablation margins in real-time. Standard practice uses intraoperative ultrasound to guide electrode-needle placement and to indirectly assess thermal damage: heating of tissue leads to hyperechoic changes that are detectable by intraoperative ultrasound.[16–18] However, these changes do not imply the extent of thermal damage, nor do they correlate with margins of ablation.[19,20] Because of this, assumptions regarding ablation power and heating time must be established to estimate ablation size. Patient-to-patient diversity, the variance of tumor geometry, location proximity to vasculature, and differences in tissue response (normal vs. cirrhotic liver) can lead to incomplete ablation and predisposition to local tumor recurrence.[21] An intraoperative system that accurately determines ablation margins would reduce recurrence rates.

Optical spectroscopy, although not a new field, has recently been demonstrated by many groups to accurately distinguish between tissue types. Distinction between normal and malignant tissue has evolved into a leading application of this technology.[22–28] Other studies of specific types of spectroscopy have indicated that this technology can distinguish between thermally damaged and native tissue.[29–33] We have recently validated the ability of fluorescence (F) and diffuse reflectance (Rd) spectroscopy to detect spectral changes resulting from thermal changes in liver tissue using an in vitro model.[33] Because optical spectroscopy manifests the ability to provide immediate feedback, it renders implications for use in many clinically valuable thermal tissue therapies such as RFA.

Because of the demonstrated ability of optical spectroscopic technology to distinguish tissue types and the emerging data that indicates the accuracy of optical spectroscopy for the detection of thermal tissue damage, optical spectroscopy manifests the potential to clinically impact thermal tissue therapies such as RFA. In this article, we demonstrate that F and Rd spectroscopy can be used in real-time during RFA to differentiate normal and coagulated liver tissue and to also accurately detect the advancing edge of the RFA ablation zone.

MATERIAL AND METHODS

Spectroscopy

A fiber-optic based spectroscopy system was designed and built in the Biomedical Optics Laboratory at Vanderbilt University (Nashville, TN). This system was used to acquire continuous real-time F or Rd spectra from liver tissue during each ablation through a microinterrogation probe (MIP) placed within the expected zone of ablation. The MIP consisted of two 200 μm excitation fibers (one for each light source, see below), two 400 μm collection fibers, and one 500 μm collection fiber. The spectrometer (S2000-FL Spectrometer; Ocean Optics, Dunedin, FL) indicated a spectral range of 350–1000 nm. Two light sources were used: diffuse Rd and F spectroscopy. For Rd spectroscopy, the excitation light source used for the Rd spectral measurements was a broadband halogen light (Fiber Lite, Model 180; Edmund Industrial Optics, Barrington, NJ). For F spectroscopy, the F excitation light source used was a nitrogen laser (337 nm emission, high-pressure nitrogen dye laser; Oriel Corporation, Stratford, CT) operated at a repetition rate of 20 Hz and pulse energy of 50 μJ at the tissue surface. Ablations were monitored with either F or Rd.

The spectrometer was interfaced with an A/D (analog/digital) converter (ADC1000-USB A/D Converter; Ocean Optics, Dunedin, FL) that communicated with a Windows-based laptop computer via a universal serial bus connection. A spectrometer (OOIBase32; Ocean Optics, Dunedin, FL) was used for spectral acquisition. An integration time of one second was used throughout the study, which yielded optimal spectral signal-to-noise ratios. The spectral acquisition interval was 5 seconds. Boxcar smoothing was used to eliminate the intrinsic noise of the system.

Spectral Data Processing

Post-processing of F and Rd spectra was performed using MATLAB programs that reduced the spectral resolution to 2 nm, establishing the data array size as more manageable and reducing the signal noise. Calibration factors were applied to remove spectral features induced by wavelength-dependent characteristics such as sensitivity of the spectroscopy system. The useful wavelength ranges (i.e., regions with sufficient signal-to-noise ratios) for F and Rd spectra were 400–650 nm and 400–750 nm, respectively. Spectra were analyzed over these ranges to search for dynamic spectral features such as intensities or ratios of intensities at particular wavelengths correlating strongly with thermal tissue damage.

Study Design and Technique

Animal study design was performed in accordance with NIH animal care procedures and was approved by the Vanderbilt University Institutional Animal Care and Use Committee. RFA was performed on dogs (15–20 kg) with healthy livers. A total of eight dogs were anesthetized with intravenous (IV)

sodium pentothal (15 mg/kg) and isoflorane (1.5%–2.5% in oxygen) via endotracheal intubation. The animals underwent midline laparotomy with mobilization of the entire liver. Random areas of healthy liver parenchyma were selected for RFA. The electrode-needle (StarBurst XL Electrosurgical Device [3–5 cm, 15 cm length]; RITA Medical Systems, Mountain View, CA) was inserted into areas of the liver such that the deployed array would achieve a 3-cm ablation if standard time-temperature protocols were used. The MIP was placed into the expected zone of ablation at varying orientations and varying distances to the RF electrode array. Preliminary experiments used ultrasound guidance to place the MIP at fixed distances (1 and 2 cm) from the center of the RFA array. Because our study was designed to determine if optical spectroscopic feedback could provide endpoint data, the results reported did not use ultrasound guidance, but rather the ablations were continued until spectral changes occurred. Up to six separate ablations were performed on each dog. Ablations were carried out using a RITA model 1500X (RITA Medical Systems, Mountain View, CA) at a constant power of 80 W. Ablations were stopped when spectral changes that had previously been validated by in-vitro studies to indicate tissue coagulation were observed.[33,34]

Overall, 25 ablations were performed: 12 were studied using F spectroscopy and 13 were studied using Rd spectroscopy. Nine of the 25 ablations (5 for F and 4 for Rd) were stopped when spectral feedback had only reached approximately 25%, 50%, or 75% of the observed maximal change. These were termed "partial ablations." The tract from the MIP was injected with India ink immediately after MIP removal. After ablations, the animals were euthanized and each ablation zone was excised. The specimens were then bivalved along the axis of the MIP to expose the interrogation tract.

Histological Evaluations and Thermal Tissue Damage Assessment

The relationship between the distal MIP and the zone of ablation (ZOA) was documented using a digital camera (Olympus D-550; Olympus America, Inc., Melville, NY). A 1×1 cm^2 tissue section containing the tip of the MIP track was taken from each specimen for histological examination. To facilitate the identification of the point of interrogation (MIP tip position) during the histological examination, the position of the MIP tip was registered by inserting a 26-gauge needle perpendicular to the MIP track. Tissue sections were fixed in 10% formalin and processed by the Vanderbilt Mouse Histopathology core lab. Routine hematoxylin and eosin (H&E) staining was performed on the tissue slices that surrounded the distal MIP. A blinded experienced hepatobiliary pathologist reviewed each tissue section and characterized the thermal tissue damage within a 4-mm area surrounding the tip of the MIP track.

Currently, there is no adequate system for the classification of thermal liver damage. Therefore, for the purposes of this study, a histological scoring system for thermal damage, detailed in Table 1, was developed to correlate thermal tissue damage with spectral changes. This system incorporated well-established histological characteristics of thermal damage.[35] In this scoring system, one point was assigned for detection of sinusoidal dilatation, vacuole formation, or tissue fragmentation. Hemorrhage received a score of 1 or 2 depending on its severity. Microscopic evidence of blood or tissue coagulation received a score of 3 because it is the most specific indicator of thermal tissue damage and was, therefore, weighted heavier in the scoring system.[35] For each sample, a total score of 0 (no evidence of thermal damage) to 8 (complete thermal damage) was possible.

RESULTS

RFA-Induced Spectral Changes in Liver Tissue

Spectral changes detected using Rd spectroscopy included the intensity of reflected light from a native liver varied within the range of monitored wavelengths. Figure 1, *A* illustrates the dynamics of Rd spectra between 400 and 850 nm over the time course of a representative full ablation. The most noticeable change in this three-dimensional plot is that the overall intensity of Rd increases as the ablation proceeds. This trend ceased eventually and then some subtle line-shape changes in Rd spectrum occurred. In the wavelengths between 600 and 850 nm, the

Table 1. Summary of the histological tissue thermal damage scoring system. One point was assigned for detection of sinusoidal dilation, vacuole formation, or tissue fragmentation. Hemorrhage received a score of 1 or 2 depending on its severity and evidence of blood or tissue coagulation received a score of 3.

Histologic characteristics	Points
Sinusoidal dilation	1
Vacuole formation	1
Tissue fragmentation	1
Hemorrhage, minor	1
Hemorrhage, major	2
Blood or tissue coagulation	3

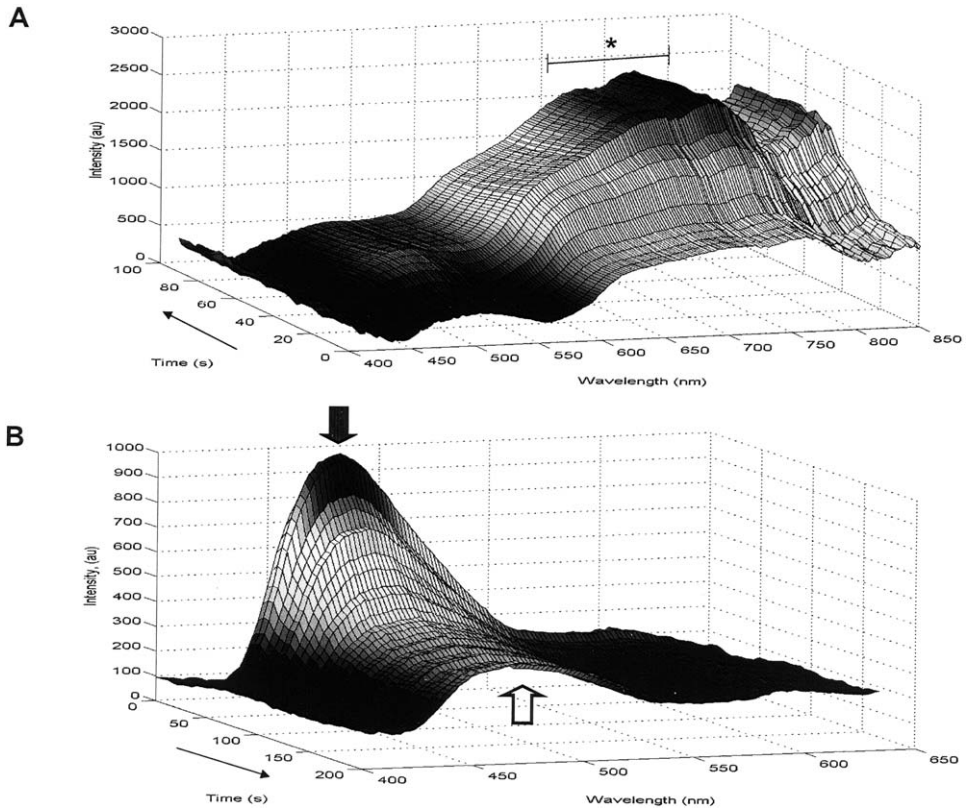

Fig. 1. Representative plots demonstrating (**A**) the dynamics of diffuse reflectance (Rd) spectra of liver tissue over the course of radiofrequency ablation (RFA). All wavelengths monitored during each ablation are indicated. Increases in Rd intensities occur in most of these wavelengths as RFA progresses. These intensity increases are as high as 2.5-fold for wavelengths between 700 and 800 nm (denoted with *asterisk*). (**B**) The dynamics of fluorescence (F) spectra of liver tissue over the course of RFA. All wavelengths monitored during each ablation are indicated. There is a decrease in overall F intensity with ongoing ablation. In addition, a subtle shift in peak intensity from 482 (*dark arrow*) to 490 nm (*light arrow*) occurs as the ablation progresses. Note the absence of substantial F intensity changes between 600 and 650 nm as the RFA progresses.

peak intensity of the Rd spectrum increased as much as 2.5-fold (Fig. 1, *A*). Analysis of the spectral changes at all wavelengths was carried out to determine the wavelength of peak reflectance. This was determined to be 720 nm. No considerable changes in Rd intensities were noted as the thermocouples in the RFA electrode tynes cooled to less than 50°C.

Spectral changes detected using F spectroscopy included changes in tissue F spectra between 400 and 650 nm that occurred during RFA (Fig. 1, *B*). Native liver, as reported previously,[33] indicates a strong F emission between 450 and 550 nm. This F intensity decreased as thermal ablation occurred and, more specifically, the primary emission peak (482 nm) decreased as much as 60% (Fig. 1, *B*). A shift in the primary F emission peak from 482–490 nm as well as a spectral broadening was also observed in the latter part of the ablation course. Similar to the dynamics of Rd, the change in F intensity ceased after it reached its maximum (i.e., 60% decrease), and this change was irreversible with cooling. Analysis was carried out using F emission intensity at 480 nm (F_{480}) to represent peak tissue fluorescence. There was no substantial tissue fluorescence during RFA in the wavelengths between 600 and 650 nm.

Rate of Spectral Changes

F or Rd spectra were continuously acquired from liver tissue during RFA. Initially, the MIP was placed at a fixed distance from the center of the RFA electrode array using ultrasonographic guidance. As the distance of the MIP from the RF array was increased, the magnitude of spectral change achieved remained constant indicating that the magnitude of spectral change was independent of position and/or orientation of the MIP to the RF electrode array.

However, the time required to achieve maximal magnitude change in the spectrum increased as the distance between the RF electrode array and the MIP increased. These findings were consistent for both F and Rd.

Phases of Spectral Change

To further characterize the dynamics of F and Rd spectral changes, we examined F and Rd intensity changes occurring over a single wavelength as a function of ablation time (t). For Rd analysis, the wavelength of peak reflectance, 720 nm (Rd_{720}), was chosen. Selection of other wavelengths between 650 and 750 nm will yield similar results. To facilitate comparisons between samples, Rd spectral measurements were normalized using the intensity value of normal liver tissue (Rd_{720} at $t > 0$ was normalized to that at $t = 0$ with each sample collection). A representative plot of normalized Rd_{720} is illustrated in Fig. 2, *A*, which indicates that the time course of normalized Rd_{720} can be divided into three phases.

Similar dynamic analysis was performed using F_{480}. However, it was necessary to account for pulse-to-pulse fluctuation in laser energy from the nitrogen laser source. To do this, the ratios of F intensities within a single spectrum were used as spectral correlates of thermal damage. As demonstrated in Fig. 1, intensity at 610 nm was altered very little by ongoing RFA, so this wavelength was chosen to normalize the primary spectral changes noted at 480 nm. The ratio of the F intensity at 610 nm to the intensity at 480 nm resulted in a normalized ($F_{610/480}$) intensity ratio. This inverted ratio was used to facilitate the comparison of F and Rd spectral changes and, when plotted, the normalized $F_{610/480}$ intensity ratio changes demonstrated the same three phases of change seen with Rd spectra (Fig. 2, *B*).

For both F and Rd, phase 1 spectral changes indicate minimal deviation from the spectral fingerprint of native liver parenchyma. During phase 2, a rapid increase in intensity (or intensity ratio for F) occurs until a plateau is reached at which point no further spectral change occurs. Phase 3 represents this plateau region. Independent of the spectroscopic monitoring method, phase 3 consistently corresponded with gross and histological evidence of complete tissue coagulation.

Rd and F Spectroscopic Changes

To investigate the thermal tissue damage occurring during phase 2 of the spectral change, we performed a series of partial ablations. During these ablations, RFA was stopped at varying times before full spectral changes were noted such as after a 25%, 50%, or 75% increase in Rd intensity or a 15%, 30%, or 45% decrease in F intensity. The position of the MIP tip was registered with India ink so that the gross characteristics of the tissue immediately surrounding the MIP tip could be accurately studied and correlated with the spectral change achieved. Figure 3 demonstrates representative time course graphs of partial and full ablations performed using F spectroscopic monitoring. Similar results were obtained

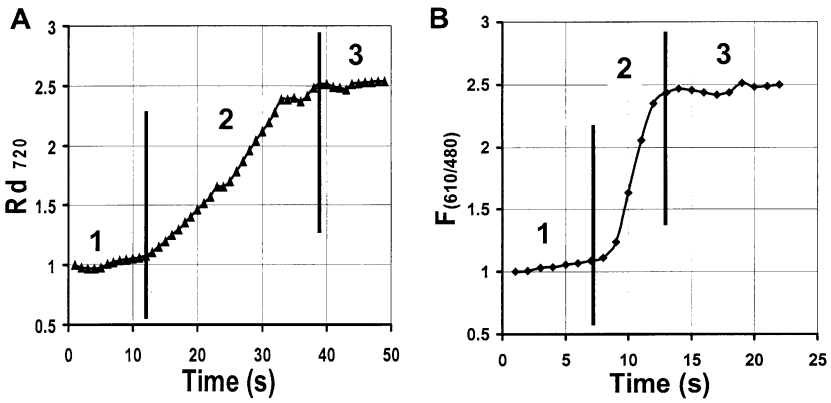

Fig. 2. Representative graft illustrating (**A**) the time course of normalized Rd intensity changes at 720 nm (Rd_{720}) of liver tissue during radiofrequency ablation (RFA). These spectral changes can be divided into 3 phases. Phase 1 indicates a period of negligible intensity change in comparison with that of native liver tissue. Phase 2 indicates rapid increases in normalized Rd_{720} intensity. Phase 3 indicates a plateau of normalized Rd_{720} intensity that does not change after tissue cooling. (**B**) The time course of normalized $F_{610/480}$ of liver tissue during an RFA that demonstrates the same three phases of intensity change seen with Rd.

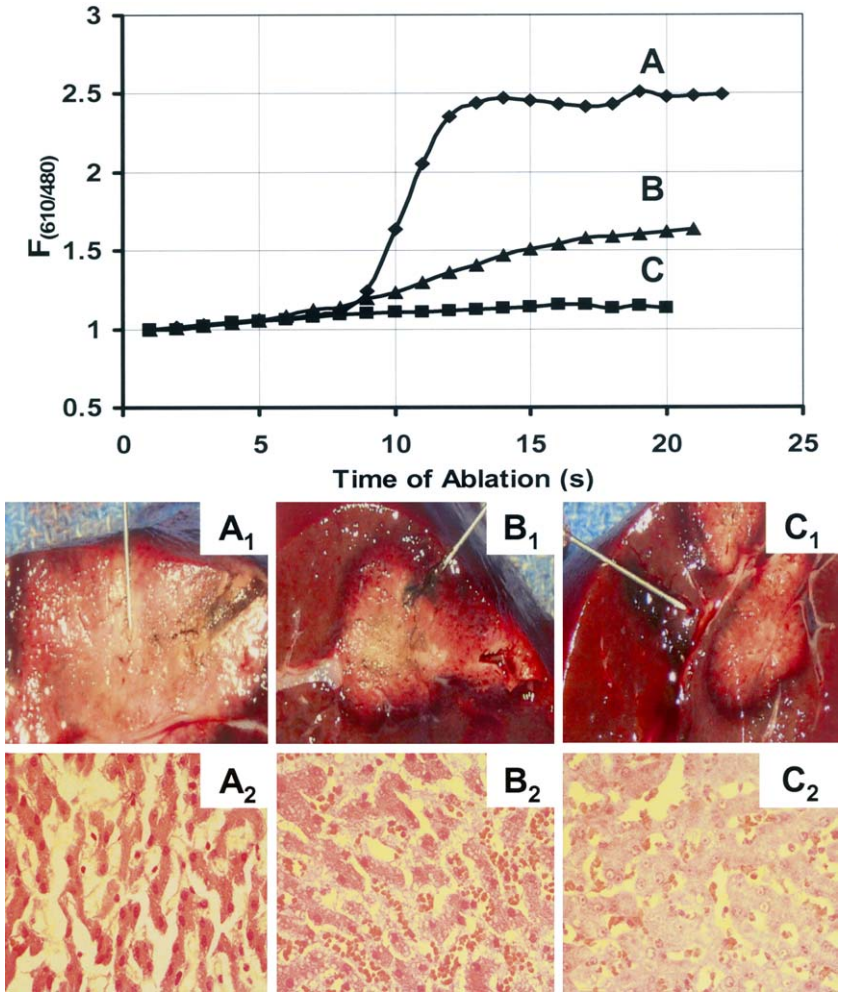

Fig. 3. A series of representative ablations demonstrating the following: **A**, full ablation indicating all three phases of spectral change. The MIP tip (marked in the photo by the needle) is located within the coagulation zone (A_2). Histology denotes tissue fragmentation, blood coagulation, sinusoidal dilatation, and vacuole formation indicating cellular and tissue destruction (A_1). The thermal tissue damage score for this sample is 6. **B**, Partial ablation reaching only phase 2. The MIP tip (needle) is located at the advancing hemorrhagic zone of the ablated tissue (B_1). Histology denotes vacuole formation and a large amount of hemorrhage indicating a moderate amount of tissue destruction (B_2); the thermal tissue damage score is 3. **C**, Ablation in which the MIP was placed outside the ablation zone. The normalized $F_{610/480}$ tracing fails to transition out of phase 1 and there is no gross evidence of tissue damage at the distal MIP (needle) (C_1). Histology indicates only mild hemorrhage (C_2). The thermal tissue damage score for this sample is 1. Taken together *A*, *B*, and *C* suggest that phase 2 changes occur as the advancing hemorrhagic zone ablated tissue reaches and passes the MIP, whereas phase 3 changes only occur when full tissue coagulation has occurred. Identical results were determined with the Rd data set. All photomicrographs were taken at 400 × magnification.

using Rd monitoring (data not indicated). The corresponding macroscopic and microscopic tissue changes are noted with each spectral fingerprint. Only ablations proceeding to maximal spectral change (full ablations) demonstrated all three phases of intensity change (Fig. 3, *A*). Ablations stopped before the maximal decrease in F intensity occurred (partial ablations) indicate only phase 1 and phase 2 changes. Fig. 3, *B* demonstrates that during phase 2 the MIP was determined to be within the advancing hemorrhagic zone of ablation. In those cases when the ablation was stopped before phase 2 occurred (Fig. 3, *C*), no gross evidence of thermal tissue damage was seen in proximity of the MIP.

The partial ablation experiments can be summarized by two results: (1) phase 3 spectral changes do not occur unless the MIP lies within coagulated tissue and (2) phase 2 spectral changes are seen when the

MIP lies within the advancing hemorrhagic edge of the zone of ablation.

Absolute Spectral Intensities

Samples for hepatic tissue immediately distal to the MIP tip were subjected to histological evaluation and classified according to our thermal tissue damage scoring system. For all 25 ablations, the microscopic thermal tissue damage scores ranged from 1–6. The histological examination of ablations achieving phase 3 yielded an average thermal tissue damage score of 4.57 for F and 3.50 for Rd. Histological examination of partial ablations (phases 1 and 2) gave an average thermal tissue damage score of 2.20 for F and 1.99 for Rd. When plotted, the thermal tissue damage scores, regardless of phase, correlate linearly with normalized Rd_{720} or normalized $F_{(610/480)}$) (see Fig. 4). The correlation coefficients, R^2, calculated from these plots are 0.74 for F spectroscopy and 0.76 for Rd spectroscopy.

DISCUSSION

RFA has become an important therapeutic modality for the treatment of liver tumors and recent advances in equipment design have enhanced enthusiasm for the technique. The success of RFA is dependent upon accurate image-guided electrode-needle placement and array deployment. Many authors have written with regard to the requirement for meticulous treatment planning and imaging to minimize local recurrence[20,36–39] Despite widespread acceptance and adherence to these principles, local lesion recurrence rates remain as high as 39%.[7–15] The major reasons cited to contribute to local recurrence are electrode misplacement and incomplete ablation of the tumor margin. Technologies that can improve these areas are required to achieve comparable oncologic results with those achieved by surgical resection.

Currently, there is no accurate method of real-time intraoperative ablation margin detection. To estimate the completeness of ablation, there are three separate protocols recommended by the three manufacturers of the available RFA systems. One system relies simply on time, another on impedance, and the third on temperature as measurable variables to gauge the volume of an ablation. Impedance measurement determines completeness of ablation based on depletion of cellular energetics and high resistance to current. Achievement of impedance roll-off, however, does not imply uniform ablation throughout the distribution of the array. The thermocouple-based feedback uses achievement of temperature during the procedure to determine completeness. These deficiencies in monitoring the completeness of an ablation in real-time are well recognized.[20] Several groups have investigated methods to improve the monitoring of an ongoing ablation. Preliminary reports have been published using magnetic resonance thermal imaging, improved ultrasound algorithms to allow enhanced thermal monitoring, and ultrasound-based tissue elastography.[17,40,41] Of these, tissue elastography is the only method that does not rely solely on temperature for estimating the size of ablation. Optical spectroscopy is independent of cellular energetics and temperature, as it provides feedback based on physical

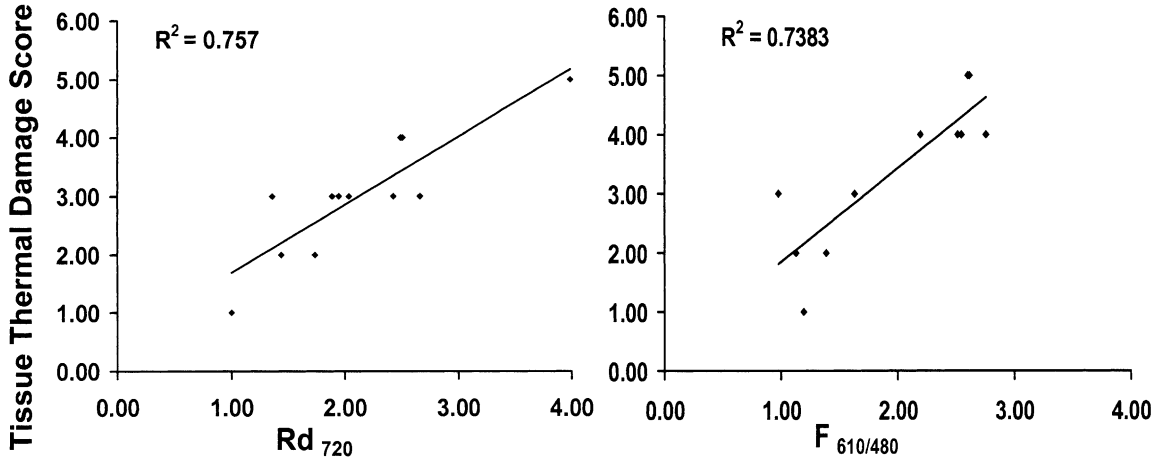

Fig. 4. Scatter plots depicting the correlation of normalized Rd_{720} and $F_{610/480}$ with the total thermal tissue damage scores from all ablation sites. Both normalized Rd_{720} ($R^2 = 0.76$) (left) and $F_{610/480}$ ($r^2 = 0.74$) (right) correlate well with thermal tissue damage. There is no remarkable difference in the degree of correlation between the two techniques.

cell changes induced by thermal damage. A key finding in our experiment was the stability of spectral changes that occurred during phase 3 even after ablation was terminated and tissue was allowed to cool. This is mainly attributed to the permanent changes in morphological and biochemical tissue characteristics resulting from irreversible thermal tissue damage. The persistence of optical tissue properties created from thermal tissue damage will allow reassessment of the margin even after the ablated tissue has cooled.

Defining the actual "margin" of a RFA zone is difficult. Cell death from RFA occurs when thermal damage is severe enough to overwhelm the usual cellular repair mechanisms. As tissue is exposed to higher temperatures or prolonged heating times, structural tissue proteins undergo denaturation and conformational changes; this is thermal coagulation. Coagulation is immediately apparent and always indicates a lethal thermal event. Macroscopically, tissue coagulation appears as a whitening of tissue,[35] a finding that was clearly seen when the RFA lesions were bivalved. Microscopically, H&E staining can demonstrate coagulation changes. Thermally coagulated cells and intracellular organelles shrink and undergo characteristic conformational changes.[35] In addition to coagulation, superheated water vapor is generated during heating, which leads to the formation of vacuoles. As these vacuoles expand and coalesce, the walls rupture and tissue fragmentation occurs.[35] In clinical practice, RFA is usually performed to achieve the maximum diameter of ablation ensuring extension of the coagulation zone beyond the tumor into normal liver parenchyma. Our findings demonstrate that both optical spectroscopic techniques studied can accurately detect a RFA "margin" if it is defined as the achievement of tissue coagulation.

It remains unclear if cells in the advancing hemorrhagic zone undergo irreversible thermal damage that renders them nonviable. Routine light microscopy cannot identify dead cells immediately after heating except in the case of severe damage (coagulation). Histochemistry techniques can demonstrate enzyme inactivation (NADH staining), but this alone cannot be used as a hallmark of cell death.[35] Whereas H&E staining can accurately indicate high-grade thermal damage indicative of tissue death, neither H&E nor histochemistry techniques can immediately predict the viability of individual cells at the advancing edge of the zone of ablation. This clearly represents a limitation of this study. The standard method employed to overcome this limitation of light microscopy concerns the examination of the ablation zone after allowing the animal to recover for several days. However, this method would designate it almost impossible to accurately define the exact portion of the ablation zone that was being monitored by the MIP and thus indicate correlation of the findings to optical spectra impossible. A second limitation of this study is the lack of a validated histological scoring system for cellular thermal damage. Although the scoring system that we employed was capable of distinguishing gross difference in thermal damage, it is not able to detect absolute cell death unless there is evidence of coagulation. Further studies are necessary to determine the exact spectral fingerprint that indicates irreversible cell injury.

Our data do not establish superiority of either technique (F or Rd) with regard to the accuracy of detecting the coagulation of tissue. There are system performance considerations that designate F as potentially less accurate than Rd. The nitrogen laser used for F spectroscopy in this study indicated a pulse-to-pulse energy fluctuation of as high as 12% of the mean pulse energy. Conversely, the fluctuation in the emissivity of the halogen light source used for Rd spectroscopy was inconsequential. In addition to the pulse-to-pulse fluctuation in laser energy, spectral acquisition was not synchronized with the laser, which means that the number of pulses binned in each integration period most likely fluctuated by a pulse or two. The combination of these laser performance factors induced a slight fluctuation in the absolute intensity of the F spectra. For the considerations noted above, Rd spectroscopy may prove more practical to use for this type of application. However, F spectral instability can be easily overcome by the use of a ratio of F intensities within a single spectra (e.g., $F_{610/480}$). Moreover, F spectroscopy should theoretically be more sensitive and specific for cellular death because intracellular proteins (such as nicotinamide adenine dinucleotide [NADH]) are responsible for producing fluorescence; when these are depleted, fluorescence will decrease. Future studies will determine if the two techniques will prove to be complementary or redundant with regard to the accuracy of ablation zone detection.

We purposely did not perform ablations using thermal dosimetry endpoints. The majority of clinical RFA protocols are based on temperature feedback from thermocouples embedded in the needle electrode, however, this study was not designed to compare the current standard of care with optical spectroscopic monitoring of RFA. We intentionally carried out ablations at a constant power and manually ended the ablation based on feedback spectra, thereby eliminating any bias that may occur with knowledge of local tissue temperature at the distal MIP. Because the results of this study validate that these optical spectroscopic techniques can reliably predict progressive thermal damage induced by RFA,

future studies using an animal tumor model are indicated to validate these observations. During these future studies, it may be appropriate to directly measure tissue temperature at the distal MIP.

In summary, the results of this study demonstrate that changes in F and Rd spectral characteristics during RFA correlate with progressive degrees of thermal damage in hepatic tissue. Both methods of optical spectroscopy studied can accurately detect tissue coagulation resulting from RFA. This data points to the potential use of spectroscopy regarding the establishment of a real-time intraoperative feedback system capable of accurately defining RFA margins. Whereas the system created for this study would be cumbersome in practice, the technology that it validates can be modified for existing RFA electrode needles to provide real-time feedback from multiple areas of the ablation simultaneously during open or percutaneous RFA. In this way, optical spectroscopy could provide real-time data during the procedure to complement other imaging modalities (e.g., ultrasound, MRI) and ensure that adequate margins of ablation are achieved. Such a system may ultimately help decrease local lesion recurrence after RFA ablation.

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Laparoscopic Ventral Incisional Hernia Repair: A More Effective Alternative to Conventional Repair of Recurrent Incisional Hernia

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Conventional repair of recurrent ventral incisional hernia is associated with a higher recurrence rate (30%–50%) than repair of primary incisional hernia (11%–20%). Laparoscopic incisional hernia repair (LIHR) can significantly reduce the recurrence rate of primary hernia to less than 5%. In this study, we evaluate the efficacy of repairing recurrent incisional hernia laparoscopically. One-hundred and seventy consecutive patients undergoing LIHR between January 1995 and December 2002 were prospectively reviewed. Patients with recurrent incisional hernia (n = 69) were compared to patients with primary incisional hernia (n = 101). Patient demographics and perioperative and postoperative data were recorded prospectively. Follow-up was obtained from office visits and telephone interviews. Statistical analysis was performed using the Student *t* test and the χ^2 test. Results are expressed as means ± standard deviation. The patients with recurrent incisional hernia had a mean of 1.9 ± 1.3 previous repairs, higher body mass index (BMI) (34 ± 6 kg/m^2 vs. 33 ± 8 kg/m^2, $P = 0.46$), larger defect size (123 ± 115 cm^2 vs. 101 ± 108 cm^2, $P = 0.06$), and longer operative time (119 ± 61 minutes vs. 109 ± 44 minutes, $P = 0.11$). The complication rate was higher in the recurrent group (28% vs. 11%, $P = 0.01$), but the recurrence rate was not different (7% vs. 5%, $P = 0.53$). The mean time to recurrence was significantly shorter in the recurrent group (3 ± 2 months vs. 14 ± 7 months, $P < 0.0001$). The mean follow-up interval was 19 ± 18 months in the recurrent group and 27 ± 20 months in the primary group. Although laparoscopic repair of recurrent incisional hernia resulted in a higher recurrence and complication rate than laparoscopic repair of primary incisional hernia, the rates were lower than those reported for conventional repair of recurrent incisional hernia. Laparoscopic repair of recurrent incisional hernia is an effective alternative to conventional repair. (J GASTROINTEST SURG 2004;8:670–674)

KEY WORDS: Laparoscopic surgery; hernia, primary incisional; recurrent incisional hernia; recurrence

INTRODUCTION

Incisional hernia is the most common complication after abdominal surgery. Approximately 3%–20% of patients undergoing laparotomy develop an incisional hernia,[1–4] resulting in about 90,000 incisional hernias repaired annually in the United States. The social and economic impacts of an incisional hernia can be enormous, because lifestyle modifications affecting employment and social interaction may be necessary to reduce the symptoms of the disorder. To further complicate this iatrogenic disease, conventional repair of incisional hernias yields poor results. The recurrence rate has been reported as high as 56% after the first repair, 48% after the second repair, and 47% after the third repair.[5]

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The introduction of prosthetic mesh to conventional incisional hernia repair has lowered recurrence rates compared to primary tissue repair of incisional hernia. Unfortunately, even the lowered rate is considerably high, ranging from 10%–24%.[6] Moreover, the lower recurrence rate achieved with prosthetic mesh is offset by a higher complication rate. Repair of incisional hernia with prosthetic mesh is associated with a higher rate of seroma, wound/prosthetic mesh infection, and (depending upon the biomaterial used) enterocutaneous fistula.[7,8] Consequently, prosthetic mesh repairs are often reserved for large complex hernias.

In the early 1990s, the laparoscopic approach to ventral incisional hernia repair was introduced.[9] Studies demonstrate that many of the typical benefits of laparoscopy have been realized in laparoscopic incisional hernia repair (LIHR), including less narcotic use, shorter length of hospital stay, and quicker return to normal activities[10,11] compared to conventional incisional hernia repair. More importantly, the recurrence rate is reduced to 2%–5% after at least a 2-year follow-up.[12,13] However, most studies report the recurrence rate for laparoscopic repair of primary incisional hernia. It is uncertain whether laparoscopic repair of recurrent incisional hernia will yield the same reduction in secondary recurrence rate. In this study we evaluate our experience in repairing both primary and recurrent hernias laparoscopically.

METHODS

A prospective review was conducted of 170 consecutive patients undergoing LIHR from January 1995 to December 2002 at St. Joseph's Hospital in Hamilton, Ontario, and the University of Kentucky, the two centers with which the senior author was associated during the 7-year period of data collection. Patient demographics, intraoperative parameters, and postoperative outcome were recorded in a computer database. The abdominal locations of the defect were classified as center, upper midline, lower midline, right lateral, or left lateral. Complications were classified as seroma persistent for longer than 2 months, hematoma, wound infection remote from the prosthesis, prosthesis infection, intraoperative bowel injury, prolonged ileus (greater than 3 days), persistent pain beyond 6 months, and cardiac, respiratory, or genitourinary complications. Patients were scheduled to follow up in clinic at 1, 6, and 12 months and then annually. Patients living in remote areas who were unable to return to the clinic were followed up by telephone interview.

Surgical Techniques

For each surgery, the patient was placed in a supine position with both arms tucked on the side. The surgical technique has previously been described in detail.[14] Pneumoperitoneum was established using a Veress needle placed in either the right or left subcostal margin. A direct-view 10 mm trocar was inserted laterally at a midpoint between the iliac crest and costal margin to accommodate a 30º 10 mm laparoscope. Two additional 5 mm ports were placed a few centimeters more anterior and lateral to the initial port in the ipsilateral upper and lower quadrants.

Adhesiolysis was then performed with limited use of cautery to delineate the margins. If mesh was present, it was left intact unless it was tenaciously adherent to the bowel. In this circumstance, mesh was dissected away from the anterior abdominal wall, leaving a "medallion" of mesh on the surface of the bowel. Fascial defects were measured via intracorporeal insertion and manipulation of a sterile plastic ruler. An expanded polytetrafluoroethylene (ePTFE), prosthetic mesh (DualMesh, Gore Medical Products, Flagstaff, AZ) was sized to overlap the hernia defect by at least 3–5 cm around its entire circumference. Distinct marks were placed on the mesh and on the external abdominal surface to assist intra-abdominal orientation. After sutures (CV2 ePTFE) were placed at four equidistant points on the mesh, it was wrapped around a laparoscopic grasper and inserted through the 10-mm trocar. Once the mesh was unfurled and oriented correctly, the preplaced sutures were pulled transabdominally with a suture passer at predetermined locations. Additional transabdominal sutures (0 prolene) were placed at intervals of no less than 5 cm around the periphery of the patch. The edges were then fixed to the peritoneum with spiral tacks placed at least 1 cm apart circumferentially.

Data Analysis

Patients were divided into two groups: the primary group consisting of patients with no previous hernia repairs, and the recurrent group consisting of patients with at least one previous incisional hernia repair. The χ^2 test and the Student t test were used to compare discrete and continuous variables, respectively, between the two groups. Statistical significance was set at $P < 0.05$.

RESULTS

One-hundred and seventy patients underwent LIHR: 69 patients in the recurrent group and 101 patients in the primary group. The groups were similar with respect to sex (52% female vs. 46% female,

$P = 0.44$), body mass index (BMI) (34 ± 6 vs. 33 ± 8, $P = 0.46$), and the American Society of Anesthesiologists (ASA) score (2.2 ± 0.7 vs. 2.3 ± 0.6, $P = 0.76$). The recurrent group was slightly younger (53 ± 13 vs. 57 ± 14, $P = 0.04$). The mean number of previous repairs in the recurrent group was 1.9 ± 1.3 (range 1–7 repairs).

The defects of the recurrent group were on average 22 cm^2 larger than those in the primary group and took 10 minutes longer to repair, although these differences were not statistically significant (Table 1). The hernias were evenly distributed in location. Two bowel injuries (2.9%) in the recurrent group and one (1.0%) in the primary group were the only intraoperative complications ($P = 0.56$). One patient with bowel injury in the recurrent group required conversion to open repair. In the other two cases, after the adhesiolysis was completed, definitive laparoscopic incisional hernia repair was delayed.

Postoperative data indicated that the length of hospital stay was equivalent between the two groups (recurrent: 2.2 ± 1.7 days; primary: 2.4 ± 2.2 days, $P = 0.32$). The mean follow-up interval was 25 ± 19 months (range 1–94 months) overall: 19 ± 18 months in the recurrent group and 27 ± 19 months in the primary group ($P < 0.01$). Postoperative complications were more frequent in the recurrent group (Table 2). Seromas were generally managed by observation. One subprosthetic mesh hematoma required laparoscopic evacuation due to the patient's discomfort.

Recurrences were documented in 10 patients (Table 2): five (7%) in the recurrent group and five (5%) in the primary group ($P = 0.53$). Recurrences occurred at a mean of 3 ± 2 months for patients in the recurrent group and 14 ± 7 months for patients in the primary group. All recurrences were repaired laparoscopically.

Table 1. Intraoperative data

	Primary (n = 101)	Recurrent (n = 69)	*P* values
Defect size (cm^2)	101 ± 108	123 ± 115	0.06
Patch size (cm^2)	250 ± 179	311 ± 185	0.001
Operating room time (mins)	109 ± 44	119 ± 61	0.11
Location of hernias			
Center	44 (44%)	29 (42%)	
Upper midline	14 (14%)	12 (17%)	
Lower midline	8 (8%)	7 (10%)	
Lateral, left	8 (8%)	4 (6%)	
Lateral, right	14 (14%)	13 (19%)	
Intraoperative complications			
Bowel injury	1 (1.0%)	2 (2.9%)	0.56

Table 2. Postoperative data

	Primary (n = 101)	Recurrent (n = 69)	*P* values
Complications			
Seroma	3	3	
Hematoma	1	1	
Wound infection	1	1	
Mesh infection	1	2	
Ileus	3	3	
Pain >6 months	0	2	
Cardiac	0	4	
Respiratory	2	0	
GU	0	2	
C. difficile	1	0	
Other	0	1	
Total complications	11 (11%)	19 (28%)	0.01
Recurrences	5 (5%)	5 (7%)	0.53

GU = genitourinary.

DISCUSSION

Incisional hernia is a vexing complication of abdominal surgery. Primary suture repair has resulted in a higher secondary recurrence rate (50%) than the initial occurrence rate (3%–20%). Introduced in 1992, LIHR has strongly impacted the management of incisional hernia. Currently, irrefutable evidence shows that repair of larger incisional hernias with mesh results in a much lower recurrence rate than primary closure with sutures alone (24% vs. 43%, [6] 8% vs. 25% [15]). However, in open repairs the use of mesh is associated with a higher morbidity rate. Leber et al. [7] reports an early complication rate of 18% and a late complication rate of 27%. Early complications consist of wound infection, hematoma, and seroma, whereas late complications include chronic sinus tract, enterocutaneous fistula, and small bowel obstruction.

Numerous varieties of open ventral herniorrhaphy exist. The Stoppa technique deserves mention. In this technique, mesh is placed posterior to the rectus muscle with wide overlap of the hernia defect. The Stoppa technique has been associated with a lower recurrence rate than other open methods (4%–18%).[16,17] The laparoscopic approach relies upon some similar technical principles as the Stoppa technique for its effectiveness including a wide overlap of the hernia defect with mesh being placed posterior to abdominal wall musculature and suture fixation.

The laparoscopic approach allows the surgeon to repair incisional hernias with lower recurrence rates than conventional approaches including those using mesh. Patients gain the benefits associated with laparoscopy, such as lower narcotic and analgesic use, shorter length of hospital stay, and quicker return to work. In addition, the recurrence rate is significantly reduced to 2%–5% with comparable or lower complication rates. Current contraindications to LIHR include inability to tolerate general anesthesia, severe cardiopulmonary disease, uncorrected coagulopathy, pregnancy, portal hypertension (relative), and major loss of abdominal domain.

We sought to evaluate the efficacy of the laparoscopic approach to recurrent incisional hernia by comparing this group of patients to those patients undergoing repair for primary incisional hernia. With respect to demographic and preoperative characteristics, the recurrent patients were younger, slightly more obese, of equivalent overall health, and had larger defects than those in the primary group. These differences were small and only the difference in age reached statistical significance.

Perioperative and postoperative outcomes were largely comparable between the recurrent and primary groups. Specifically, the lengths of hospital stay and recurrence rates were not significantly different. This finding demonstrates that the benefits of laparoscopy can be extended to those with recurrent as well as primary incisional hernia.

The most notable difference in outcome between the two groups was the complication rate (28% for recurrent, 12% for primary, $P < 0.05$). The complication rate in the recurrent group, however, is similar to reported complication rates from open mesh repair. The seroma rate is slightly higher for the recurrent group (6.4%) than for the primary group (4%). This rate compares favorably to reported seroma rates of 16%–20% in open incisional hernia repairs using expanded polytetrafluoroethylene (ePTFE).[18] Because aspiration of seromas has been associated with mesh infection,[19] these were managed by observation. Patients were routinely advised of the possibility of postoperative seroma formation. The infection rate of 2% is equivalent for the two groups and is also lower than reported rates of 4%–26% in open repairs.[20–23] One complication, a symptomatic subprosthetic mesh hematoma, occurred over 1 year postoperatively.

Of note is that surprisingly few patients complained of pain extending 6 months beyond surgery in this series. Two patients, both in the recurrent group, complained of persistent pain at sites of suture fixation and were treated with site-specific injections of local anesthetic. One patient was locally explored to remove a suture responsible for the pain and experienced subsequent relief.

The only major intraoperative complication that was noted in this study was bowel injury. This complication rate was not significantly different between the two groups. Only 1 patient early in the series required conversion to open repair due to enterotomy. Two other patients with bowel injury underwent repair of enterotomy; definitive laparoscopic repair of incisional hernias was delayed until the patients had sufficient time to heal from the initial surgery. All 3 patients recovered without any evidence of mesh infection. Although there may be minimal contamination, we believe that this two-stage approach reduces the risk of mesh infection.

Operating time was 10 minutes longer for the recurrent patients (119 minutes vs. 109 minutes, $P = 0.11$). This difference is attributed primarily to the greater amount of adhesiolysis required for recurrent hernias, as well as the larger defect size in this group. The locations of the hernias were similar; however, the recurrent group tended to have more hernias in the lateral positions and upper midline locations.

The incidence of recurrence between the recurrent and primary hernia groups is not statistically significant (7% vs. 5%). These rates, however, are still lower than reported recurrence rates for open repair of recurrent hernias (50%), for suture repair of primary hernias (24%),[5] and for open repair of primary hernias with mesh (10%–24%).

CONCLUSION

Laparoscopic repair of recurrent ventral incisional hernia is as effective as laparoscopic repair of primary ventral incisional hernia but carries a higher complication rate. This complication rate, however, is comparable to rates reported for open incisional hernia repair. The major advantage of the laparoscopic repair over open hernia repair remains the lower recurrence rate, even for recurrent hernias. This study demonstrates that the laparoscopic approach is safe and effective not only in the repair of primary but also in the repair of recurrent incisional hernia.

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Colonic Interposition vs. Gastric Pull-Up After Total Esophagectomy

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Gastric pull-up is the most frequent reconstruction after esophagectomy. In this report we aimed to compare gastric pull-up with colonic interposition in terms of graft function and patient satisfaction. Of 62 patients undergoing esophagectomy, reconstruction was performed by colonic interposition in 11 and gastric pull-up in 51 (without pyloric drainage in 44 and with pyloric drainage in 7). All esophagectomies were performed transhiatally. Patient follow-up ranged from 6 to 132 months (median 14 months). Follow-up examinations were performed 1, 9, 15, and 24 months postoperatively. The following factors were evaluated: time to the start of oral liquid and solid nutrients without vomiting, frequency of regurgitation, presence of pillow staining (night regurgitation), postprandial fullness, and degree of satisfaction during and after eating compared between groups undergoing colonic interposition and gastric pull-up with or without pyloric drainage. Among patients undergoing gastric pull-up, regurgitation was observed in 22% to 27% during follow-up. None of the patients with colonic interposition had reflux or regurgitation. Twenty-five percent of patients with gastric pull-up without drainage and 66% of patients with gastric pull-up plus drainage had reflux esophagitis at 15 months. No esophagitis was observed in patients with colonic interposition during the same period. Overall satisfaction was superior in patients undergoing colonic interposition followed by gastric pull-up with no drainage. Colonic interposition after esophageal resection is a viable option. Our study suggests that function of the replacement is better in this group of patients. (J GASTROINTEST SURG 2004;8:675–678)

KEY WORDS: Esophagectomy, gastric pull-up, colon interposition

Colon interposition has been used for esophageal replacement since the beginning of the last century and was the preferred method of replacement for a number of decades. As surgical techniques and technologies have progressed, the use of colon has decreased.[1] At the present time, reconstruction with stomach has become the preferred replacement at most institutions.[2] Among various reconstruction techniques, colonic interposition is usually performed when the stomach is unavailable or not feasible for gastric pull-up. Nevertheless, some surgeons prefer to use the colon as an esophageal replacement particularly in patients requiring esophagectomy for nonmalignant diseases.[3] Biliary reflux is one of the major discomforts encountered after gastric pull-up even in patients with no pyloroplasty or pyloromyotomy. Tight anastomoses and long suture lines in the mediastinum are other apparent disadvantages of this type of reconstruction. In this study we assessed early results with regard to quality of life following colon interposition with special emphasis on reflux/regurgitation, weight gain, and patient satisfaction during and after meals.

MATERIAL AND METHODS

Among 62 patients undergoing esophagectomy (58 for cancer and 4 for stricture), colon interposition was performed in 10 patients with esophageal tumors (4 with hypopharyngeal cancer) and one patient with benign esophageal stricture following esophageal resection with or without laryngectomy. Tumors were less than T4. In all patients esophagectomy was performed by the same surgeon transhiatally; long colonic interposition using left hemicolon preserving

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the colica media artery was performed in seven patients (isoperistaltic), and left colon–preserving left colic artery was used in four patients (antiperistaltic). Pyloric drainage was not performed in colon reconstructions. Gastric pull-up was performed in another 51 patients, and in 44 of these patients no pyloromyotomy or pyloroplasty was performed. A feeding jejunostomy was used in all patients, and enteral feeding was begun after 24 hours with 5% dextrose in water (D/W; 30 ml/hr) and continued with an elemental diet (60 ml/hr) after 48 hours. Time to the start of oral liquid and solid nutrients without vomiting, frequency of regurgitation (secretions, mostly bile stained, coming up into the mouth between meals), presence of pillow staining (night regurgitation), postprandial fullness, and degree of satisfaction during and after eating were compared between patients undergoing colonic interposition and gastric pull-up with or without drainage. Overall satisfaction was determined on the basis of pleasure of eating, which is thought to be affected by the fear of vomiting during or after meals, early satiety, and dumping. Pleasure of eating was divided into three categories as determined by comparing pleasure as follows: "as well as" preillness status, "less than" preillness status, and "eat just to stay alive." The response "as well as" preillness life was accepted as satisfaction and was compared between groups.

Patients were followed up monthly for 3 months postoperatively and every 3 months thereafter. Data were assessed after 1, 9, 15, and 24 months. During follow-up, upper endoscopy was performed if macroscopic esophagitis (erosion and edema with hyperemia) was found in the remnant esophagus, and a biopsy was obtained. For patients with stricture, yearly follow-up was performed after 1 year. Patient follow-up ranged from 6 to 132 months (median 15 months).

RESULTS

The male/female ratio was 39/23, and the mean age was 65 years (range 41 to 82 years). Perioperative (within 30 days postoperatively) mortality ratio was zero for all types of reconstructions. Hospitalization periods were not significantly different with either type of reconstruction (range 8 to 32 days, median 9 days).Time to the start of oral liquids and solids, vomiting with or after meals, postprandial fullness, regurgitation (night and day), and overall satisfaction data for both types of reconstruction are presented in Table 1. Vomiting during meals occurred in 38% of patients with gastric pull-up and drainage, and remained until 1 month. None of the patients undergoing other types of reconstruction had this complaint. Vomiting after meals was not seen in patients with colonic interposition. In all patients with gastric pull-up with drainage, vomiting after meals occurred after 1 month and persisted throughout follow-up. In patients with gastric pull-up without drainage, vomiting occurred in 45% of patients during the in-hospital period and fell to 30% after 15 months postoperatively. Regurgitation and pillow staining (regurgitation during the night) was not a complaint in patients with colonic interposition. Among patients with gastric pull-up and drainage, 28% had regurgitation during the in-hospital period that continued throughout follow-up. In patients with gastric pull-up without drainage, regurgitation occurred in 22% of the patients during the in-hospital period but showed somewhat of a decrease through follow-up. Overall percentages of regurgitation at 1 month and 15 months in patients undergoing gastric pull-up were 22% and 27%, respectively. Pillow staining was seen in 28% of patients undergoing gastric pull-up with drainage and increased during follow-up (in 2 of 3 patients at 15 months). Twenty-five percent of patients with gastric pull-up without drainage and 66% of patients with gastric pull-up and drainage had reflux esophagitis (remnant) at 15 months' follow-up. No esophagitis was observed in patients with colonic reconstruction at any time. Fewer patients with colonic interposition complained of postprandial fullness compared to other types of reconstruction. Weight gain was not significantly different between groups. But at 9 months' follow-up, patients with colonic interposition had significantly increased weight gain (5 kg vs. 2.2 kg). Although satisfaction during the in-hospital period was expressed in 68% of patients with gastric pull-up without drainage, it rose to 87% at 15 months; relevant values for patients with drainage were 85% and 60%, respectively. The percentage of patients expressing satisfaction was significantly lower at 15 months in patients with gastric pull-up with drainage. Ninety percent of patients with colonic interposition expressed satisfaction during the in-hospital period and 100% of patients at 15 months' follow-up.

DISCUSSION

Colon interposition is a well-known reconstruction technique that can be used as an esophageal replacement after total esophagectomy for malignancies or strictures. Most surgeons reserve the use of an isoperistaltic segment of colon for patients in whom the stomach is not suitable or for those whose

Table 1. Early postoperative and follow-up data of the patients

		Follow-up			
	In-hospital	**1 mo**	**9 mo**	**15 mo**	**>24 mo**
Colonic interposition (n = 11)					
	(n = 11)	(n = 11)	(n = 10)	(n = 5)	(n = 1)
Time to start oral liquids	3 days (mean)				
Time to start oral solids	6 days (mean)				
Vomiting during meals	0	2	1	0	0
Vomiting after meals	0	0	0	0	0
Fullness after meals	4	5	4	1	1
Regurgiation	0	0	0	0	0
Pillow staining	0	0	0	0	0
Esophagitis	—	0	0	0	0
Weight gain (mean)	—	2	5	3	2
Overall satisfaction	10	8	9	5	1
Gastric pull-up without drainage (n = 44)					
	(n = 44)	(n = 41)	(n = 19)	(n = 8)	(n = 3)
Time to start oral liquids	3 days (mean)				
Time to start oral solids	6 days (mean)				
Vomiting during meals	17	15	0	1	0
Vomiting after meals	20	11	2	0	0
Fullness after meals	37	15	6	3	1
Regurgitation	10	5	2	1	1
Pillow staining	8	0	0	0	0
Esophagitis	—	4	2	2	1
Weight gain (mean kg)	—	2	2.5	3	2
Overall satisfication	30	40	15	7	2
Gastric pull-up with drainage (n = 7)					
	(n = 7)	(n = 7)	(n = 6)	(n = 3)	(n = 1)
Time to start oral liquids	3 days (mean)				
Time to start oral solids	6 days (mean)				
Vomiting during meals	1	2	2	1	0
Vomiting after meals	1	3	3	2	1
Fullness after meals	5	3	0	0	0
Regurgitation	2	6	6	2	1
Pillow staining	2	5	5	2	1
Esophagitis	—	5	4	2	1
Weight gain (mean kg)	—	2	2	2	2
Overall satisfication	6	4	3	2	1

favorable long-term prognosis justifies the longer operative time and creation of an additional anastomosis. The advantages of this reconstruction are it provides a good length of graft, which is essential for a safe anastomosis, and it allows a tube of a good diameter. The use of a colonic interposition reduces the incidence of reflux esophagitis and stricture associated with esophagogastrostomy.[4]

Regurgitation is one of the major problems in patients undergoing gastric pull-up. Between 25% and 30% of our patients had regurgitation during follow-up. The incidence of reflux esophagitis in the remnant esophagus when the stomach was used as a substitute ranges from 30% to 78%.[5,6] However, Shibuya et al.[5] found no correlation between reflux symptoms and endoscopic findings of reflux esophagitis. Gutshow et al.[6] noted that gastric acidity in the denervated stomach is strongly related to the incidence of reflux esophagitis.They pointed out that the decreased acidity after vagotomy recovers its normal pH profile with time.[7] We did not qualify the refluxate but biliary-stained material was observed in all patients with regurgitation. Also, the number of patients with regurgitation was significantly increased in the drainage group all of the time (12% vs. 85% during the first month and 5% vs. 83% at 9 months). After esophagectomy and gastric pull-up, there is no reliable structure to prevent duodenogastric and gastroesophageal reflux-regurgitation because of the

resection of the esophagogastric junction. Eliminating pyloric drainage only partially decreases the problem. A prospective randomized trial demonstrated that not performing a drainage procedure affected the gastric emptying time, but the difference in symptomatic delayed emptying between drainage and nondrainage groups was not significant, and clinical outcome long term was comparable in both groups. Thus the authors concluded that drainage procedures would be of benefit in only a few patients who might manifest symptomatic gastric stasis.[8] Bemelman et al.[9] showed that gastric emptying was not dependent on pyloric drainage in these patients but rather on the size of the gastric substitution. Deglutition and regurgitation are important after esophageal substitution. The motility of the colon interposition used to restore transit after esophagectomy was shown to be similar to that described for the colon.[10] The contractions may be the consequence of graft distention after successive swallows, and emptying is more rapid in isoperistaltic loops.[11] There appears to be no difference in the complication rate between gastric pull-up procedures and colon interpositions.[12] Colonic grafts are not associated with increased postoperative mortality or complications.[13] Wain[14] reported long-term results of 136 long-segment colon interpositions and found excellent function in 88%, good function in 10%, and poor results in only 2.5% of patients; function in their study was attributed to the absence of dysphagia and weight gain. Operative mortality in that study was 16% in the malignant group and 0% in the nonmalignant group. The 0% operative mortality in our study groups might be explained by the small number of patients. Mathisen and Wilkins[15] pointed out that this operation requires meticulous attention to technical detail for a successful outcome. They concluded that when the outcome was successful, the colon had proved to be an effective lasting viscus with which to replace the esophagus. In our limited experience with colon interposition, we found that the degree of difficulty of the operation was comparable to that of gastric pull-up.

Patient satisfaction inferred from eating pleasure seemed to be superior in the colon interposition group (72% to 100%) compared to gastric pull-up without drainage (78% to 97%) and gastric pull-up with drainage (50% to 60%). Our early results suggest that the colon is one of the best substitutes for the esophagus, and there is no need to perform a routine pyloroplasty or antireflux procedure as an adjunct to the primary surgery.

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Major Bile Duct Injuries After Laparoscopic Cholecystectomy: A Tertiary Center Experience

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Bile duct injury is a severe and potentially life-threatening complication of laparoscopic cholecystectomy. Several series have described a 0.5% to 1.4% incidence of bile duct injuries during laparoscopic cholecystectomy. The aim of this study was to report on an institutional experience with the management of complex bile duct injuries and outcome after surgical repair. Data were collected prospectively from 40 patients with bile duct injuries referred for surgical treatment to our center between April 1998 and December 2003. Prior to referral, 35 patients (87.5%) underwent attempts at surgical reconstruction at the primary hospital. In 77.5% of the patients, complex type E1 or type E2 BDI was found. Concomitant with bile duct injury, seven patients had vascular injuries. Roux-en-Y hepaticojejunostomy was carried out in 33 patients. In two patients, Roux-en-Y hepaticojejunostomy and vascular reconstruction were necessary. Five patients, one with primary nondiagnosed Klatskin tumor, required right hepatectomy. Two patients, both with bile duct injuries and vascular damage, died postoperatively. Because of progressive liver insufficiency, one of them was listed for high-urgency liver transplantation but died prior to intervention. At the median follow-up of 589 days, 82.5% of the patients are in excellent general condition. Seven patients have signs of chronic cholangitis. Major bile duct injuries remain a significant cause of morbidity and even death after laparoscopic cholecystectomy. Because they present a considerable surgical challenge, early referral to an experienced hepatobiliary center is recommended. (J GASTROINTEST SURG 2004;8:679–685)

KEY WORDS: Laparoscopic cholecystectomy, major bile duct injuries

Since its introduction in the 1990s by Dubois et al.,[1] laparoscopic cholecystectomy has become the "gold standard" treatment for symptomatic gallstone disease. Limited postoperative discomfort, shorter hospitalization, and rapid postoperative recovery proved to be advantages of the procedure. Concomitantly it became obvious that the incidence of bile duct injury (BDI) rose from 0.06% to 0.3%, as known for open cholecystectomy,[2–5] to 0.5% to 1.4% when gallbladder removal is performed laparoscopically.[6–11] In addition, injuries of the bile duct system after laparoscopic cholecystectomy are more complex than after an open approach and cause significant morbidity and even death. Associated vascular lesions, in particular injuries to the right hepatic artery, or longitudinal strictures of the common bile duct due to failed repair attempts are not uncommon.

In the initial studies on laparoscopic gallbladder removal, complications such as bleeding, wound infections, respiratory insufficiency, trocar injury to the intra-abdominal viscera, major vascular injuries, and bile leaks accounted for reported morbidity rates ranging from 1.0% to 8.0%.[12,13] Despite the completion of the learning curve and the recognition of preventive maneuvers to avoid ductal injury during laparoscopic cholecystectomy,[14] the rate of BDI remains stable. Failure to identify the injury immediately after its occurrence and consecutive switch to

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an open procedure with an attempt to perform definitive repair, inappropriate management of a recognized injury, and subsequent delay in adequate treatment are key issues in the outcome of patients with bile duct damage. We report our experience with treatment of BDI in patients referred to our institution after laparoscopic cholecystectomy performed at a primary hospital.

MATERIAL AND METHODS

Patients

From April 1998 to December 2003, a total of 40 consecutive patients (25 women and 15 men), aged 25 to 77 years (median 49 years), with biliary tract injuries after laparoscopic cholecystectomy were referred to our unit for further surgical treatment. The data from these patients were evaluated prospectively. The indication for primary operation was symptomatic cholecystolithiasis in 27 patients, acute cholecystitis in 12 patients, and suspected gallbladder perforation in one patient.

Management at the Primary Hospital

Laparoscopic cholecystectomy was described as complicated in 25 patients and uneventful in the remaining 15. Intraoperative cholangiography was a routine component of the procedure in 8 (20.0%) of the 40 patients. In 13 patients the primary operation had been converted to open laparotomy after bile leaks (50%), bleeding, or anatomic anomalies were observed. Bile duct injuries were recognized in 10 of these patients and followed by a subsequent surgical intervention (biliary-enteric anastomosis, duct-to-duct anastomosis, or T-tube placement). In one patient, reconstruction of the hepatic artery was carried out in addition to hepaticojejunostomy. In three patients undergoing laparotomy, no BDI was identified despite intraoperative cholangiography.

At a median of 2 days (range 1 to 33 days) after laparoscopic cholecystectomy, the clinical course (abdominal pain, elevated serum bilirubin levels, evidence of bile in the abdominal drainage) led to a suspicion of BDI in 22 additional patients. To further identify the location of the suspected injury, endoscopic retrograde cholangiopancreatography (ERCP) was performed in all 22 patients. Consecutively, in 15 of the patients one or more laparotomies and different surgical procedures (local drainage, T-tube drainage, hepaticojejunostomy) took place. Endoscopic interventions and stent implantation were carried out in the remaining seven patients. During the follow up in five patients with an uneventful early postoperative course, bile duct strictures occurred. Laparotomy and T-tube insertion were carried out in two patients at 6 and 8 months after laparoscopic cholecystectomy, respectively. In three patients endoscopic intraluminar stent implantation was performed (1 to 4 years after laparoscopic cholecystectomy).

Indications for referral to our institution were bile duct strictures, asymptomatic bile leaks, biliary-enteric anastomotic strictures, peritonitis due to intra-abdominal collection of bile, bile leak and pancreatitis, recurrent cholangitis, and biliary-enteric anastomotic stricture in combination with a liver abscess. The median time between the diagnosis of biliary tract injury and referral was 12 days (range 2 hours to 4.5 years).

Management at Our Institution

Classification of BDI according to Strasberg et al.[14] and Bismuth[15] was determined after reviewing the medical files from the referring hospital and consideration of the results of our own imaging studies (Table 1). ERCP was performed in 28 patients (70.0%), percutaneous transhepatic cholangiography in eight patients (20.0%), and helical CT in 12 patients (30.0%). All patients with type E1 or E2 injuries underwent magnetic resonance cholangiopancreatography or angiography to rule out combined vasculobiliary lesions. To accurately assess the extent of the injury, more than one imaging study was necessary in 18 patients (Figs. 1, 2, 3, 4, and 5).

Thirty-one patients (77.5%) had type E1 (circumferential injury to the common duct >2 cm from the bifurcation) or E2 (circumferential injury to the common duct <2 cm from the bifurcation) bile duct injuries (see Figs. 1 and 4). Type A injury was found in three patients, type C and D injury each in one patient, and type E3 and E4 injury each in two patients. In seven patients, biliary tract injuries were associated

Table 1. Classification of bile duct injury during laparoscopic cholecystectomy according to Strasberg et al.[14] and Bismuth[15]

Type A injury:	Bile leak from minor duct still in continuity with common bile duct
Type B injury:	Occlusion of part of biliary tree
Type C injury:	Bile leak from duct not in communication with common bile duct
Type D injury:	Lateral injury to extrahepatic bile ducts
Type E injury:	Circumferential injury of one or more major bile ducts (Bismuth class 1 to 5; subclassification in class 1 to 4 relates to the upper level of injury, class 5 is a combined common hepatic duct and aberrant right duct injury)

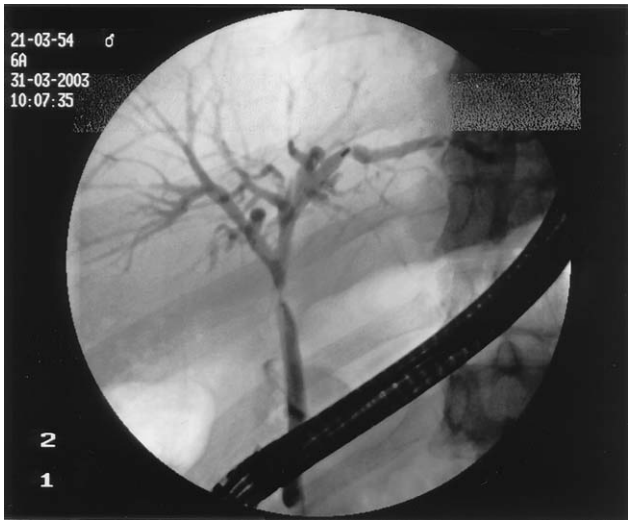

Fig. 1. Patient with type E1 injury. Endoscopic retrograde cholangiography demonstrates nearly complete obstruction of the common hepatic duct.

with concomitant vascular injuries; five of these injuries affected the right hepatic artery and two affected the common hepatic artery. Infectious complications and renal insufficiency were present in 23 (57.5%) and 4 (11.4%) patients, respectively.

Among these 40 patients, five underwent laparotomy immediately after referral to our institution. Twenty-five patients underwent surgery shortly after referral, and in the remaining subgroup of patients

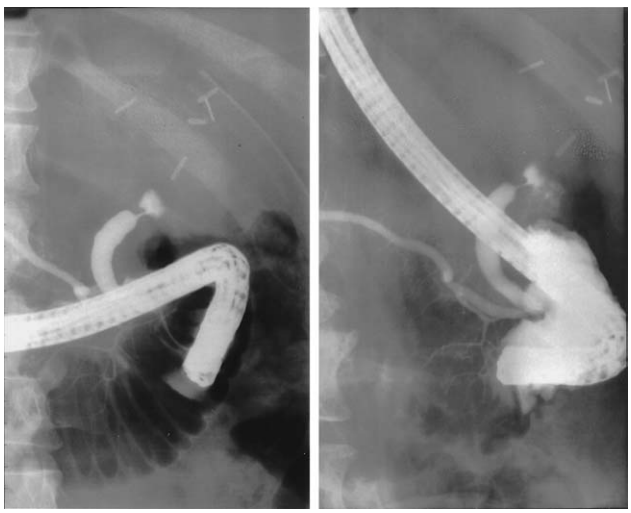

Fig. 2. Endoscopic retrograde cholangiogram of a patient with the common hepatic duct cut totally. Several metallic clips are placed into the hilar region. Typically the proximal portion of the bile duct is not imaged.

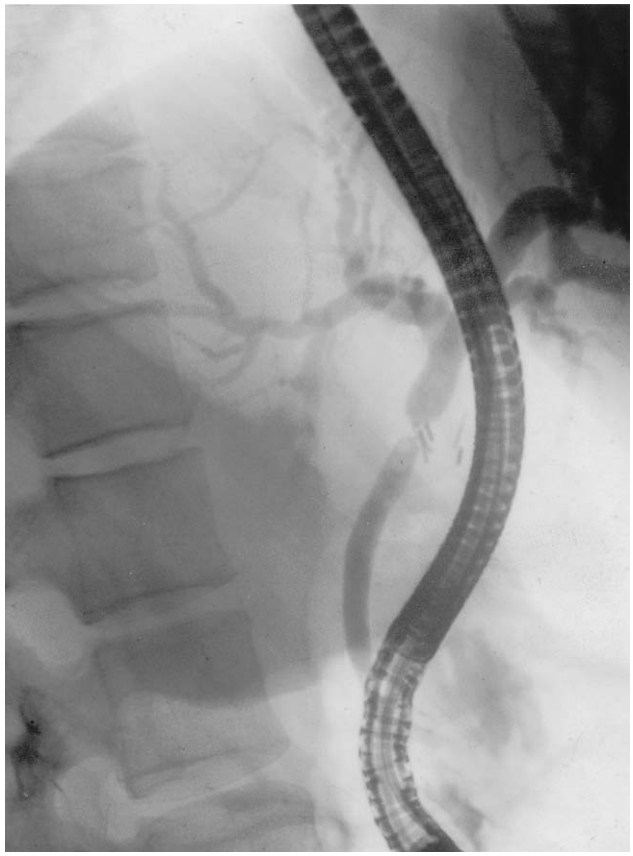

Fig. 3. Endoscopic retrograde cholangiogram showing metallic clips occluding the common bile duct below the confluence.

reoperation was postponed to eradicate biliary peritonitis and local inflammation. The damage was managed with a proximal tension-free direct mucosa-to-mucosa Roux-en-Y hepaticojejunostomy with interrupted, absorbable sutures in 33 patients. Careful consideration was given to complete removal of local inflammatory material and scar tissue. Roux-en-Y hepaticojejunostomy and vascular reconstruction using a mesenteric venous graft provided by our tissue bank was carried out in two patients. In one patient, significant acute parenchymal necrosis and in another three patients sclerosing cholangitis due to chronic biliary necrosis confirmed histologically required right hepatectomy. All four patients had not only biliary but also vascular lesions. In one patient, resection of the right hepatic lobe and Roux-en-Y hepaticojejunostomy were performed because of an injury to the hepatic duct bifurcation and a Klatskin tumor not recognized during laparoscopic cholecystectomy. Transanastomotic drains were placed in five patients with difficult reconstruction. Postoperatively one patient underwent relaparotomy after failed attempts to percutaneously drain a subhepatic abscess. The

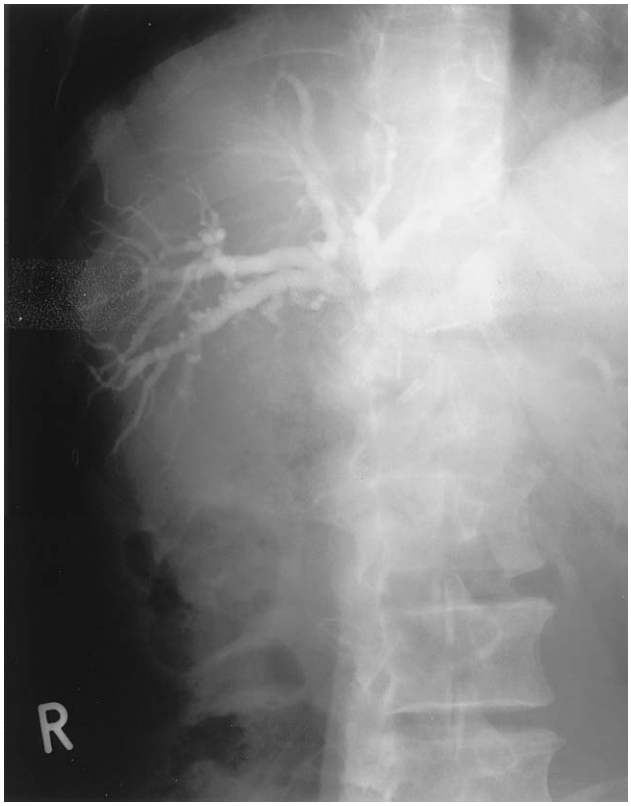

Fig. 4. Patient with type E2 bile duct lesion after laparoscopic cholecystectomy. A hepaticojejunostomy had been performed at the primary hospital. Because of persisting cholestasis, the patient was referred to our institution for reoperation. Percutaneous transhepatic cholangiogram shows near-total stricture of the anastomosis and several metallic clips in the hilum.

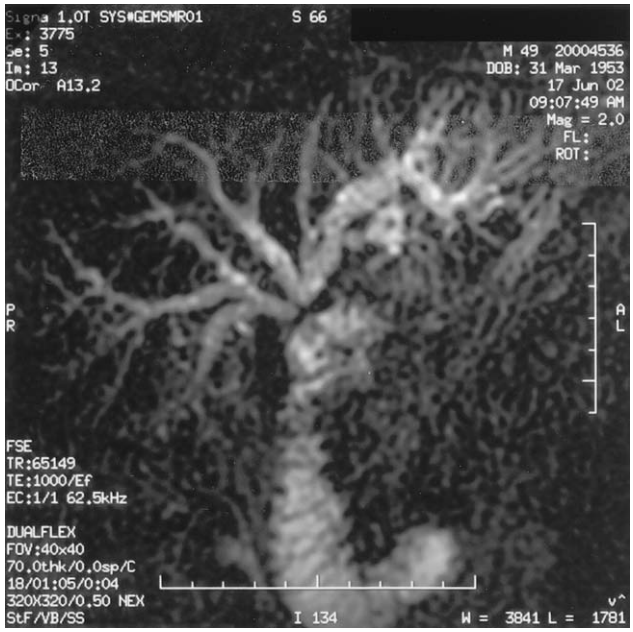

Fig. 5. Magnetic resonance cholangiopancreatographic sequence in a patient with a tight stenosis of a hepaticojejunostomy performed after BDI in a primary hospital setting.

duration of postoperative in-hospital stay ranged from 7 to 37 days with a median duration of 12 days.

Two patients (5.0%), both with type E2 bile duct injuries and concomitant vascular lesions, died during the hospital stay. In one 35-year-old patient, failed repair of the vascular and biliary damage led to referral to our institution on day 16 after laparoscopic cholecystectomy. Bile leak, ligated right hepatic artery, thrombosis of the portal and superior mesenteric vein, necrosis of the right hepatic lobe, and acute pancreatitis were found during relaparotomy. Four days after right hepatectomy and hepaticojejunostomy, perforation of the duodenum required relaparotomy and duodenojejunostomy. Because of liver insufficiency, the patient was placed on the high-urgency list for liver transplantation; however, she died on postoperative day 28 of septic complications and multiorgan failure. The second patient, who was 52 years of age, had a common hepatic artery injury and a type E1 biliary lesion. After an unsuccessful explorative laparotomy on day 17 after laparoscopic cholecystectomy, the patient was referred to our department. Reconstruction of the common hepatic artery using a venous graft placed between the celiac trunk and the proper hepatic artery and drainage of the transected hepatic ducts was performed during the first operation. Advanced biliary peritonitis of the right upper abdomen was evident. After stabilization of the general condition of the patient and normalization of the parenchymal blood supply, hepaticojejunostomy was carried out 3 days later. Acute pancreatitis and renal failure developed postoperatively. The patient died of acute cardiac arrest on postoperative day 37.

At a median follow-up of 16 months (range 1 to 42.7 months), 33 patients (82.5%) are clinically and biochemically stable without any pathologic findings. In three patients who were clinically symptom free, liver tests indicate chronic cholangitis. Two patients have clinically evident mild recurrent cholangitis. In order to assess our long-term results, follow-up was extended in all 38 patients.

DISCUSSION

Injuries to the bile duct system during laparoscopic cholecystectomy are an unaltered cause for concern not necessarily related to the "learning curve" of the operating surgeon as suggested in the past.[7,9,11] In recent studies, it was demonstrated that in more than one third of all bile duct injuries the basic cause of

error is not the inexperience of the surgeon but the use of an improper approach to the fundamental structures of the extrahepatic biliary tree because of a visual perceptual illusion.[7,16] Correspondingly, in most cases the problem is not recognized at the time of the initial procedure, particularly in the presence of acute inflammation or chronic fibrosis. The role of intraoperative cholangiography and laparoscopic ultrasonography in prevention of BDI during laparoscopic cholecystectomy is a matter of ongoing debate.[17,18] In our opinion, intraoperative imaging of the bile duct system does not prevent the surgeon from making this false interpretation; however, it may contribute to a timely recognition of the injury and shorten the delay in appropriate repair.

Classically, the hepatocholedochal duct is mistaken for the cystic duct. In contrast to the open approach, this situation is frequently associated with damage to hilar vascular structures. The most common injuries in reports from tertiary centers such as ours involve transection of the common bile duct (CBD) combined with a variable loss of ductal tissue or stenosis at or below the hepatic bifurcation. This situation, which leads to a "separation" of liver parenchyma from the lower CBD and duodenum,[14] was found in 77.5% of the patients referred to us. In accordance with our experience, damage to the CBD corresponding to type E injury[14] was evident in 61% of the patients treated by Way et al.,[16] in 65% of the cases analyzed by Strasberg et al.,[14] and in 72.7% of patients in the series published by Rossi et al.[19] Because the incidence of this severe type of injury is much lower in reports presenting data from surveys,[9] questionnaires,[6] or multiinstitutional reviews,[12,20] one may presume that once a diagnosis of CBD transection is made, the patient will most likely be referred to a specialized center rather than undergoing treatment at the institution where the primary operation took place.

In accordance with this experience, the rate of concomitant injuries to vessels in the hepatoduodenal ligament (i.e., right hepatic artery) documented in referral centers is much higher: 17.5% in our series and 24% in a report from a tertiary referral center from the University of Oslo[21] vs. 0.057% in a 1993 United States national survey.[6] Vascular injuries contribute significantly to postoperative morbidity and mortality, particularly in cases of delayed diagnosis. It has been shown that ductal ischemia due to concomitant hepatic arterial damage may be a cause of failed primary hepatojejunostomal reconstruction[22,23] or late peripheral bile duct stenosis. Occlusion of the right artery can lead to necrosis of the right hepatic lobe and the need for a right hepatectomy. Particularly devastating are simultaneous portal vein lesions because normal portal circulation is a prerequisite for recuperation of dearterialized hepatic parenchyma. In a report from Northwestern University Medical School, 83% of the referred patients with failed primary management of a BDI had Bismuth level 3 or 4 lesions. Concomitant vascular injury was present in 71% of those with Bismuth level 4 lesions and in 63% of the patients with Bismuth level 3 BDI.[22] Both patients who died postoperatively in our series, despite aggressive surgical and antibiotic treatment, had complex vasculobiliary injuries; in one of these patients not only was an arterial lesion found but damage to the portal and mesenteric vein as well. The prognostic impact of vascular damage has been underlined by Buell et al.,[24] who reported on a 38% mortality rate in the presence of arterial lesions as opposed to 3% in patients with injuries limited solely to the bile duct. When vascular injury is recognized during the original operation, we would recommend immediate arterial reconstruction if the surgeon is capable of doing it or transfer of the patient to a tertiary speciality center for definitive surgical repair. Delayed diagnosed vascular lesions are mostly not accessible for revascularization and can be followed by hepatic necrosis or persistent cholangitis resulting in end-stage liver cirrhosis. Because of our experience in one patient who died while waiting for a suitable organ, and data reported by others, BDI associated with complex vascular lesions might even necessitate liver transplantation.[25]

Besides the type of BDI, the skill level of the primary surgeon in advanced hepatobiliary techniques and the interval between the BDI and referral to a tertiary center are significant predictors of outcome. In the present study, 87.5% of the patients were subjected to attempts at surgical repair at the primary hospital, some of them numerous times (see Figs. 4 and 5). Most of the failed biliary-enteric anastomoses were placed at too low a level and exhibited technical faults such as use of nonabsorbable suture material or two-layer anastomotic technique. Poor arterial supply to the bile duct contributed to the high rate of failure. Although concomitant vascular injuries were present in seven of these patients, only one surgeon recognized this problem; however, he failed to cope with it. In cases of delayed recognition of a BDI, local inflammation and high-grade of fibrosis complicated its management. These observations are in agreement with the experience of others; although the success rate of biliary-enteric anastomoses amounts to 98% in specialized centers, it drops below 30% in a primary hospital setting.[25–27] In addition, recurrent infection due to chronic biliary stasis may lead to sclerosing cholangitis frequently necessitating further surgical interventions. The median time between the

recognition of a BDI in the primary hospital and referral of the patient to our center amounted to 12 days. Only five patients, two of them directly from the primary operating room, were referred within 24 hours after laparoscopic cholecystectomy to our institution. In all of these five patients, immediate reoperation was performed yielding an uncomplicated postoperative course and short hospitalization. Both patients who died after reoperation at our center were transferred with a delay of 16 and 17 days, respectively. In both patients the course of the disease was exacerbated by an advanced local infection and septic complications. Furthermore, patients initially managed in nonspecialized centers had a significantly longer overall duration of illness compared to those promptly referred to a tertiary facility.

Bile duct injuries not only contribute to immediate postoperative morbidity but also can have a negative impact on the long-term quality of life after laparoscopic cholecystectomy. In a recent study by Boerma et al.,[28] the most powerful factors influencing quality of life were the type of BDI and the subsequent management form. In contrast, the group from The Johns Hopkins Medical Institutions in Baltimore showed that quality of life is impaired after surgical repair of BDI independent of the characteristics in each subgroup of patients.[29] Besides the medical issues, the significant costs related to this complication must also be considered. In comparison to an uneventful gallbladder removal, total treatment costs for complicated laparoscopic cholecystectomy are 4.5- to 26.0-fold higher. Again, early recognition and appropriate treatment reduce the overall costs of bile duct injuries by 43% to 83%.[30]

CONCLUSION

Laparoscopic cholecystectomy is associated with a 0.5% to 1.4% rate of bile duct injuries. In contrast to open cholecystectomy, not only complex BDI but also damage to vascular structures within the hepatic hilum can be found in a large number of patients referred to tertiary centers. Early recognition and adequate treatment at specialized institutions account for the key prognostic parameters. Significant costs for hospitalization and outpatient care and impaired long-term quality of life after treatment are factors that additionally underline the problems of the occurrence of a BDI during laparoscopic cholecystectomy.

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Extrahepatic Bile Duct Resection in Combination With Liver Resection for Hilar Cholangiocarcinoma: A Report of 42 Cases

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From September 1986 until December 2001, 42 patients (20 males and 22 females) underwent a combined extrahepatic bile duct resection (EHBDR) and liver resection (LR) for hilar cholangiocarcinoma (HC). The aim of this study was to analyze patient survival, morbidity, and mortality as well as to seek predictive factors. The 1-, 3-, and 5-year actuarial patient survival was 72%, 37%, and 22%, respectively. Median survival was 19 months. Hospital mortality, all due to septic complications, was 12%. Morbidity was observed in 32 patients (76%). Infections were the most dominant complication. Patients (n = 11) with American Joint Committee on Cancer (AJCC) stage I or stage II tumors exhibited a superior survival compared with patients (n = 31) with stage III or IV tumors ($p = 0.023$). Patients with tumor-free lymph nodes (n = 26) indicated a greater survival compared with patients with tumor-positive lymph nodes (n = 16) ($p = 0.004$). Patients undergoing vascular reconstructions indicated a trend toward higher mortality and lower survival ($p = 0.068$). Over 20% of the patients with hilar cholangiocarcinoma can survive more than 5 years after a combined EHBDR and LR at the cost of 12% perioperative mortality and a 76% morbidity. Results might improve with the prevention of infectious complications and improved selection of patients to avoid vascular reconstruction and to predict a negative nodal state. (J GASTROINTEST SURG 2004;8:686–694)

KEY WORDS: Curative resection, hilar bile duct carcinoma, surgical treatment, survival rate

INTRODUCTION

Hilar cholangiocarcinoma and proximal bile duct carcinoma are both synonyms for the tumor that Klatskin gave his name to in 1965.[1] Hilar cholangiocarcinoma is a rare tumor. The overall incidence of cholangiocarcinoma is 0.8/100,000 in females and 1.2/100,000 in males.[2] Hilar bile duct carcinomas are predominantly adenocarcinomas.[3,4] The properties of this tumor often make it difficult to treat. It is a slow but infiltrative growing carcinoma. It tends to infiltrate into the liver along perineural spaces, periductal lymphatics, and perivascular spaces. In addition, it also spreads along the bile duct wall.[5] The carcinoma is located close to other essential structures like hepatic artery and portal vein bifurcations and tends to invade the caudate lobe.[6]

Because of its localization, the first symptoms usually present themselves late. In most cases, the tumor obstructs the hilar bifurcation. Hence, jaundice is the presenting complaint in over 90% of patients.[4,7] Proper treatment for this type of tumor has been discussed for a long time. Debate still remains as to whether to apply surgery or palliative stenting procedures to achieve the longest survival with the best quality of life. Surgery, initially confined only to a resection of the extrahepatic bile duct, offers the only chance for cure.[4,8] In the following years, it seemed that adding a partial hepatectomy to extrahepatic bile duct resection (EHBDR) offers a survival benefit.[7,9–11] The aim of this study is to evaluate our results of combined EHBDR and liver resection (LR) for hilar cholangiocarcinoma and to analyze if predictive factors for survival exist.

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PATIENTS AND METHODS

Study Design

Data was collected from a database at the Division of Hepatobiliary Surgery and Liver Transplantation (Groningen, The Netherlands) started in 1986. These data included patient demographics, operative data, morbidity, mortality, follow-up, and pathology data concerning resection planes. This information was put into the database directly upon discharge of the patient after their initial operation and after the outpatient visits during follow-up. Only data concerning pathology required for staging of the carcinoma, hospital stay, and comorbidity were retrospectively collected from patient records. Patient inclusion ended on December 31, 2001 and follow-up was continued until March 31, 2002.

Patient Demographics

In the study period, 42 patients (20 males and 22 females) underwent a combined resection of the EHBDR and LR for treatment of a hilar cholangiocarcinoma. The median age of the patients was 60 years (range 35–74). Comorbidity was present in 19 (45%) patients. The majority of the patients (n = 8) exhibited cardiovascular comorbidity, mainly myocardial infarctions. Two patients exhibited primary sclerosing cholangitis, 4 patients exhibited chronic obstructive pulmonary disease, 2 patients exhibited diabetes mellitus (1 patient was type I and 1 patient was type II), 3 patients exhibited a combination of these diseases, 1 patient exhibited chronic obstructive pulmonary disease and diabetes mellitus type I, and 2 patients exhibited cardiovascular comorbidity and diabetes mellitus type II.

Patient Selection and Work-Up

All patients were diagnosed as exhibiting hilar cholangiocarcinoma on the basis of their histories combined with findings on endoscopic retrograde cholangiopancreaticography (ERCP), percutaneous transhepatic cholangiography (PTC), or both. Computed tomography (CT) scanning of the thorax was performed to exclude metastases. Preoperatively, all patients exhibited either an arteriography or a Doppler ultrasound of the liver vasculature to investigate whether involvement of the portal vein or hepatic artery was present. Patients with thrombosis of the portal vein or one of its main tributaries were still considered candidates for resection if the thrombosed section of the portal vein could be removed and a reconstruction of portal inflow to the liver remnant could be foreseen. Occlusion of the hepatic artery belonging to the part of the liver to be resected was accepted. In all patients, adequate preoperative biliary drainage was secured. This was performed preferably by endoscopic stents with or without a rendezvous procedure if necessary. If this was not possible, percutaneous drainage was accepted. Independent of the type of drainage, care was taken to drain both left and right hepatic duct systems. To prevent atrophia of jejunal villi and to conserve the hepato-enteric loop, collected bile was given back to the patient via a nasal jejunal feeding tube during the waiting time for surgery. If required, patients also received additional enteral feeding through this tube. A preoperative laparoscopy was not performed in any of the patients.

Until the end of 1999, all patients were given selective decontamination of the bowel, starting 2 days preoperatively, as described earlier by our group.[12] It consisted of a combination of orally given nonabsorbable antibiotics: tobramycine, amphothericine-B, and colistine. Additionally, parenteral antibiotics were given for the first 48 hours. Since 1999, only parenteral antibiotics were given for the first 24 hours after surgery.

Surgical Techniques

Laparotomy was performed via a bilateral subcostal incision with an extension in the midline to the xyphoid process. First, the abdominal cavity was inspected to exclude peritoneal and omental carcinomatosis. If free fluid was present, cytology was performed to exclude free malignant cells. The liver and hepatoduodenal ligament was inspected to see whether the planned procedure was feasible. The gallbladder was retrogradely freed from its liver bed and kept in continuity with the common bile duct. Next, all lymphatic tissue around the celiac trunk, the cranial border of the upper flexure of the duodenum, and hepatoduodenal ligament was dissected. Care was taken to maintain the continuity of the lymph-node dissection with the extrahepatic bile duct and the part of the liver to be resected. If suspicion on extranodal tumor growth was present, this was checked by frozen section. If positive, the operation was aborted.

The common bile duct was transected just above the duodenum. The resection margin was checked for tumor growth. Next, the common bile duct was dissected from the portal vein and right hepatic artery toward the hilum of the liver. If no invasion in the portal vein was present, exploration was continued in the hilum of the liver after dividing the hilar plate. The bile duct connecting to the future liver remnant was dissected as far as possible into the parenchyma and transected. A frozen section of the resection

margin was performed to see if the margin was free of tumors. If a positive margin was obtained, the resection was continued further if possible.

If the tumor invaded only the ipsilateral portal vein, this branch was separated from the bifurcation with a sufficient margin. The margin was checked by frozen section. If the tumor invaded the portal vein bifurcation, the main portal vein branch on the contralateral side of the tumor was dissected and sufficiently mobilized so that it could be clamped. During this phase of the operation it was checked as to whether the artery toward the projected liver remnant was patent. If so, the portal vein stem and the main portal vein branch belonging to the projected liver remnant were clamped with vascular clamps and the portal vein bifurcation was resected. First, the continuity of the portal vein was reconstructed either by an end-to-end anastomosis or by an interposition graft of an external iliac vein graft of the patient. In this phase, the ipsilateral hepatic artery was closed as well. By traction on the common bile duct, the main bile duct toward the projected liver remnant was pulled from the parenchyma and dissected as far as possible in the parenchyma from the projected remnant to get a free (frozen section) cut surface. After transsection of the bile duct, the part of the liver to be resected was freed and dissected from the inferior caval vein. The hepatic veins belonging to it were dissected and closed. Guided by the discoloration of the hepatic parenchyma it was transected with the cavitron ultrasonic surgical aspirator (CUSA, Valley Lab, Boulder, CO) ultrasound dissector. After hemostasis, the continuity of the biliary tract was reestablished with a Roux-en-Y hepaticojejunostomy over a silastic stent. In case, a percutaneous transhepatic catheter for drainage (PTCD) was still present in the liver remnant. This was kept in place as stent for the hepaticojejunostomy. The operation was concluded with the insertion of a needle feeding jejunostomy.

In Table 1, the type of LRs performed concomitant with the EHBDR is indicated. In 20 patients, segment 1 was included. In addition to the hepatic resection, 5 patients underwent a reconstruction of the portal vein, 2 patients underwent an arterial reconstruction, and 2 patients underwent combined portal vein and arterial reconstruction.

Table 1. Type of liver resections performed

Segments	N	%
123	1	*2%*
1234	16	*38%*
123458	1	*2%*
14	1	*2%*
145678	5	*12%*
234	2	*5%*
4	4	*10%*
45678	9	*21%*
5678	3	*7%*

Follow-Up

After hospital discharge, patients were seen every 3 months during the first 2 years and every 6 months until at least 5 years after the resection. At each visit, an abdominal (Doppler) ultrasound was performed. Follow-up was defined as the number of months between the operation date and the date of death or, if the patient was alive, the end date of the study period (March 31, 2002).

Outcome Parameters

Patient survival was defined as the number of months between the operation and patient death. Surviving patients were censored after the end of the study period (March 31, 2002). Recurrence was defined as a histologically proven recurrent tumor by biopsy, brush cytology, clinical suspicion on the CT scan, or cholangiography. Mortality was defined as in-hospital mortality during the initial hospitalization for the operation. Morbidity was assessed by analyzing the incidence of bleeding and hepatic, biliary, lung, wound, and infectious complications. Furthermore, morbidity was expressed as the proportion of patients exhibiting one or more complications and as the mean number of complications per patient.

Study Parameters

Patients were staged on the basis of the pathology reports of the operative specimens according to the American Joint Committee on Cancer (AJCC) staging system.[13] To investigate whether predictive factors for survival were present, the relation with the following study parameters was assessed: age, presence of comorbidity, and AJCC stage of disease. Furthermore, resection margins, nodal status, vascular reconstructive surgery, side of hepatectomy, and blood loss were taken into account. Resections were defined as follows: R0 resection when bile duct, vascular, and parenchymal margins were all free of tumor cells, R1 resection when tumor cells were identified on light microscopy in one or more of the mentioned margins, and R2 resection when a macroscopic tumor was left behind in one or more of the indicated margins. Nodal status was considered positive if one or more of the lymph nodes in the resection specimen contained a tumor. Finally, whether segment I was included in the resection or not was analyzed.

Statistical Methods

The parameters were compared with the χ^2 test. The exact test was applied when appropriate. Survival curves were constructed using the methods described by Kaplan and Meier.[14] The log-rank test was used to determine statistical significance. A significant difference was defined as a p value < 0.05.

Table 2. Morbidity figures

Infections sepsis/abcesses/mof	24*
Biliairy leaks	11
Lung complications	10
Liver insufficiency	6
Postoperative bleeding	3
Morbidity episodes 1.5/patient	

*Including 5 deceased patients.

RESULTS

Median follow-up of the patients was 19 months (range 0–178). The median hospital stay of the patients was 35 postoperative days (range 13–176). The 1-, 3-, and 5-year overall survival was 72%, 37%, and 22%, respectively. The overall median survival was 19 months. Fifteen patients (36%) were still alive at the end of the observation period. In Fig. 1, the overall survival of the 42 patients from this series is illustrated. The longest period after which recurrence occurred was 70 months.

Five patients (12%) died postoperatively during their initial hospitalization. All 5 patients died as a result of infectious and septic complications leading to multiorgan failure. In 32 patients (76%), morbidity was observed (Table 2). The mean number of complications per patient was 1.5 (range 0–6). Age, comorbidity, resection margin status, side of hepatectomy, and blood loss did not influence survival ($p > 0.4$).

According to the pathology report, 1 patient exhibited AJCC stage I disease, 10 patients exhibited stage II, 10 patients exhibited stage III, and 21 patients exhibited stage IVa disease. In Fig. 2, the influence of tumor stage on survival is illustrated. Patients with tumor stage I or II exhibited a significantly longer survival compared with those with tumor stage III or IVa ($p = 0.023$). Patient survival according to R status is indicated in Fig. 3. Patients with R0 type resection indicated no difference in survival compared with those with R1 type resection ($p = 0.867$). Two patients with R2 type resection died within 6 months

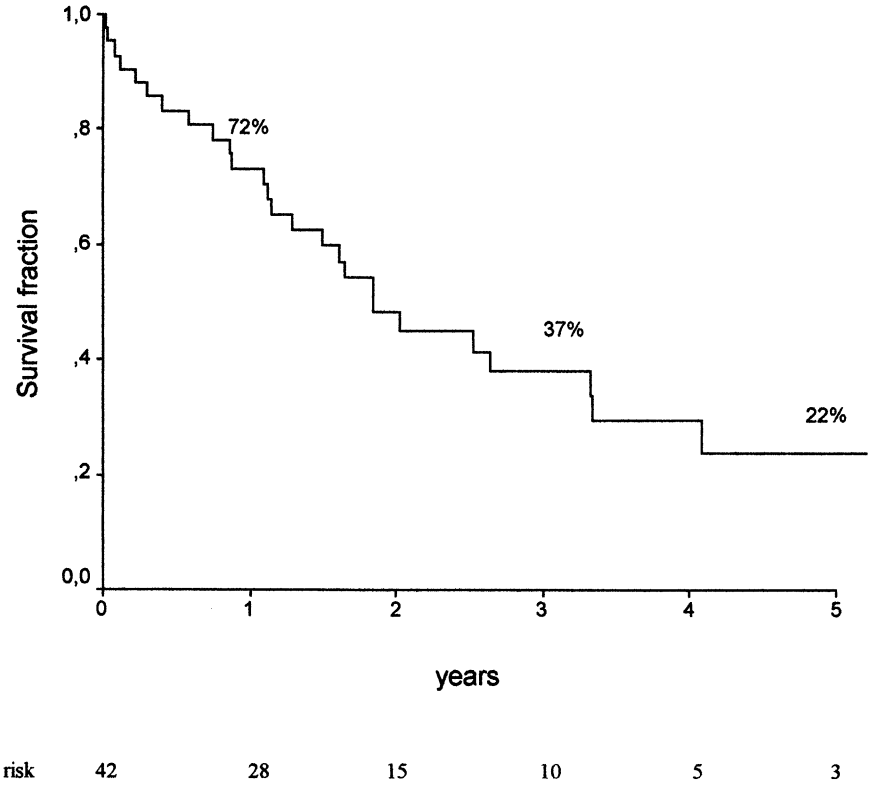

Fig. 1. Kaplan–Meier survival analysis for the total population.

postoperatively. Patient survival was dependent upon nodal status of the resection specimen (Fig. 4). The 1-, 3-, and 5-year survival was respectively 84%, 53%, and 45% in patients with negative nodes (n = 26) compared with 56%, 15%, and 0% in patients with positive nodes (n = 16) ($p = 0.004$).

Patients without vascular reconstructive surgery indicated a trend toward longer survival. The 1-, 3-, and 5-year patient survival in patients with no vascular reconstruction (n = 33) was respectively 81%, 46%, and 24% compared with 44%, 11%, and 11% in patients undergoing vascular reconstructive surgery (n = 9) ($p = 0.068$). Three out of 9 patients (33%) undergoing vascular reconstructive surgery died postoperatively during their hospitalization whereas only 2 out of 33 patients (6%) without vascular reconstructive surgery died during their hospitalization ($p = 0.057$). Whether segment I was included in the resection or not did not influence survival (Fig. 5) ($p = 0.308$). Complications occurred mainly in patients undergoing right-sided resections. Seventeen out of 18 patients (94%) undergoing right-sided resections experienced complications compared with 11 out of 19 patients (60%) undergoing left-sided resections ($p = 0.01$).

DISCUSSION

Hilar cholangiocarcinoma is an uncommon tumor associated with poor survival. The question of treatment strategy is still debated among experts.[4,7,9–11,15–30] Issues include whether such patients should be treated only by stenting or resection of the tumor with or without an additional LR. Also, the role of (neo) adjuvant radiotherapy or chemotherapy is up for discussion.[4,7,18,26] Most series exhibit a selection bias because patients in suitable condition are often referred for surgery and older and frail patients are referred to the endoscopist or interventional radiologist for stenting. Furthermore, most series contain different types of surgical interventions like bypass surgery and bile duct resections alone or in combination with LRs. Additionally, (neo)adjuvant therapy is applied in selected patients.

When patients are fit for surgery, the choice can be made between an EHBDR or the combination of an EHBDR and a LR. Several reports claim that when the bile duct resection is combined with a LR, the frequency of R0 resections is higher than in EHBDRs alone.[7,9,11] Patients with R0 resections, however, did not indicate a survival benefit compared with those with R1 resections in our series.

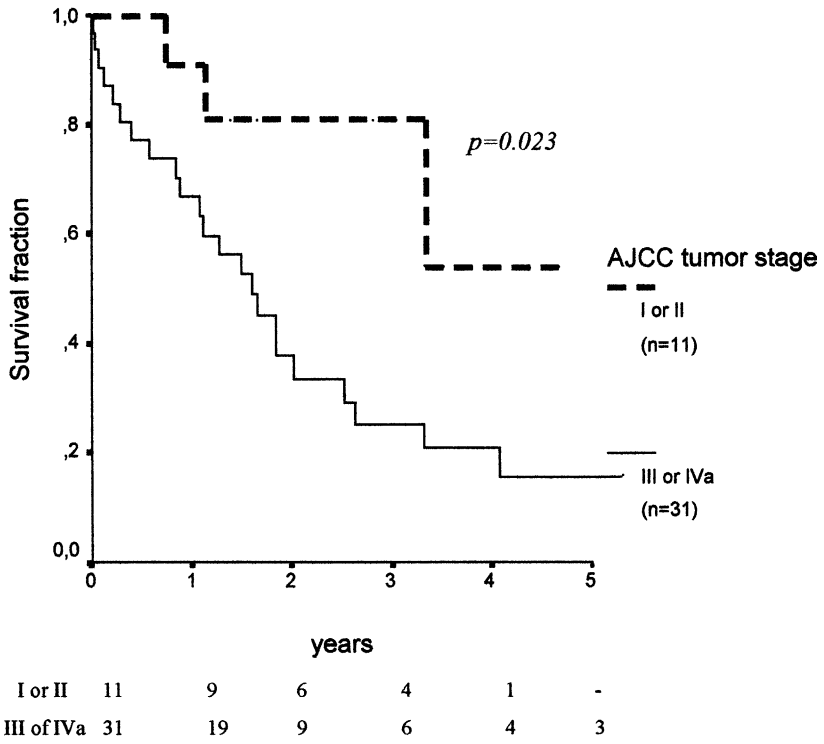

Fig. 2. Kaplan–Meier survival analysis stratified by tumor stage. AJCC = American Joint Committee on Cancer.

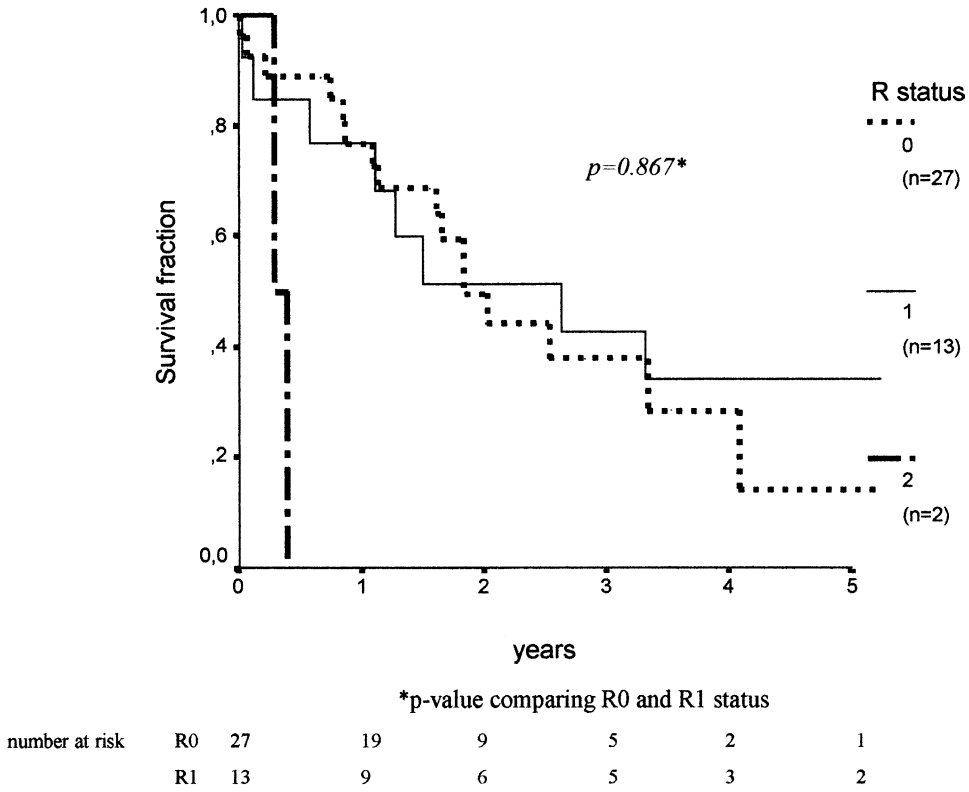

Fig. 3. Kaplan–Meier survival analysis stratified by R status.

Some authors claim that patients survive longer after a combined EHBDR and LR whereas others see no advantages of such an extended procedure.[4,7,9–11,18–20,24–27,29] Unfortunately, methodologically sound comparisons between bile duct resections alone or in combination with LRs are not available. Also, some reports indicate greater survival figures for patients in whom segment I is resected compared with patients in whom segment I is not resected.[31] Survival figures reported in our series do not indicate survival benefit for patients in whom segment I is resected. Addition of radiotherapy and/or chemotherapy has not demonstrated to produce greater survival.[4,32,33] Also, the role of liver transplantation in the treatment of hilar cholangiocarcinoma has been discussed.[7,8,22,28–30] Klempnauer and associates concluded that liver transplantation does not play a role in the treatment of hilar cholangiocarcinoma at present. More encouraging results have been reported recently by the Mayo Clinic group, but at this moment the numbers of patients included are too small to provide conclusions.[34]

The ethical question still remaining is whether to use scarce donor livers for such a procedure, when in other patients they might be used with greater success. Our report indicates that with a combined bile duct and LR for hilar cholangiocarcinoma, a 5-year patient survival of 22% and a median survival of 19 months can be obtained. The claimed advantage of a combined liver and EHBDR is the supposed increased possibility of obtaining tumor-free resection margins. This could be accomplished in our series in 27 patients (64%). These outcomes are comparable with those reported in the literature.[4,10,19,21,30,35,36] The results, however, exact a price in terms of a hospital mortality of 12% and a morbidity rate of 76%, both of which are substantial but not different from those reported by others.[4,10,16,19,21,27,30,35,36] Right-sided resections indicated a significantly higher morbidity rate in our series compared with left-sided ones. This might be related to the fact that right-sided resections, such as hemihepatectomies or extended hemihepatectomies, are larger compared with left-sided resections.

The 5 patients in our series that died all did so as a result of sepsis. Sepsis was also a substantial part of the postoperative morbidity (14%). An important cause might be that we operated on patients with a colonized bile duct as a result of preoperative stenting procedures.[9,18,24,37] Most of our patients were stented preoperatively because of the long waiting time for surgery. A reduction of morbidity and

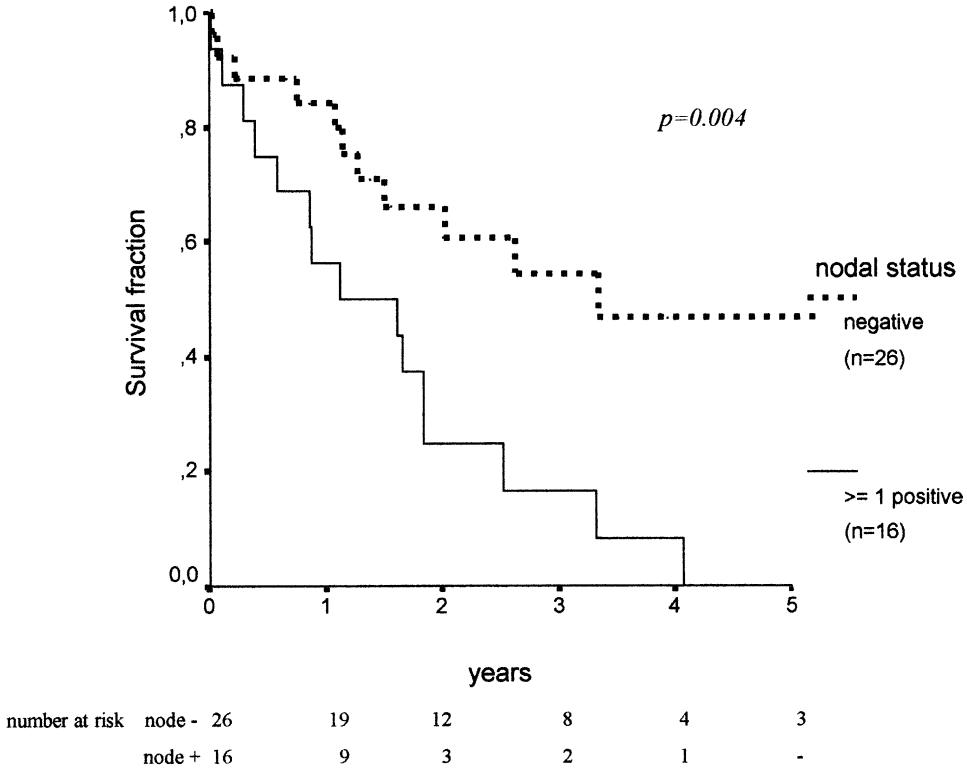

Fig. 4. Kaplan–Meier survival analysis stratified by nodal status.

even mortality can be obtained if patients are operated on early after the establishment of the diagnosis by noninvasive methods like magnetic resonance cholangiopancreatography or magnetic resonance angiography (MRCP/MRA) and Doppler ultrasound, as has been proposed by Jarnagin.[38]

Another way to improve results can be obtained by improved patient selection, avoiding those patients with advanced tumor stages (AJCC stage III or IVa, Fig. 2) or positive lymph nodes (Fig. 4), and avoiding R2 resections. Endoultrasonography (EUS) combined with endobiopsies of lymph nodes may be of value in excluding patients with positive lymph nodes preoperatively.

Whether patients with vascular involvement of the tumor requiring a vascular reconstruction exhibit disease that is too advanced and thus need to be excluded from resection cannot be answered from this study. In our series, there was a trend toward higher postoperative mortality and a trend toward inferior survival in patients requiring vascular reconstruction. Therefore, it is doubtful whether such reconstructions should be performed. Recent literature indicates contradictory results regarding this subject. Ebata and associates revealed macroscopic portal vein invasion to be an independent prognostic factor that exhibited a negative impact on long-term survival in patients with hilar cholangiocarcinoma.[39] Neuhaus and associates regards adding a portal vein resection to a right trisegmentectomy as the surgical procedure of choice. In his series, the addition of a portal vein resection led to a higher number of microscopically radical resections.[40] Muñoz and associates reviewed 28 patients undergoing surgery for hilar cholangiocarcinoma and concluded portal vein reconstruction to not exhibit a significant influence on survival.[41] The few reports in the literature concerning arterial or combined arterial and portal reconstructions do not provide evidence for recommendations.

CONCLUSION

Despite substantial morbidity and mortality, patients with hilar cholangiocarcinoma eligible for major surgery exhibit a 22% 5-year survival probability after a combined EHBDR and LR. It is clear from this series as well as reports from the literature that outcome after surgical resection of hilar cholangiocarcinoma can be improved. Adapting the diagnostic

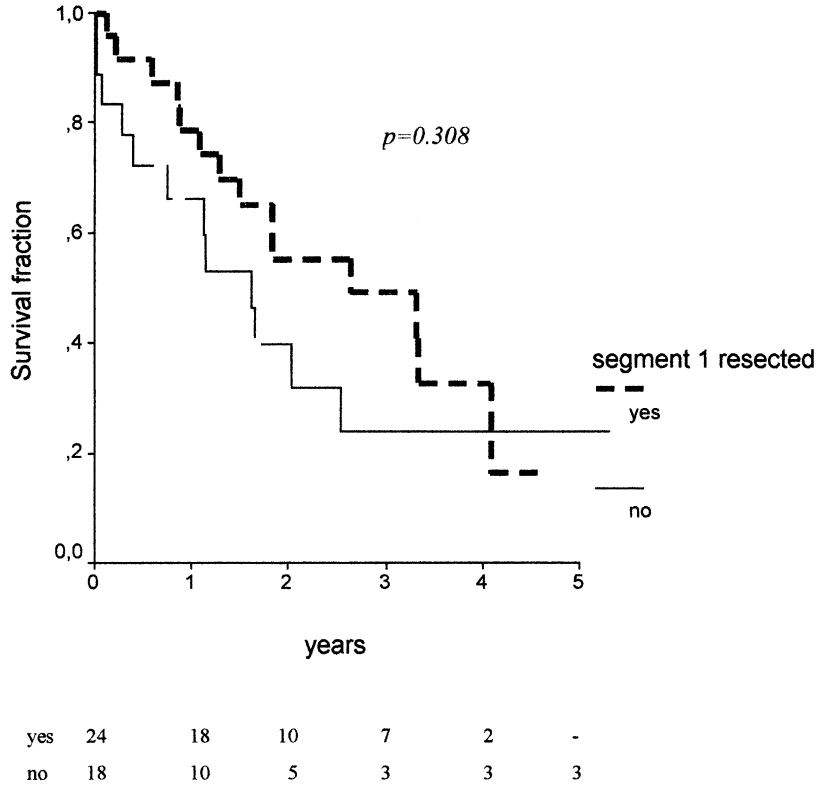

Fig. 5. Kaplan–Meier survival analysis stratified by resected segment 1.

work-up and the selection procedure seems to be the most beneficial way to achieve greater results after surgical resection.

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Hepatocellular Ultrastructure After Ischemia/Reperfusion Injury in Human Orthotopic Liver Transplantation

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The number of patients requiring organ transplants still outpaces the number of available transplantable organs. During the process of orthotopic liver transplantation (OLTx), donor organs undergo significant stress resulting from ischemia and reperfusion. Healthy organs respond to this stressful environment with compensatory mechanisms that ideally allow for complete recovery. However, "marginal" organs do not compensate as well. Hepatic steatosis typically renders an organ nontransplantable; a liver with 30% or more fat has a 25% chance of primary nonfunction (PNF) or graft failure after a technically sound operation. In this study, we report on the significant markers of cellular ultrastructural change in steatotic livers. These include glycogen content, mitochondrial swelling, and hepatocellular blebbing. The data disclosed here argue that further investigation of these factors in marginal organs subjected to I/R may better facilitate our understanding of PNF. (J GASTROINTEST SURG 2004;8:695–700)

KEY WORDS: Mitochondrial swelling, primary nonfunction, steatosis, transmission electron microscopy (TEM), ultrastructural changes

INTRODUCTION

Liver transplantation is the treatment of choice for patients with end-stage liver disease. The patient population requiring transplantable livers is growing while the number of viable donor livers is declining.[1] Historically, factors that would have rendered an organ unsuitable for donation included donor age, vasopressor use, fat content, hypernatremia, and an intensive care unit stay of greater than 48 hours. However, given the severe shortage, criteria have been extended to include "marginal" livers in an effort to counter the growing organ shortage.

Hepatic steatosis is a common finding with regard to the evaluation of livers for donation and the severity of steatosis, specifically the degree of microvesicular and macrovesicular lipid deposition, as it determines whether the organ is transplantable.[2] This is critical in light of the fact that greater than 30% of the U.S. population is considered obese; therefore, greater numbers of livers available for donation are being discarded because of a high fat content. Hepatic steatosis, which is prevalent in obesity, may occur in people who are as little as 10% heavier than their ideal body weight. Livers that are greater than 30% fat have a 25% chance of developing primary nonfunction (PNF) after transplantation, resulting in retransplantation or even the death of the patient.[3] Severely fatty livers are more susceptible to the insults faced during organ preservation and reperfusion.[4,5] These insults can include changes to the liver parenchyma, increased sensitivity to endotoxin, endothelial damage, decreased adenosine triphosphate (ATP) stores, sinusoidal swelling, and congestion after ischemia/reperfusion (I/R).[6,7] Early hepatic dysfunction associated with steatotic livers can arise from

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several causes, but the actual mechanism of graft failure in fatty livers is unclear. PNF in steatotic livers has also been attributed to sinusoidal microcirculatory disorders in that the sinusoidal endothelium deteriorates during cold preservation.[7] Reperfusion injury has been associated with the activation of Kupffer cells in response to endotoxin insult and previous cold-storage injury.[8] Additionally, it has been reported that liver mitochondrial function and plasma membrane fluidity are altered during I/R.[9] When insults are exacerbated in the fatty state, they eventually lead to PNF and/or early graft failure.[7]

The early graft dysfunction after liver transplantation is multifactorial and is dependent on both donor and recipient factors. The standard preservation injury, even in its most severe form, is histologically reversible within 3–4 weeks.[10] However, early postoperative graft complications including rejection and graft failure may ensue if the allograft is at all compromised by fat content.

Marked evidence of obesity, chronic alcohol use, and diabetes are current causes for concern with respect to the usability of livers for organ transplantation. Animal studies support these concerns.[2,3] Hepatic steatosis in rats has been indicated to exacerbate cold and warm I/R injury and eventually lead to PNF of liver allografts. Fatty droplets in Wistar rat hepatocytes fed a choline-deficient diet have been indicated to expand during cold preservation altering the infrastructure of the cell itself by displacing the surrounding organelles.[2] Although expansion of these fatty droplets does not fully account for hepatocellular demise, it is contributory. Additionally, evidence of free radical formation by Kupffer cells after cold preservation has been revealed to compromise graft function by mediating lipogenesis through the inhibition of beta-oxidation.[2,11] With the expansion of these droplets and the increase in girth of the hepatocytes secondary to swelling, the microcirculation of the liver tends to deteriorate. Sinusoidal congestion occurs, eventually causing a decrease in blood flow when compared with lean livers.[12] In states of hypoxia secondary to preservation, the endothelial cells are more susceptible to ischemic damage than the parenchyma cells.[13] Hence, hepatic steatosis exhibits a direct impact on the ultrastructure of the hepatocyte leading to cellular dysfunction and an increased postoperative morbidity and mortality.

Most of the available information dealing with steatotic livers uses genetically or diet-induced obese mouse and rat models. However, data from humans are retrospective and only a limited number of studies have concentrated on the effects of changes in cellular architecture and ultrastructure in the steatotic liver after I/R and transplantation. One parameter used in the assessment of the dysfunction of fatty livers from I/R is the amount of glycogen stores in the hepatocyte. The glycogen deposits are seen as dark granulated pellets and may be quantified by observation. During states of ischemia, livers are forced into anaerobic metabolism, which depletes glycogen stores. A second well-characterized ultrastructural change indicative of I/R injury is mitochondrial swelling, which is early evidence of mitochondrial integrity and damage. An additional ultrastructural change that may be used to assess dysfunction is cellular membrane blebbing. Harman and associates described blebbing in three stages.[14] In stage 1, small surface blebs form and these distortions coalesce to form fewer larger blebs in stage 2 that eventually rupture in stage 3. The mechanism of plasma membrane blebbing remains a mystery; however, some studies suggest that in states of oxidative stress, calcium-dependent cytosolic proteases, such as calpain-μ, are activated and degrade cytoskeletal proteins leading to plasma membrane blebbing and, ultimately, hepatocyte death.[15]

The investigation presented here evaluates the ultrastructural differences observed in human livers in relation to their degree of steatosis 1-hour postreperfusion. Transmission electron microscopy (TEM) was used to evaluate the presence of glycogen deposition, mitochondrial swelling, and membrane blebbing associated with I/R in transplantation. The data illustrate that certain ultrastructural hepatocellular markers significantly reflect the rate of graft dysfunction in steatotic livers compared with normal livers.

MATERIAL AND METHODS

Tissue Procurement

The appropriate institutional internal review board approved the protocol for this study. Next, adult liver transplant recipients were given information regarding the protocol and informed consent was obtained from each participant before transplantation and participation in the study. Samples from 47 livers representing a continuous series of patients were evaluated. Liver tissue was obtained by Tru-cut needle and wedge biopsies taken from the left lobe of the liver at two time points during the transplant. The first biopsies were taken during cold preservation while the organ was being prepared for implantation and this tissue was designated as prereperfusion. The second biopsies were taken 1-hour postreperfusion and the tissue was appropriately labeled. The tissue was partitioned into two pieces: specimen 1 was fixed in glutaraldehyde solution for transmission electron

microscopy (TEM) and specimen 2 was snap-frozen in Tissue Tek (Pelco International, Redding, CA) OTC medium for cryostat sectioning.

Histology

Frozen tissue sections were fixed with Oil-Red-O (ORO) stain to quantify fat and subsequently grouped by fat content into the following categories: less than 10% fat, 10–30% fat, and greater than 30% fat. The snap-frozen specimens were first sectioned and then fixed onto slides. The slides were then dipped in distilled water and 70% isopropyl alcohol. After the quick dips, the slides were immersed in the fat soluble ORO solution (1.0 g Oil-Red-O, 99% isopropanol) for 15 minutes. After staining, the slides were washed first in 70% isopropyl alcohol and then three times in distilled water. The slides were stained in Ehrlich's hematoxylin and eosin (H&E) for 3 minutes followed by three washes in distilled water. After H&E staining, the slides were placed in lithium carbonate. The samples were washed again in distilled water and then mounted in glycerin jelly. With the ORO staining method, fat appears bright red, nuclei stain appears blue, and the background stains pink.

Transmission Electron Microscopy

Tissue was prepared for TEM via fixation according to the following schedule: (1) fixed at room temperature in 2.5% glutaraldehyde with 1.5% paraformaldehyde in 0.1 M sodium cacodylate buffer (pH 7.5); (2) washed with cacodylate buffer; (3) postfixed in 1% osmium tetroxide in 0.1 M sodium cacodylate buffer; (4) dehydrated in a graded series of ethanol concentrations; and (5) embedded in EM bed-812 (Polysciences, Inc., Warrington, PA) standard media. Ultrathin sections (silver to gold interference colors) were cut with a Diatome (Hatfield, PA) diamond knife using a Sorvall MT-IIB Ultramicrotome (Kendro Laboratory Products, Newtown, CT). Sections were stained with uranyl acetate and lead citrate and examined with a JEOL (Peabody, MA) 100CX transmission electron microscope operated at 60 or 80 kV. All TEM digital sample images were evaluated by a single pathologist (SES).

Statistical Methodology

Data was analyzed using the SAS System, version 9.0 (SAS Institute, Cary, NC). Specimens were defined as being low (<10 %), medium (10%–30%), or high in fat content (>30 %). A visual inspection of the distribution of dependent variables was performed and, subsequently, variables were tested for normality using the D'Agostino–Pearson χ^2 test. Kruskall–Wallis one-way analysis of variance (ANOVA) was then performed to ascertain significant differences among mitochondrial swelling, membrane blebbing, and glycogen content (all measurements, prevalues, and postvalues were determined independently). Bonferroni methodology was employed to control for the experiment-wise error rate.

RESULTS AND DISCUSSION

To address the effect of steatosis on hepatocyte cellular and ultrastructural architecture, samples were collected from three distinct categories of livers based on their total fat content. The fat content was determined by ORO estimation and varied from 0%–76% with mean fat content values of 3.3% in group I, 18.7% in group II, and 57.4% in group III (Table 1).[16] Glycogen content and mitochondrial swelling were evaluated in the three steatotic groups by TEM comparing processed liver biopsies prereperfusion and 1-hour postreperfusion. Samples from 47 livers were biopsied, sectioned as necessary, treated as described, and evaluated by TEM. Blinded examination of sections revealed two consistent ultrastructural markers subject to the effects of I/R: the presence of glycogen and mitochondrial swelling. Concluding that these two markers were susceptible to the effects of I/R, we developed a scoring system to address the potential for using glycogen content and mitochondrial swelling to predict liver function posttransplantation. The scoring system for glycogen content and mitochondrial swelling ranged from 0–5. Representative examples are indicated in Fig. 1. All sections were blindly evaluated and scored appropriately. Absence of glycogen and mitochondrial swelling in the TEM examination was scored as 0 (Fig. 1, *A*). Extensive evidence of the presence of glycogen and significant mitochondrial swelling was scored as 5 (Fig. 1, *E*). In addition, the presence or absence of membrane blebbing was scored as positive or negative, respectively. At the 1-hour postreperfusion time

Table 1. Number of patients in each steatotic subset and mean liver fat content by group. Forty-seven patients included in a retrospective analysis were divided into three groups based on fat content determined by Oil–Red–O analysis

Group	Fat content	Mean fat content (%)	Number of samples
I	<10%	3.3 ± 3.2	18
II	10%–30%	18.7 ± 6.6	17
III	>30%	57.4 ± 15.9	12

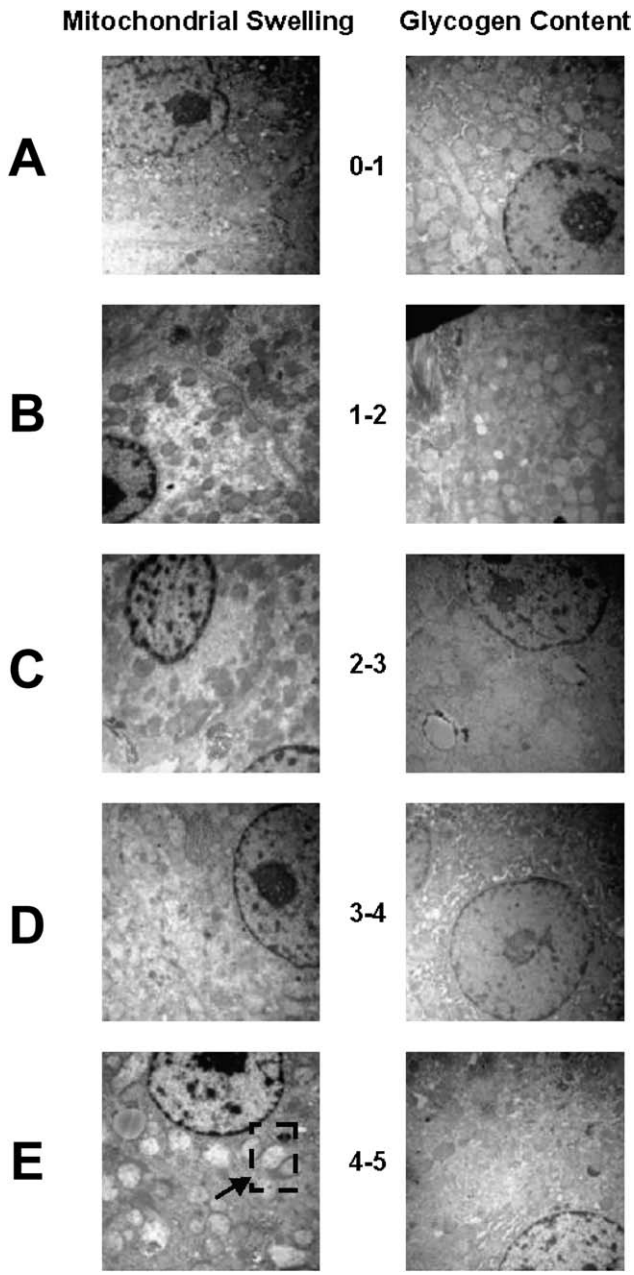

Fig. 1. Retrospective examples of mitochondrial swelling and glycogen content on the 0–5 scale.

point, average scores were not significant between groups.

In Fig. 2 representative examples from three different patients illustrate the extremes of the identified ultrastructural changes of glycogen content, mitochondrial swelling, and membrane blebbing, which are altered as a result of I/R. Patient 1 demonstrated a marked decrease in glycogen stores upon reperfusion of the liver (Fig. 2, *A*). In patient 2, mitochondrial swelling was significantly increased as the organelles attempted to compensate for energy losses (Fig. 2, *B*). Finally, samples from patient 3 revealed evidence of hepatocellular membrane distortion 1-hour postreperfusion (Fig. 2, *C*). Evidence of plasma membrane blebbing was defined as the dissociation of the lipid bilayer from the membrane cytoskeleton.[15]

Differences were observed between prereperfusion and postreperfusion glycogen content. Subset analysis revealed a statistically significant difference between prereperfusion and postreperfusion glycogen content for groups I (<10% fat) and III (>30% fat) (Table 2). Glycogen content changed significantly over the course of I/R in livers with prereperfusion glycogen scores greater than 1.5. Prereperfusion and postreperfusion mitochondrial swelling were not significantly different at 1 hour for any group (Table 2).

To summarize, we noted significant changes in glycogen content associated with the cellular injury caused by I/R. However, mitochondrial swelling at 1-hour postreperfusion was not statistically different than prereperfusion. Mitochondrial swelling is likely of significance but not at the early 1-hour postreperfusion time point. Additionally, we observed distortions in the hepatocellular membrane (blebbing) that were exacerbated in the fatty state after I/R injury. This was not always evident and may be caused by the time points selected for study as blebbing is an ongoing cellular repair process and it may occur at any time postreperfusion between 15 minutes and 24 hours. Furthermore, given that the initial time point for the prereperfusion biopsy was after the organ had been removed from the donor, the true changes in these ultrastructural markers may not be appreciated or captured.

CONCLUSIONS

Many factors play a role in the early demise of liver graft function, including alterations of biochemical processes throughout the liver. In addition, patient outcome is dependent upon factors irrespective of graft fat content such as the model for end-stage liver disease (MELD) status, operative difficulty, and retransplantation to name a few. Patient outcomes in the groups evaluated in this study are, therefore, not a representation of the observed parameters and were not included.

This was a prospective TEM analysis focusing on morphological changes in the ultrastructure of the hepatocyte in an attempt to understand the role of these changes in the development of PNF following transplantation. The prereperfusion and postreperfusion parameters of mitochondrial swelling and hepatocellular blebbing were not significantly different between livers of differing fat content. However, our

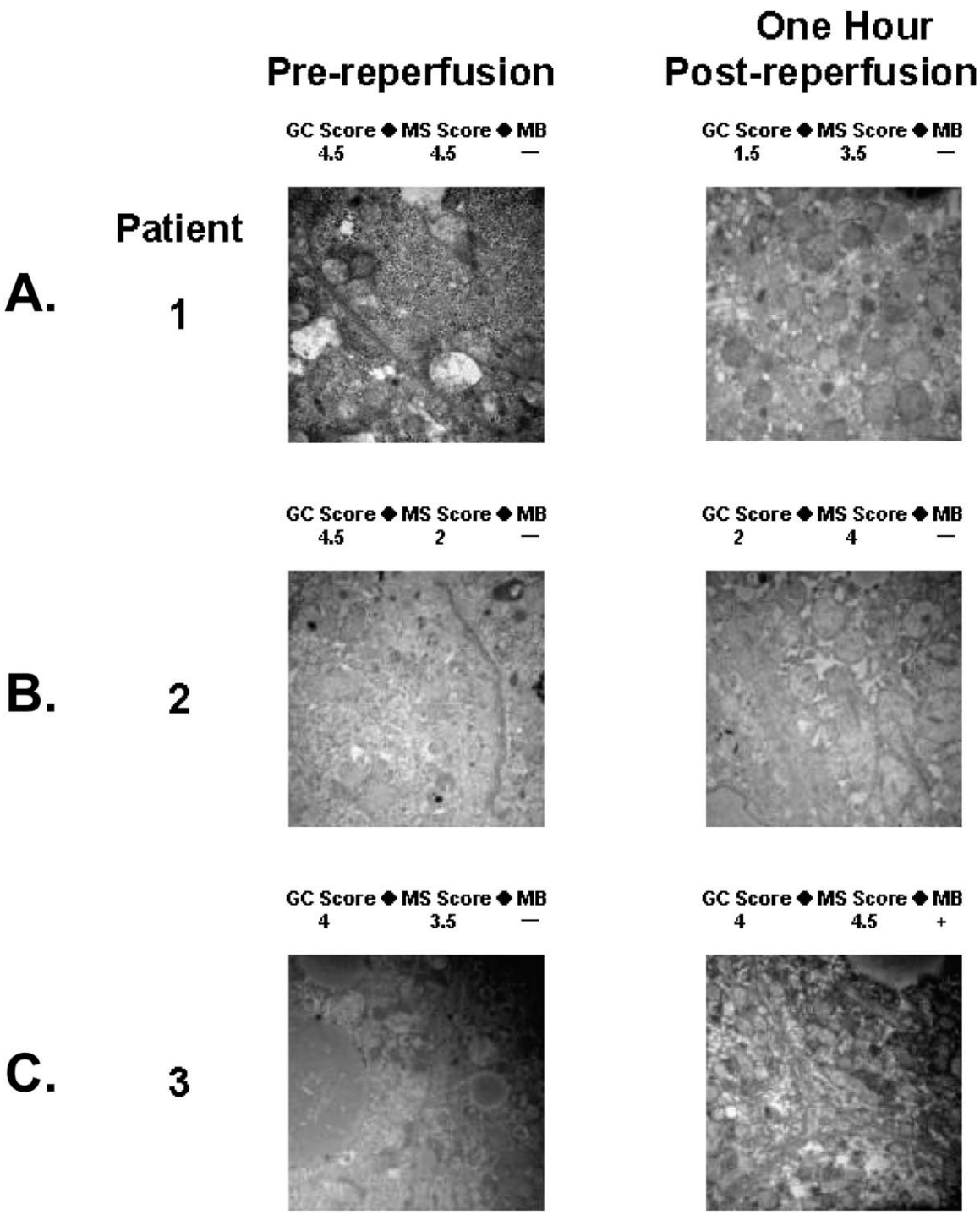

Fig. 2. Retrospective examples of mitochondrial swelling, membrane blebbing, and glycogen content on 0–5 scale prereperfusion and 1-hour postreperfusion. Prereperfusion and postreperfusion samples are from 3 representative patients. GC score = glycogen content score; MS score = mitochondrial swelling score; MB = membrane blebbing; absent (−) present (+).

data indicated that in steatotic livers, glycogen deposition and the other parameters were overall markers of cellular change between prereperfusion and 1-hour postreperfusion. This may in part be due to the timing of the initial biopsy that was procured after the organ was already flushed with under water solution and exposed to cold perfusion. Thus, this is only a small window in the ultrastructural state of the hepatocyte.

Table 2. Transmission electron micrograph (TEM) analysis of hepatocellular markers among human steatotic liver samples. TEMs were evaluated for mitochondrial swelling and glycogen content. Average prereperfusion and postreperfusion measured values are reported per fat content group as well as total average

	Fat content							
	0%–10%		11%–29%		>30%		Total average	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Glycogen content	1.76 ± 1.30*	1.28 ± 1.06*	1.41 ± 0.99	1.03 ± 0.93	1.88 ± 1.40*	1.17 ± 1.11*	1.65 ± 1.2	1.16 ± 1.02
Mitochondrial swelling	1.94 ± 1.82	1.92 ± 1.4	0.91 ± 0.89	1.38 ± 0.76	1.13 ± 1.07	1.50 ± 1.55	1.34 ± 1.27	1.61 ± 1.19

*Prevalues vs. postvalues are statistically significant ($p < 0.05$) in group I (0%–10%) and group III (>30%).

We anticipate the power of our study to improve as more samples are collected. Furthermore, in situ samples from the donor may indicate a greater change in these ultrastructural markers. This may be due to the snapshot that is captured at a particular time point in the donation process. Ultimately, dissecting out these structural changes as potential markers for I/R injury should allow for the closer monitoring and greater understanding of the processes that may eventually lead to steatotic liver allograft injury and failure.

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Isolated Roux-Loop Pancreaticojejunostomy: A Series of 61 Patients With Zero Postoperative Pancreaticoenteric Leaks

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There have been approximately 70 reported variations of reconstruction after pancreaticoduodenectomy (PD). The pancreaticojejunal (PJ) anastomosis is the source of most reported morbidity and mortality. In this study, we aimed to identify the anastomotic leak rate in patients undergoing PD for malignant disease using a proximal isolated jejunal pancreatic anastomosis. Sixty-one consecutive patients undergoing PD (26 women and 35 men; age range, 41–79 years, mean age, 62 years). had an identical reconstruction. The PJ anastomosis was performed using the most proximal isolated jejunum in two layers: interrupted 4.0 Prolene was used to achieve mucosal/ductal continuity, and 3.0 Prolene was used for the serosal/parenchymal anastomosis, around an appropriately sized stent. All postoperative complications were recorded. A pancreatic leak was defined as persistent discharge of amylase-rich pancreatic drain fluid. The overall complication rate was 44% (27 of 61, including 15 chest infections, 8 wound infections, and 2 postoperative cardiac arrhythmias). There were 3 deaths (30-day mortality rate, 5%). One patient died after a cerebrovascular accident, one from respiratory failure secondary to pneumonia, and the third of methicillin-resistant *Staphylococcus aureus* septicemia after small bowel ischemia caused by pressure necrosis from a drain. There were no PJ anastomotic leaks. This method of pancreatojejunostomy has produced a 0% leak rate in this center. (J GASTROINTEST SURG 2004;8:701–705)

KEY WORDS: Pancreaticoduodenectomy, pancreatic anastomosis, isolated Roux-en-Y

Walter Kausch performed the first successful pancreaticoduodenectomy (PD) in Berlin in 1912,[1] and Allen Whipple et al. were responsible for popularizing the operation and its eponym in 1935.[2] Despite being a complex and technically demanding operation, PD is established as the treatment of choice in the treatment of cancer of the head of the pancreas and periampullary region. The initial prohibitive mortality and morbidity associated with the operation have dramatically reduced over the years since its introduction. Although ligation of the pancreatic stump was common in the initial evolution of pancreatic surgery, it was associated with a high fistula rate, infection, and exocrine insufficiency.[3] It has become standard practice to perform a pancreaticoenteric anastomosis using one of two conduits, the stomach or the jejunum.

The pancreaticoenteric anastomosis has remained the Achilles heel of pancreatic surgery. Leakage from the pancreatic stump accounts for most of the morbidity and mortality of pancreatic surgery.[4–6] Despite the fact that there are more than 70 described techniques for pancreaticoenteric anastomosis, the leakage rate has not changed significantly with time (4–22%).[7–11] It has been postulated that the use of separate Roux-en-Y limbs for biliary and pancreatic anastomosis may limit the potentially fatal consequences of a pancreatic leak, activated by biliary secretions[12–14]; indeed, the incidence of pancreatic leak is lower when isolated Roux-en-Y limbs are used.[12] This study reports of a series of 61 patients undergoing pancreatic resections with subsequent pancreaticoenteric reconstruction using a defunctioned Roux-en-Y loop, as described by Kingsnorth,[12] with a 0% leak rate with their anastomosis.

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METHODS

We conducted a retrospective, consecutive review of all patients undergoing PD with an isolated Roux-en-Y reconstruction who were identified from the surgical theatre records, from 1995 to the time of writing. All postoperative complications were recorded, specifically any incidence of pancreatic leak, defined as the recovery of fluid from the peripancreatic drains with an amylase content 5 times greater than normal. Silicon drains (26 or 30 Fr gauge) were inserted at the time of operation. All patients received nothing by mouth for 5 days postoperatively. On commencement of feeding, if drainage was negligible, the drains were removed routinely. Any suspicious drainage (bile-stained or over 50 ml daily) was analyzed for amylase levels. If amylase levels were inconsistent with a pancreatic leak (see earlier), then drains were removed. Information was entered into a computerized database for subsequent analysis.

Surgical Technique

The duodenal-jejunal flexure was mobilized and divided with a GIA 60 linear stapler (Auto Suture, Auto Suture Co., Amersham, Bucks, UK), oversewn with a 3.0 polydioxanone (PDS) suture and advanced behind the mesenteric vessels to lie adjacent to the transected pancreatic surface. The posterior wall of the pancreatic capsule was secured with a continuous 3.0 Prolene suture. A small jejunotomy was made adjacent to the suture line, and a series of at least three interrupted 4.0 PDS sutures were placed along the anterior aspect of the pancreatic duct. Posteriorly, the sutures passed through the pancreatic duct and jejunal mucosa. An appropriately sized internal stent was introduced between the pancreatic duct and jejunotomy across the posterior suture line; anterior sutures were placed along the anterior jejunotomy and secured to complete the ductal anastomosis. All patients had internal stenting. Finally, the continuous suture was extended anteriorly, completing the capsular anastomosis. The jejunum was divided approximately 40 cm distal to the pancreaticojejunostomy (PJ), forming a Roux-loop for biliary and gastric/duodenal reconstructions. The biliary anastomosis was constructed in an end-to-side fashion with interrupted 30 PDS. Two tube drains were juxtaposed to the pancreatic and biliary anastomoses. Figure 1 shows the final anatomy after reconstruction.

Fig. 1. Final reconstruction, displaying anatomy of the isolated Roux-loop pancreaticojejunostomy (drains not shown).

RESULTS

We identified 61 consecutive patients (26 woman and 35 men; mean age, 62 years; age range, 41–75 years) who underwent PD over a 5-year period. The most frequent presenting symptoms were as follows: 74% (n = 45) of the patients experienced prediagnosis weight loss with a range of 4–21 kg (mean, 6 kg); 55% described upper abdominal discomfort of between 1 and 32 weeks' (mean, 4 weeks') duration; 70% (n = 43) presented with jaundice of 1–8 weeks' (mean, 2.5 weeks') duration, and bilirubin range was 5–505 μmol/l (mean, 174 μmol/l). Preoperative imaging included abdominal ultrasound, spiral computed tomography in all cases, and endoscopic retrograde cholangiopancreatography in 80% (n = 49). Duration of surgery ranged between 4.5 and 7 hours (mean, 5.5 hours); mean blood loss was 600 ml (range, 200–1800 ml).

The histology of the lesions resected were pancreatic adenocarcinomas (n = 25), carcinoma of ampulla (n = 20), duodenal adenocarcinoma (n = 6), cholangiocarcinoma (n = 5), and cystadenocarcinoma (n = 5).

Twenty-eight patients experienced mostly minor postoperative complications (8 wound infections, 14 chest infections, 2 with hematemesis, and 2 new cardiac arrhythmias, successfully managed on the ward) (Table 1). There were three deaths (30-day mortality rate, 5%). One patient died after a cerebrovascular accident, one died from methicillin-resistant *Staphylococcus aureus* septicemia after small bowel ischemia caused by pressure necrosis from a drain, and one died from overwhelming sepsis secondary to severe pneumonia. There were no PJ leaks. A drain amylase level was determined in 66% of all patients with a mean range of 9 IU/L (range, 2–10 IU/L).

Table 1. Mortality and morbidity following pancreaticoduodenectomy and isolated limb Roux-en-Y reconstruction

Critical care stay postoperatively	Mean, 3 days; range, 2–6 days
Total hospital stay	Mean, 16 days; range, 10–45 days
Postoperative complications (n)	
Wound infection	8 (13%)
Chest infection	14 (23%)
Tachyarrhythmia	2 (3%)
Cerebrovascular infarct	1 (2%)
Hematemesis	2 (3%)
MRSA septicemia	1 (2%)
Readmission to critical care (n)	2 (3%)
In-hospital mortality (n)	3 (5%)
Drain amylase sent (n)	40 (66%)
Pancreatic leak (n)	0 (0%)

DISCUSSION

The mortality rate after PD has been reported in some of the largest series as between 3% and 5%,[5,9,11] which compares well with the mortality rate demonstrated from our study. There are reports in the literature of 0% mortality in series of over 100 pancreaticoduodenectomies using both pancreaticogastrostomies and pancreaticojejunostomies as reconstructive conduits.[8,15,16] Developments in surgical technique, in addition to improved perioperative patient care, have resulted in this considerable reduction in postoperative mortality, to the extent that pancreaticoduodenectomies are now being offered first to patients previously deemed unfit for the operation and second for the management of nonmalignant disease, such as chronic pancreatitis.

Despite these improvements in mortality, postoperative complication rates range from 30% to 65%.[5–8] The common causes of morbidity specific to the procedure include metabolic disorders such as pancreatic exocrine insufficiency, hemorrhage, intra-abdominal abscess formation, delay in gastric emptying, and perhaps most important, pancreatic anastomotic leaks. Pancreatic anastomotic leaks, defined as the drainage of 5 times greater than normal amylase-rich fluid from peripancreatic drains, occur due to impaired healing of the pancreaticoenteric anastomosis and represent the second largest overall cause of morbidity after pancreaticoduodenectomies.[17] Clinically, anastomotic leaks commonly present as postoperative pyrexia of greater than 38°C and abdominal pain. Intra-abdominal collections, abscesses, and intra-abdominal hemorrhage are the leading complications relating to pancreatic leaks. Once identified, anastomotic leaks are initially managed conservatively, with maintenance of drains inserted intraoperatively, intravenous antibiotics, percutaneous drainage of collections, and the use of octreotide.

Table 2 demonstrates reported pancreatic leakage rates and subsequent mortality secondary to leakage. Because failure of healing is seen as the leading cause of anastomotic leaks, studies have attempted to identify the relationship between the management of

Table 2. Rates of pancreatic leakage after pancreaticoduodenectomy

Series	Type of anastomosis	Leak rate (%)	Mortality secondary to leak (%)
Matsumoto et al.[18]	PJ	16	67
Miedema et al.[4]	PJ	17	3
Cullen et al.[19]	PJ	18	33
Anderson et al.[20]	PJ	9	25
Marcus et al.[21]	PJ	17	100
Van Berge Henegouwen et al.[22]	PJ	11	80
Aranha et al.[16]	PG	21	0
Srivastava et al.[6]	PJ	12.5	20
Hyodo and Nagai[23]	PG	4.5	0
Arnaud et al.[24]	PG and PJ	3.7 and 13	1 and 3
Tuech et al.[25]	PG and PJ	3.8 and 13	—
Kapur et al.[26]	PG	0	0
O'Neil et al.[27]	PG	8.8	—
Schlitt et al.[28]	PG and PJ	2.8 and 12.6	1.6 and 5.2
Yeo et al.[29,*]	PG and PJ	12.3 and 11.1	—

PJ=pancreaticojejunostomy anastomosis; PG=pancreaticogastrostomy anastomosis.
*Randomized controlled trial.

the pancreatic stump and the incidence of leaks, such as comparing pancreaticogastrostomy with PJ, end-to-side versus end-to-end anastomoses, external duct stenting, numerous reconstruction techniques, and the use of fibrin glue. Presently, data suggest that pancreaticogastrostomy may have a slightly lower complication rate than PJ with regard to pancreatic fistula, but results thus far are not conclusive (Table 2). The texture of the pancreas may also have some bearing on postoperative leak rates with firmer glands, such as those found in patients with chronic pancreatitis, being technically easier to anastomose and hence have a lower leak rate. A randomized controlled trial by Yeo et al.[29] failed to find any significant difference in leakage rates between pancreaticogastrostomy and PJ in 145 patients.[29] Indeed, factors such as ampullary or duodenal disease and lower surgical volume were highly associated with pancreatic fistulas, rather than pancreatic texture, method of anastomosis, or duration of operation.

The use of octreotide preoperatively has also been assessed in randomized-placebo trials, and although a significant reduction in overall postoperative complications was observed,[30–32] only one study[31] found that the fistula rate was diminished. A further study found no impact with octreotide on either fistula rate or overall complication rate.[33]

Conflicting data also surround the use of stents in the pancreatic ducts. Some studies report a lower incidence of fistula rate[34–36] after stenting of the PJ anastomoses, whereas others have found no advantages after stenting.[37]

To date, the two largest series of isolated Roux-en-Y pancreaticoenteric anastomosis have been reported by Kingsnorth et al.[12] and Khan et al.[38] These reports incorporated a series of 52 and 41 patients, respectively, with no pancreatic leakage rate. It is unclear as to why isolated Roux-en-Y pancreaticoenteric anastomoses may result in a lower leak rate. One factor could be that biliary and gastric secretions are diverted from the PJ anastomoses, and there is a resultant reduced intraluminal flow past the PJ anastomosis. This may reduce mechanical stress on the PJ anastomosis and also reflux of biliary and gastric contents up the PJ anastomosis. Diverting biliary contents away from the PJ junction will also avoid activation of pancreatic secretions, which could, in theory, weaken the PJ junction. One danger of the technique is temporary obstruction (or partial obstruction) of the distal jejunojejunal anastomoses secondary to edema. The increase in intraluminal pressure could provoke a pressure-induced leak. Laboratory trials examining these ideas are needed to further elucidate these theories.

Our study of 61 patients is the largest series thus far of patients with isolated limb Roux-en-Y alimentary reconstruction. The results of this study contribute to the growing evidence that isolated limb Roux-en-Y may be associated with a lower rate of postoperative pancreatic leak; however, randomized controlled trials are needed.

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Clinical Characteristics, Treatment, and Outcome of Pancreatic Schwannomas

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This article involves the study of a patient with a rare benign schwannoma in the body of the pancreas. After reviewing 39 patient cases previously reported in the literature, a discussion of the schwannoma with regard to clinical presentation, diagnosis, and treatment is examined. A review of the patient's chart was performed along with a review of the literature using a Medline search. Translations were performed whenever necessary. There are 23 reports of 29 patient cases of pancreatic schwannomas in English and European literature and one report of 10 patient cases in the Japanese literature. The mean age was 57.75 years (range 32–89) and the male-to-female (M:F) ratio was 17:23. The mean reported size was 8.79 cm. The lesion was located in the head in 16 patients (40%), the body in 8 patients (20%), the body and tail in 8 patients (20%), the tail in 6 patients (15%), the head and body in 1 patient (2.5%), and the location was not specified in 1 patient (2.5%). Of the English and European patients, 11 out of 30 patients (36.7%) exhibited solid tumors and 14 out of 30 patients (46.7%) exhibited cystic tumors. The majority of the tumors (35 out of 40) were benign, but there were five reported malignancies. There were no deaths or recurrences reported with a follow-up of 18.68 months ± 24.09 (range 3–108 months). Pancreatic schwannomas are rare, and the preoperative diagnosis is difficult. Intraoperative frozen section can confirm the diagnosis of a benign schwannoma. Enucleation of the tumor from the surrounding parenchyma is recommended, if possible. Patients undergoing resection indicate an excellent long-term prognosis. (J GASTROINTEST SURG 2004;8:706–712)

KEY WORDS: Pancreas, schwannoma, enucleation

Pancreatic masses often present challenging diagnostic and therapeutic scenarios. A recent patient, who presented with a solitary mass in the body of the pancreas that was determined to be a benign schwannoma, illustrates this problem. This led us to a review of the literature regarding this rare tumor, which we hoped would enable us to determine the tumor's imaging characteristics and biologic behavior, as well as the ability to establish a preoperative or intraoperative diagnosis and, hence, the most appropriate surgical treatment. Our analysis of this patient and the current literature is presented.

MATERIALS AND METHODS

A review of the patient's chart was performed along with a review of the literature using a Medline search. Translations were performed whenever necessary. Details of the 29 English and European patients are summarized in Table 1 along with the current patient. Table 2 summarizes the important available facts regarding all 40 patients.

Midepigastric abdominal pain associated with a 6-lb weight loss developed in a 77-year-old female. A computerized tomography (CT) of the abdomen was performed. She exhibited a history of non-insulin-dependent diabetes mellitus and an elevated cholesterol level. The CT scan demonstrated a 2.3 cm × 2.5 cm enhancing mass in the body of the pancreas and resection was recommended. She arrived at our institution 3 months later with persistent abdominal pain. A repeat CT scan of the abdomen demonstrated that the mass did not increase in size, was exophytic, and was located between the splenic artery and vein (Fig. 1). The mass indicated increased enhancement

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Table 1. Summary of schwannomas in the English and European literature

Patient No.	Reference	Gender	Age (yrs)	Presenting symptoms	Location of Mass	CT findings (solid/cystic)	Size (cm)	Treatment	Malignacy	Follow-up (months)
1	Current article	F	77	Upper abdominal pain, weight loss	Body	Solid	3.5	Enucleation	−	3
2	1	F	47	Back pain (7 days)	Head	Solid	5.5	Whipple	−	15
3		F	73	Acute abdominal pain	Head	Cystic	3.0	Whipple	−	17
4	2	F	63	Upper abdominal pain	Tail	Cystic	10	Distal pancreatectomy	−	6
5	3	F	50	Upper abdominal pain	Body/Tail	Cystic	9.5	Distal pancreatectomy	−	7
6	4	M	52	Asymptomatic	Body	Cystic	5.5	Local resection*	−	NS
7		M	69	Asymptomatic	Head	Cystic	6	Whipple	−	NS
8	5	M	63	Asymptomatic	Body	Solid	2	Enucleation	−	24
9		F	54	Abdominal pain ref to back	Head	Solid	2	Enucleation	−	24
10	6	M	47	Right-sided abdominal pain	Body	NS	3.5	Distal pancreatectomy	−	48
11		M	63	Abdominal pain	Body	Cystic	NS	Distal pancreatectomy	−	NS
12		F	68	Upper abdominal pain	Head/Body	Cystic	NS	NS	−	6
13	7	M	59	Asymptomatic	Uncinate process	Solid	4	Whipple	−	10
14	8	M	89	Upper abdominal pain, fever, vomiting	Body/tail	Cystic	20	Distal pancreatectomy	−	NS
15	9	M	46	Right-sided abdominal pain	Uncinate process	Cystic	6	Resection*	−	NS
16	10	F	56	Right-sided hip pain	Body	Cystic	4	Distal pancreatectomy	−	NS
17	11	M	73	Right upper quadrant abdominal pain	Body/tail	Solid	2	? Resection*	−	NS
18	12	F	72	Anemia, melena	Head	Solid with necrotic center	7	Whipple	+	NS
19	13	F	75	Acute abdominal pain, vomiting, diarrhea	Head	Solid	7	Refused surgery	−	7
20	14	F	35	Abdominal pain, melena, anemia	Head	NS	NS	Whipple	+	24
21	15	F	46	Biliary colic	Head	Solid	4	Enucleation	−	108
22	16	F	40	Upper abdominal pain, jaundice, weight loss	Head	Solid with necrotic center	10	Whipple	+	9
23	17	M	70	Abdominal pain constipation, fullness	Body	Cystic	4	Resection*	−	NS

Continued

Table 1. Continued

Patient No.	Reference	Gender	Age (yrs)	Presenting symptoms	Location of Mass	CT findings (solid/cystic)	Size (cm)	Treatment	Malignacy	
24	18	M	60	Lumbar back pain, weight loss	Body / tail	Cystic	17.5	Unresectable	+	4
25	19	F	48	Upper abdominal discomfort, belching	Body / tail	Cystic	26	Distal pancreatectomy	–	NS
26	20	F	50	Painless lump in abdomen	Tail	Solid	19	Distal pancreatectomy	–	13
27	21	F	66	Asymptomatic, seen as posttraumatic cyst	NS	Cystic	"Large"	Local resection*	–	NS
28	22	F	65	Abdominal pain	Tail	N/A	NS	Distal pancreatectomy	–	12
29		F	32	Abdominal pain	Tail	N/A	NS	Distal pancreatectomy	–	12
30	23	M	36	Melena	Head	N/A	NS	Biopsy	–	6

CT = computed tomography; N/A = not applicable because CT was not available; NS = not specified.
*The term local resection/resection was reported without any additional details.

relative to the pancreatic body on the delayed images and exhibited a rounded central focus of low density (Fig. 2). No lymphadenopathy or free fluid was noted in the abdomen. Her CA 19-9 was 21 U/ml (normal 0–37 U/ml) and her serum gastrin was 114 pg/ml (normal 0–150 pg/ml).

At the time of exploration, the patient exhibited a well-circumscribed 3.5 cm mass in the body of the pancreas that was located between the splenic artery and vein along the superior-posterior aspect of the body of the pancreas. Intraoperative ultrasound confirmed a solitary mass in the midbody of the pancreas splaying the splenic artery and vein. The mass was enucleated and a frozen section demonstrated a probable benign schwannoma or leiomyoma. No further resection was performed based on these findings. The final pathology report confirmed a benign schwannoma strongly positive for S-100 and mildly positive for actin, c-Kit (CD-117), and CD-34 (Fig. 3).

Table 2. Summary of all reported cases of schwannomas

	English/European literature	Japanese literature	Total
Patient cases	30	10	40
Average age (yrs)	58.13	56.6	57.75
M:F ratio	12:18	5:5	17:23
Location			
Head	12	4	16
Body	7	1	8
Head/Body	1	0	1
Body/Tail	5	3	8
Tail	4	2	6
Not stated	1	0	1
Total	30	10	40
Average size in cm	8.04 (23 patient cases, 7 unknown)	10.5	8.79
Operation			
Whipple	7	4	11
Distal pancreatectomy	10	6	16
Resection*	5	0	5
Unresectable	1	0	1
Refused	1	0	1
NS	1	0	1
Enucleation	4	0	4
Biopsy	1	0	1
Total	30	10	40
Reported malignancy	4	1	5
Nature of tumor			
Solid	11	…	11
Cystic	14	…	14
NS	5	10	15

M:F ratio = male-to-female ratio; NS = not specified.
*Term "resection" was reported without any additional details.

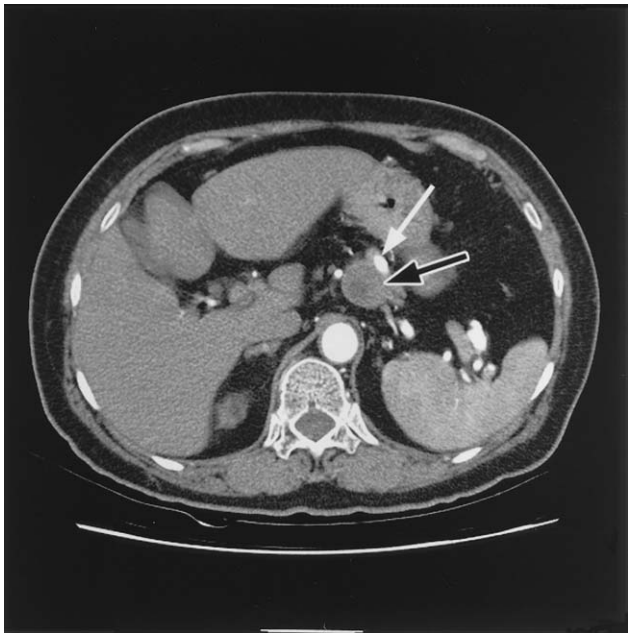

Fig. 1. Schwannoma of the pancreas: An axial contrast enhanced computed tomograph (CT) scan obtained in the early arterial phase indicating the mass in the pancreas (*black arrow*) abutting the splenic artery (*white arrow*). No pancreatic ductal dilatation or invasion into adjacent arteries or veins was noted.

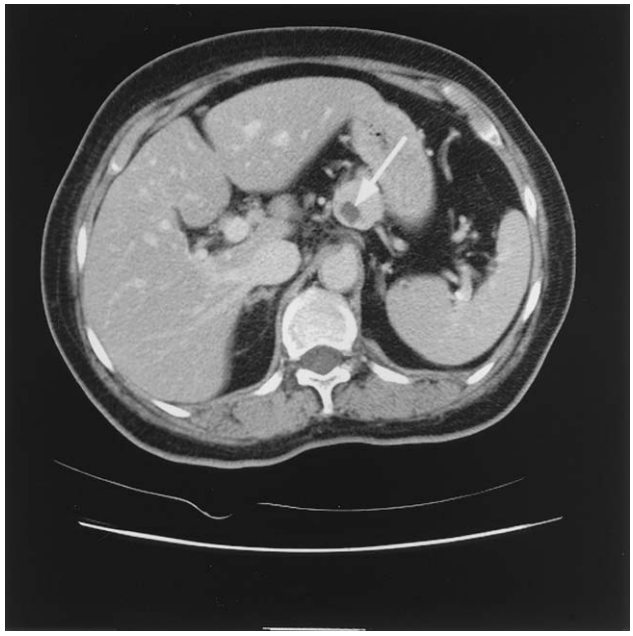

Fig. 2. Schwannoma of the pancreas: An axial contrast computed tomograph (CT) scan obtained in the delayed phase indicating the mass in the body of the pancreas with central cystic component (*arrow*). Close proximity to the posterior wall of the stomach is noted.

She experienced an uneventful postoperative recovery and was discharged on postoperative day 6. At 6 months postoperative follow-up, she indicates a full recovery and has not experienced any abdominal pain.

RESULTS

A Medline search of the literature indicated 23 reports[1–23] of 29 patient cases of pancreatic schwannoma in the English and European literature and one review[3] of 10 patient cases in the Japanese literature. Details of the 29 English/European patient cases are summarized in Table 1 along with the current patient, but there was insufficient information from the 10 Japanese patient cases to include them in this summary. Table 2 summarizes the important available facts for all 40 patient cases.

The mean age at the time of diagnosis was 57.75 years (range 32–89) and the male-to-female (M:F) ratio was 17:23. The mean reported size was 8.79 cm (range 2–26 cm). The lesion was located in the head in 16 patients (40%), the body in 8 patients (20%), the body and tail in 8 patients (20%), the tail in 6 patients (15%), the head and body in 1 patient (2.5%), and the location was not specified in 1 patient (2.5%). Of the English and European patients, 11 out of 30 patients (36.7%) exhibited solid tumors by CT with some having central necrosis and 14 out of 30 patients (46.7%) exhibited primarily cystic tumors. In 2 patients, the nature of the tumor was not specified and 3 patients were reported before the

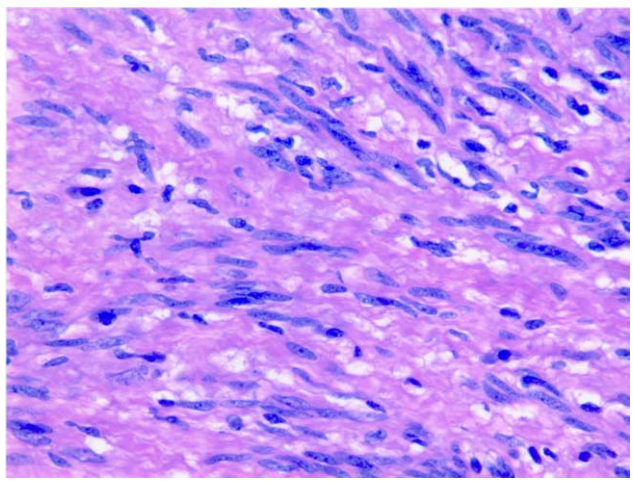

Fig. 3. High-power photomicrograph of the tumor illustrating proliferation of uniform spindle cells together with variable amounts of collagen. The cells indicate no nuclear atypism and mitoses were rare. Immunostaining of the tumor was positive for S-100, which is supportive of Schwann cell origin.

introduction of CT. The details of the Japanese patients were not available.

All four patients with lesions in the head of the pancreas reported in the Japanese literature underwent a Whipple operation. Out of the 12 patients with head lesions in the English and European literature, 7 patients underwent a Whipple operation, 2 patients underwent enucleation, 1 patient underwent biopsy, 1 patient underwent uncinate process resection, and 1 patient refused surgery. Patients with lesions in the body of the pancreas (n = 8) underwent distal pancreatectomy (5 patients), enucleation (2 patients), or local resection (1 patient). Patients with body/tail lesions (n = 8) underwent distal pancreatectomy (6 patients), local resection (1 patient), or were unresectable (1 patient). Patients with tail lesions (6 patients) underwent distal pancreatectomy (5 patients) or local resection (1 patient). In 1 patient the location of the tumor was not stated, whereas in another patient whose tumor was located in the head and body, the surgical procedure was not specified.

The mean follow-up of 19 out of 30 patients from the English and European literature was 18.68 months ± 24.09 (range 3–108 months). No follow-up was reported in 11 out of 30 patients from the English and European literature. The follow-up of the Japanese patients was not available. There were no recurrences or deaths at the end of the reported follow-up period.

There were five patient cases histologically reported to be malignant: 4 out of 30 patients (13.3%) in the English and European literature and 1 out of 10 patients (10%) in the Japanese literature. The interpretation of malignancy was based on light and/or electron microscopy. Immunostaining was used in only 1 of these patients. Of the 4 patients in the English and European literature, 3 patients exhibited a tumor in the head and underwent a Whipple procedure, whereas 1 patient who exhibited a tumor in the body and tail was determined to be unresectable. There was no reported evidence of any nodal or distant metastasis. Follow-up was reported in 3 out of 5 patients and there were no instances of local recurrence, metastases, or death.

DISCUSSION

Mesenchymal tumors account for approximately 1%–2% of all pancreatic tumors and are classified according to their cell of origin.[24] Schwannomas are benign spindle cell tumors derived from Schwann cells that line the nerve sheaths and are sometimes also referred to as neurilemmomas. The most common locations in descending order of frequency include the lower extremity, upper extremity, trunk, head and neck, retroperitoneum, mediastinum, and pelvis.[1,9,25] Pancreatic schwannomas arise from either autonomic sympathetic or parasympathetic fibers, both of which course through the pancreas as branches of the vagus nerve.[5,10]

Schwann cells can give rise to two types of tumors—schwannomas or neurofibromas. The distinction between these tumors is important because neurofibromas are associated with von Recklinghausen's disease and can undergo malignant degeneration more frequently. A few prior reports of schwannomas in patients with von Recklinghausen's disease, including those arising in the pancreas, are believed to be misdiagnosed neurofibromas.[5,25]

Microscopically, schwannomas are encapsulated, possess an organized cellular component (Antoni A area), a loose hypocellular component (Antoni B area), and their immunostaining for the S-100 protein is uniformly positive.[25] Neurofibromas can be differentiated from schwannomas by the absence of Antoni A and B areas and less uniform staining for S-100. Schwannomas are slow-growing benign neoplasms that rarely undergo malignant transformation, but when they do they exhibit an epithelioid appearance with patchy S-100 positivity and are referred to as "epithelioid malignant peripheral nerve sheath tumors."[25,26] They possess the potential to recur locally and metastasize.[26] There is also an infrequent tendency for angiosarcomas to arise in schwannomas.[26]

The symptoms of the reported patient cases of pancreatic schwannomas vary. Vague upper abdominal pain was the most common symptom reported, along with weight loss, nausea, melena, and jaundice. A few patients were asymptomatic and the lesions were incidentally discovered on CT scans performed for other reasons. Schwannomas with pronounced degenerative or cystic changes such as calcification or hemorrhage are termed "ancient schwannomas." These changes result from vascular thrombosis and subsequent necrosis. Cystic schwannomas of the pancreas can mimic a pancreatic pseudocyst and an absence of a history of pancreatitis can be important in the differential diagnosis.[10,25]

The preoperative diagnosis of schwannoma is very difficult. Most patients with a pancreatic mass have undergone ultrasound (US) and either CT or magnetic resonance imaging (MRI). Schwannomas are usually enhancing and well-circumscribed encapsulated masses on CT, oftentimes with areas of cystic degeneration, with a reported range in the English and European literature of 2–26 cm. Thus, the radiological differential diagnosis includes neuroendocrine tumors, epithelial tumors (microcystic serous adenoma, solid and papillary neoplasm, mucinous macrocystic tumor), hydatid cysts, lymphangiomas,

Von Hipple-Lindau syndrome, and pseudocysts.[10,27] The CT appearance of a schwannoma correlates well with the pathological type of these tumors. In schwannomas with a predominantly Antoni A appearance, the CT indicates a solid enhancing mass with varying degrees of central necrosis or inhomogeneous hypodense foci similar to that indicated in our patient.[24,27] Schwannomas with a prevalence of Antoni B areas are often associated with a cystic appearance without much contrast enhancement.[24,27,28] MR findings in schwannomas of the extremities have been well described. They are isodense with the muscle on T-1 images, indicate marked hyperintensity on T-2 images, and a capsule is identified in 70% of the patient cases.[5] Two patients exhibiting pancreatic schwannomas reported by Feldman and associates,[5] 3 patients exhibiting pancreatic schwannomas reported by Morita and associates,[3] and 1 patient exhibiting a pancreatic schwannoma reported by Ferrozzi and associates[6] were all hypointense on T-1 images and indicated hyperintensity on T-2 images. It has been illustrated that the hyperintensity on T-2 images of the schwannomas and their marked enhancement in comparison with the rest of the pancreas helps differentiate them from adenocarcinomas, but differentiation from islet cell tumors is still difficult.[3,5] Studies have revealed that CT and MR findings cannot distinguish benign from malignant lesions.[5,24]

The most common location is in the head (40%), followed by the body in 8 patients (20%), the body and tail in 8 patients (20%), the tail in 6 patients (15%), and the head and body in 1 patient (2.5%). Most of the schwannomas can be treated with simple enucleation depending on their size and location. An intraoperative frozen section should be performed, as it helps to establish the diagnosis of a benign neoplasm/schwannoma and obviates more radical resection. Intraoperative consultation with a pathologist was infrequently sought in this reported series of patients. It is interesting to note that of the 40 patient cases reported, only 4 patients (10%) underwent enucleation (size ranging from 2–4 cm). Large tumors, tumors in the head of the pancreas or involving the ampulla, or tumors involving the splenic hilum may require a more radical resection than simple enucleation.

In the reported literature, with the longest follow-up being 9 years, there have been no reports of local recurrence or metastasis of pancreatic schwannomas. There are 4 patient cases of "malignant" schwannomas reported in the English and European literature and 1 patient case reported in the Japanese literature. The methods of diagnosing malignancy were inconsistent. Immunostaining was not used or was not available in 3 out of 4 patients in the English and European literature. There were no recurrences, metastases, or deaths at the follow-up of 4–24 months in 3 out of 5 patients (not reported in 1 patient in the English literature and not available in the Japanese literature). These reported malignancies could represent misdiagnosed neurofibromas that underwent malignant degeneration.[12,14,16,18,25]

CONCLUSION

In summary, pancreatic schwannomas, although rare, deserve attention with regard to the differential diagnosis of pancreatic lesions. Preoperative diagnosis is difficult, but certain imaging features should raise the suspicion of this diagnosis. Differentiation of schwannomas from neurofibromas can be accomplished on the basis of histology and immunostaining and is important because of the risk of malignant degeneration of neurofibromas. Frozen section diagnosis is usually possible. Simple enucleation of the tumor from the surrounding parenchyma is recommended if possible, but in some instances more radical resection may be necessary. In either scenario, virtually all patients seem to be cured based on the current literature.

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Pancreatic Head Resection With Segmental Duodenectomy for Intraductal Papillary Mucinous Tumors of the Pancreas

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Various modifications of organ-preserving pancreatic resections have been performed for intraductal papillary mucinous tumor (IPMT) of the pancreas. The aim of this study was to evaluate usefulness of pancreatic head resection with duodenal segmentectomy (PHRSD), which is one of the organ-preserving pancreatic resections for IPMT. Pancreatic head resection with duodenal segmentectomy was indicated for the branch duct type of IPMT. Eight patients underwent PHRSD. The mean operative time was 390 minutes, and the mean blood loss was 1270 ml. Duodenal ischemia was prevented by preserving the duodenal branches of the gastroduodenal artery and the anterior inferior pancreaticoduodenal artery. Complications occurred in four patients: one with pancreatic leak, one with choledochoduodenal anastomotic stenosis, and two with delayed gastric emptying. However, no deaths occurred. The final pathologic diagnosis was adenoma in seven patients and carcinoma in situ in one patient. Six of eight patients had an adenoma with papillary growth in the main pancreatic duct. Postoperative pancreatic endocrine and exocrine functions were satisfactory. All patients were alive without recurrent disease at a median follow-up of 30 months. Pancreatic head resection with duodenal segmentectomy appears to be a useful procedure as an organ-preserving pancreatic resection for the branch duct type of IPMT, because this procedure allows a safe and complete resection of the pancreatic head without ischemia of the common bile duct and the duodenum. (J GASTROINTEST SURG 2004;8:713–719)

KEY WORDS: Pancreatic head resection with duodenal segmentectomy, organ-preserving pancreatic resection, intraductal papillary mucinous tumor of the pancreas

Intraductal papillary mucinous tumor (IPMT) of the pancreas is a relatively new clinical entity characterized by a relatively favorable clinical prognosis. Various modifications of pancreatic resection have been advocated for IPMT, because this tumor includes a wide variety of pathologic findings, such as hyperplasia, adenoma, carcinoma in situ, and invasive carcinoma. Recently, organ-preserving pancreatic resections for benign and noninvasive IPMT located at the head of the pancreas, including duodenum-preserving pancreatic head resection (DPPHR)[1–6] and partial resection of the pancreatic head,[7–9] have been described by several authors. However, there are two major problems with these procedures. First, complete extirpation of IPMT cannot be performed with certainty, because IPMT tends to spread into the main or branch pancreatic duct. Second, postoperative ischemia of the common bile duct and the duodenum occasionally occurs after these procedures. For these reasons, we selected pancreatic head resection with segmental duodenectomy (PHRSD) as an organ-preserving pancreatic resection for benign and noninvasive IPMT located at the head of the pancreas. The pancreatic head can be completely resected in this operation without causing ischemia of the common bile duct and the duodenum, and the major portion of the duodenum can be preserved by this procedure. There have been only three reports concerning PHRSD in the English literature.[10–12] The aim of this study was to evaluate the usefulness of PHRSD, which is one of the organ-preserving pancreatic resections for IPMT.

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PATIENTS AND METHODS

Indication for PHRSD

According to previous reports, the main duct type of IPMT was sometimes diagnosed as adenocarcinoma involving the surrounding organs or the regional lymph nodes in the resected specimens, whereas the branch duct type of IPMT was almost adenoma or adenocarcinoma in situ.[13–16] In addition, there have been several reports concerning the presence of adenoma-carcinoma sequence in IPMT.[17,18] For these reasons, we decided that PHRSD was indicated for the branch duct type of IPMT, more than 20 mm in diameter, where the preoperative cytologic examination of the pancreatic juice showed benign cells, because only a short segment of the duodenum along with the pancreatic head was resected without lymph node dissection by PHRSD.

Surgical Procedures

The most important point of this procedure was to preserve the duodenal branches of the gastroduodenal artery and the anterior inferior pancreaticoduodenal artery (AIPDA). This prevents ischemia of the preserved duodenum (Fig. 1). The details of this procedure are as follows. A midline upper abdominal incision was performed, and the duodenum was mobilized by Kocher's maneuver. After opening of the greater omentum, the size and location of the cystic lesion were evaluated with intraoperative ultrasonography. After tunneling posterior to the pancreatic neck, the pancreas was divided at a distance of 1 cm from the cystic lesion. The cut end on the tumor side was histologically examined on frozen section and confirmed to be negative for adenoma and carcinoma. Then, the pancreatic branches of the AIPDA were carefully ligated and divided with preservation of the duodenal branches. The AIPDA was ligated and divided near the major papilla. The duodenum was divided 1 to 2 cm distal to the major papilla. The uncinate process of the pancreas was dissected from the superior mesenteric vein and the extrapancreatic nerve plexus, and the posterior inferior pancreaticoduodenal artery was ligated and divided. The upper edge of the pancreas was dissected, and the anterior and posterior superior pancreaticoduodenal arteries were ligated and divided at their origins with preservation of the duodenal branches of the gastroduodenal artery. The common bile duct was divided at the upper border of the pancreas. At this time, ischemic changes were observed in a 2- to 3-cm segment of the duodenum. The duodenum was divided at 1 to 2 cm proximal to the major papilla to include all of the ischemic duodenum. A 2- to 3-cm segment of the duodenum, including the major and minor papilla, was resected by this procedure (Fig. 2). Subsequently, cholecystectomy, pancreatogastrostomy, duodenoduodenostomy, and choledochoduodenostomy were performed to reconstruct the alimentary tract. Gastrostomy tube and pancreatic ductal stents were routinely used (Fig. 3).

Clinical Data Analysis

Eight patients with branch duct type of IPMT underwent PHRSD. Clinical data were obtained from the patients' medical records, including surgical reports, pathologic records, hospital course, and outpatient medical records. The perioperative results, patient characteristics, surgical parameters, complications, and pathologic findings of these patients were analyzed. The postoperative long-term outcomes, including pancreatic endocrine function, and recurrence, were also evaluated. The endocrine function was measured by serum hemoglobin A_{1c} levels. The median follow-up period was 30 months (range, 5–46 months). Results were presented as mean ± SD. Mean values were compared using the paired *t* test. The difference was considered significant at $P < 0.05$.

RESULTS

Patient Characteristics

The patients who underwent PHRSD consisted of seven men and one woman (mean age, 63 ± 13 years; age range, 35–73 years). Mean maximal diameter of the cystic lesion was 25.8 ± 6.4 mm (range, 20–35 mm), and mean diameter of the main pancreatic duct was 3.5 ± 0.6 mm (range, 3.0–4.5 mm). Preoperative cytologic examinations of the pancreatic juice, which was obtained by endoscopic retrograde pancreatography, were all consistent with a benign process (Table 1).

Surgical Parameters

The operative time of this procedure ranged from 306 to 497 minutes (mean, 390 ± 69 minutes). Mean blood loss was 1270 ± 900 ml (range, 360–3000 ml), but only one patient required perioperative blood transfusions. Four units of packed red blood cells were transfused to the patient with liver cirrhosis (Table 1).

Complications

Postoperative complications occurred in two patients. One patient with a leak in pancreaticogastric anastomosis was cured without surgery through continual aspiration using the drain that had been placed

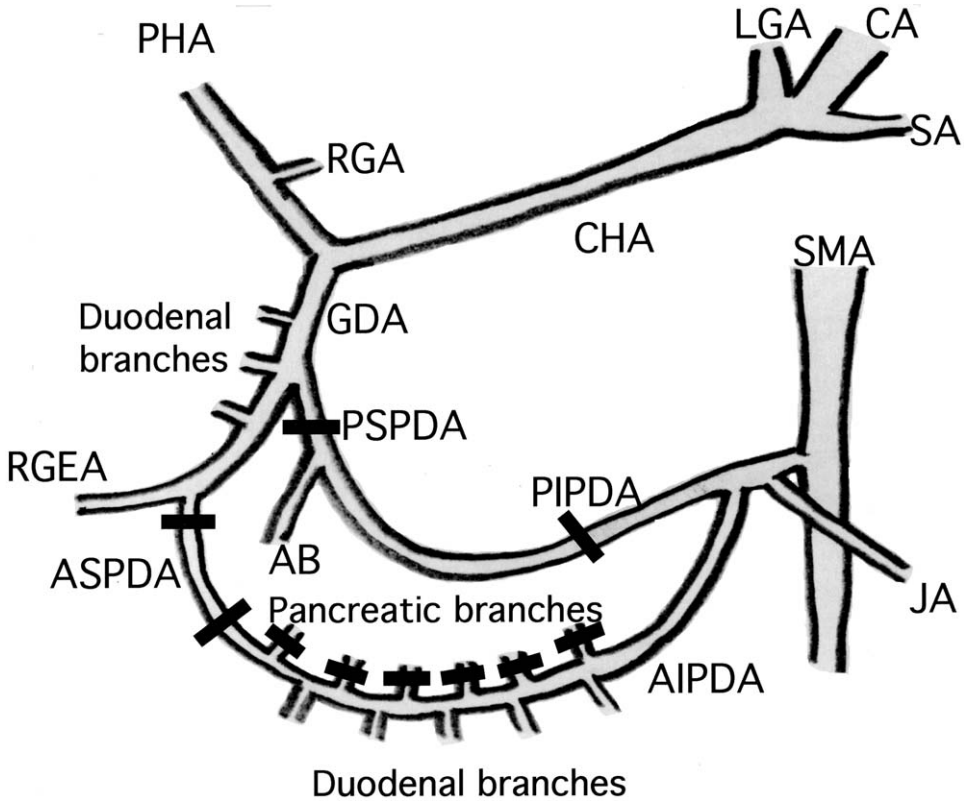

Fig. 1. Divided lines of the pancreaticoduodenal arteries in pancreatic head resection with segmental duodenectomy. CA = celiac artery; SA = splenic artery; LGA = left gastric artery; CHA = common hepatic artery; RGA = right gastric artery; PHA = proper hepatic artery; GDA = gastroduodenal artery; RGEA = right gastroepiploic artery; PSPDA = posterior superior pancreaticoduodenal artery; ASPDA = anterior superior pancreaticoduodenal artery; PIPDA = posterior inferior pancreaticoduodenal artery; AIPDA = anterior inferior pancreaticoduodenal artery; AB = ampullary branch; JA = jejunal artery; SMA = superior mesenteric artery.

intraoperatively. The other patient had stenosis of choledochoduodenostomy that was cured nonsurgically through percutaneous transhepatic biliary drainage, using a biliary tube stent. Delayed gastric emptying was defined as drainage from a gastrostomy tube for longer than 10 days or a failure to tolerate a semisolid diet 14 days after surgery. Delayed gastric emptying developed in two patients and was managed conservatively for 21 days with a complete recovery. There were no in-hospital deaths in this study (Table 1).

Pathologic Findings

Final pathologic diagnosis was adenoma in seven patients and carcinoma in situ in one patient. Six of eight patients had adenoma with papillary growth in the main pancreatic duct (Table 1).

Long-term Outcomes

All patients are currently alive without recurrent disease. The mean serum hemoglobin A_{1c} levels before surgery and 1, 2, and 3 years after surgery were 5.4%, 6.2%, 5.9%, and 6.0%, respectively. There were no significant differences between preoperative and postoperative values. Postoperative steatorrhea and abdominal cramping pain were not seen in any of the patients during the follow-up period, and oral pancreatic enzyme supplements were not used.

DISCUSSION

Although IPMT has been reported to have a favorable prognosis, the survival rate of patients with invasive carcinoma derived from IPMT—that is, tumor involving the pancreatic parenchyma—is not always high compared with that of noninvasive neoplasms.[19–22] The reason is that invasive carcinoma derived from IPMT frequently metastasizes to the regional lymph nodes and invades the surrounding organs. In our experiences, three of seven patients with invasive carcinoma died of recurrence, whereas all patients with noninvasive neoplasms survived without

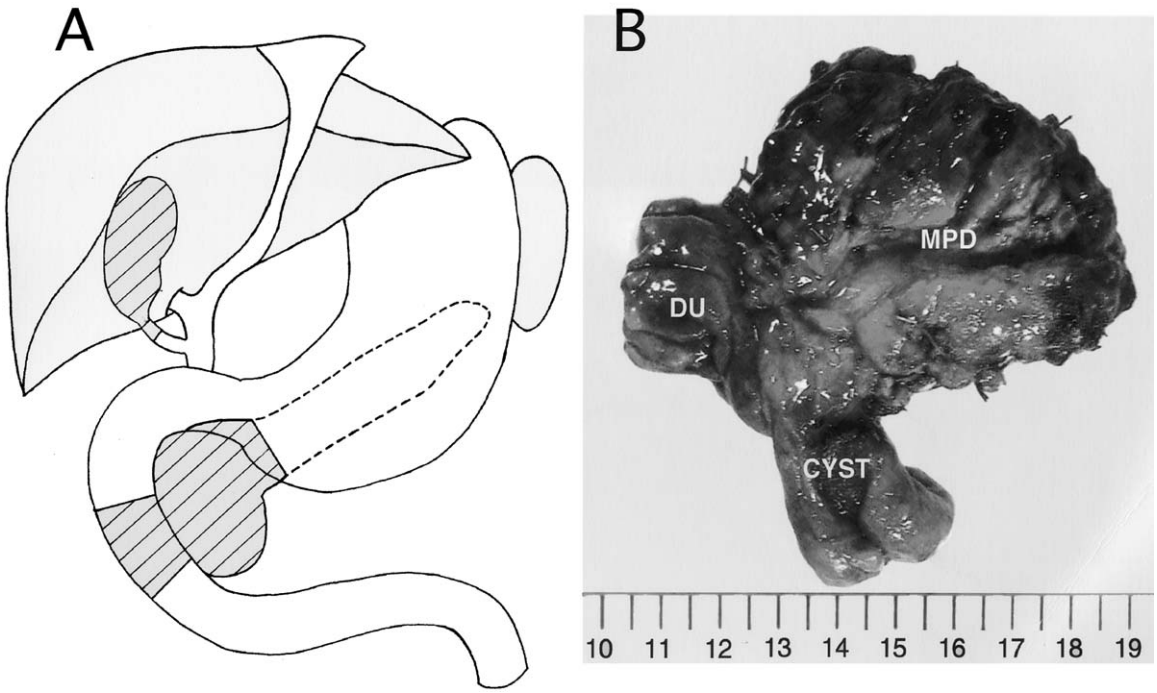

Fig. 2. (A) Resected portion (shaded areas) in pancreatic head resection with segmental duodenectomy. **(B)** Resected specimen. Only a 2- or 3-cm segment of the duodenum including the major and minor papilla was resected along with the pancreatic head. MPD = main pancreatic duct; DU = duodenum; CYST = cystic tumor of the pancreatic head.

recurrence. Therefore, it is important to distinguish invasive from noninvasive IPMT preoperatively.

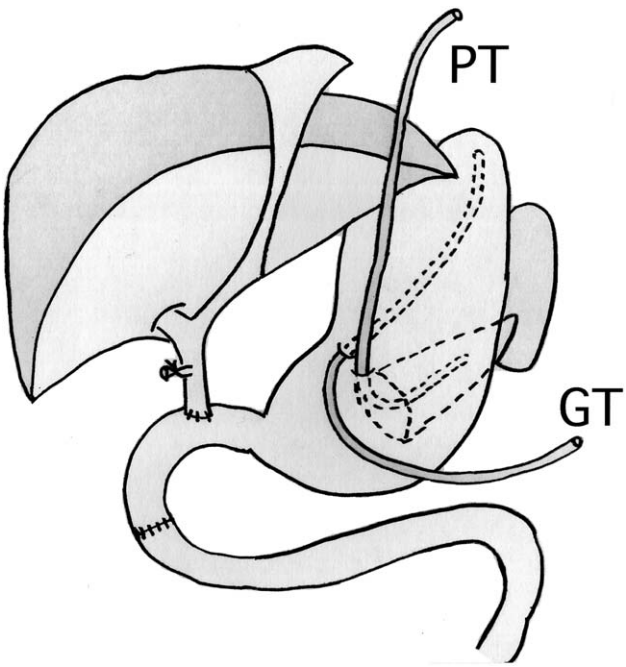

Fig. 3. Reconstruction of the alimentary tract following pancreatic head resection after segmental duodenectomy. PT = pancreatic external drainage tube; GT = gastrostomy tube.

There have been several reports concerning the differential diagnosis between benign and malignant IPMT. Peroral pancreatoscopy,[23] intraductal ultrasonography,[19] and molecular diagnosis of the pancreatic juice[24,25] have been reported to be useful for the differential diagnosis between benign and malignant IPMT. However, these new modalities can not definitely differentiate invasive from noninvasive IPMT. In our experiences, 18 of 19 patients with the branch duct type had noninvasive neoplasms, and 5 of 8 patients who had malignant cells in the pancreatic juice obtained preoperatively on endoscopic retrograde pancreatography were finally diagnosed as invasive carcinoma pathologically. Several authors reported that the branch duct type of IPMT without mural nodule was almost benign and might be treatable with organ-preserving pancreatic resection.[15,16] These results suggested that organ-preserving pancreatic resections should be indicated only for the branch duct type of IPMT, in which the preoperative cytological examination of the pancreatic juice is benign. As a result, the resected specimens of eight patients undergoing PHRSD revealed adenoma or adenocarcinoma in situ, that is, noninvasive IPMT.

Various modifications of organ-preserving pancreatic resections for IPMT have been reported. Segmental pancreatectomy[26] and spleen-preserving distal

Table 1. Patient characteristics and perioperative parameters of patients undergoing pancreatic head resection with segmental duodenectomy

Patient characteristics	
Gender (male/female) (n)	7/1
Age (yr)*	63 ± 13
Type of IPMT (main duct/ branch duct) (n)	0/8
Serum level of carcinoembryonic antigen (ng/ml)*	3.2 ± 2.0
Serum level of carbohydrate antigen 19-9 (U/L)*	22 ± 16
Maximal diameter of the cystic lesion (mm)*	25.8 ± 6.4
Diameter of the main pancreatic duct (mm)*	3.5 ± 0.6
Cytological examination of the pancreatic juice (benign/malignant) (n)	8/0
Surgical parameters	
Operative time (min)*	390 ± 69
Blood loss (ml)*	1270 ± 900
Blood transfusion (yes/no)	1/7
Complications (n)	
Leak of pancreaticogastrostomy	1
Stenosis of choledochoduodenostomy	1
Delayed gastric emptying	2
Pathologic findings (n)	
Adenoma/adenocarcinoma	7/1
Involvement of the main pancreatic duct (yes/no)	6/2

*Values are given as ratios mean ± SD.
IPMT = intraductal papillary mucinous tumor.

pancreatectomy[27] are commonly performed when IPMT is located in the body or tail of the pancreas. Recently, DPPHR,[1–6] inferior head resection of the pancreas,[7] and ventral pancreatectomy[8] have been described as organ-preserving pancreatic resections for IPMT located in the head of the pancreas. However, there are two major problems with these procedures. First, it is very difficult to ensure complete extirpation of IPMT with partial resection of the pancreatic head, such as is done during inferior head resection of the pancreas and ventral pancreatectomy, because IPMT tends to spread into the main or branch pancreatic duct. Actually, Nakagohri et al.[7] reported one patient with IPMT who died of recurrent disease 18 months after inferior head resection of the pancreas. In addition, in this study, six of eight patients had adenoma in the main pancreatic duct. Complete resection of the pancreatic head should be performed for this tumor to prevent recurrence of the tumor. Second, postoperative ischemic necrosis or perforation of the common bile duct and the duodenum occasionally occur with DPPHR.[6] According to previous literature reports, DPPHR is divided into two types, with preservation of the common bile duct and with resection of the common bile duct. Recently, Kimura and Nagai[28] studied the surgical anatomy of the pancreatic head and reported that preservation of the branches of the posterior superior pancreaticoduodenal artery (PSPDA), which runs through the pancreatic parenchyma between the common bile duct and the duodenum and toward the major papilla, is required to maintain the arterial blood supply to the common bile duct and the major papilla. Based on this evidence, complete resection of the pancreatic head is impossible on DPPHR with preservation of the common bile duct because preservation of the pancreatic parenchyma between the common bile duct and duodenum is required to maintain the arterial blood supply of the common bile duct and the major papilla. If DPPHR with resection of the common bile duct is performed for complete resection of the pancreatic head, ischemia of the major papilla may result, because it is technically impossible to preserve only the ampullary branches of the PSPDA. Also, Kimura and Nagai[28] described invasion of the pancreatic parenchyma into the submucosal or muscular layer of the duodenum in the neighborhood of the accessory papilla. For these reasons, we confirm that only PHRSD enables us to perform complete resection of the pancreatic head safely without ischemia of the common bile duct and duodenum.

In the present study, stenosis of choledochoduodenostomy was experienced in one case. The patient was successfully managed with temporary percutaneous trashepatic biliary stenting. Ahn et al.[12] described a similar complication in PHRSD. They reported that this complication was caused by the small choledochoduodenostomy stoma (owing to the normal caliber of the common bile duct). Therefore, we recently used an internal biliary stent when performing choledochoduodenostomy to prevent this complication.

Delayed gastric emptying has been described as one of the leading complications after pylorus-preserving pancreatoduodenectomy. It occurs in 20–30% of patients after surgery.[29] Several factors have been suggested in the pathogenesis of delayed gastric emptying, including gastric dysmotility secondary to anastomotic leakage or abscess, gastric atony after resection of the duodenal pacemaker, and gastric atony due to reduced circulating levels of motilin. Isaji and Kawarada[11] reported that 38.8% of the patients undergoing PHRSD developed delayed gastric emptying. In our series, the incidence of delayed gastric emptying was 25%, which is comparable to that found after pylorus-preserving pancreatoduodenectomy.

With regard to postoperative endocrine function after PHRSD, Isaji and Kawarada[11] reported that pancreatic endocrine function at 6 months after surgery, which was evaluated by measuring plasma

immunoreactive insulin during a 75g oral glucose tolerance test, was not significantly decreased compared with the preoperative value. In the current study, serum hemoglobin A_{lc} levels of the patients undergoing PHRSD have not been significantly increased compared with the preoperative value, at least during the first 3 postoperative years. In addition, steatorrhea was not seen in any of our patients after PHRSD, although postoperative pancreatic exocrine insufficiency was reported in one of seven patients undergoing PHRSD by Ahn et al.[12] Postoperative endocrine and exocrine function after PHRSD was, in general, altered little by the operation.

CONCLUSION

PHRSD allows complete resection of the pancreatic head without causing ischemia of the common bile duct and duodenum. PHRSD preserves a major portion of the duodenum and maintains satisfactory postoperative pancreatic endocrine and exocrine function. PHRSD appears to be a useful procedure as an organ-preserving pancreatic resection for branch duct type of IPMT located at the head of the pancreas.

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Early Results of One-Year Robotic Surgery Using the Da Vinci System to Perform Advanced Laparoscopic Procedures

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Robotic technology has recently been introduced to gastrointestinal laparoscopic surgery. We prospectively evaluated early results of robotic surgery using the Da Vinci system in our department. Data were prospectively collected in 40 patients who underwent robotic surgery during a 1-year period. We performed 3 cholecystectomies, 10 anterior fundoplications for gastroesophageal reflux disease, 17 transperitoneal adrenalectomies, 2 Heller myotomies, 5 procedures for rectal prolapse, and 3 colpohysteropexies for genital prolapse. The results for robotic adrenalectomies and anterior fundoplications were compared with the results from patients who underwent these procedures laparoscopically without robotic assistance at our department during the same period. We encountered two conversions to laparotomy (5%) and one conversion to standard laparoscopy (2.5%). There was no morbidity imputable to the robotic approach and no deaths. The mean operative times were significantly longer in robotic groups compared with laparoscopic groups for adrenalectomies and fundoplications. The Da Vinci robotic system enables surgeons to perform advanced laparoscopic procedures with ease, safety, and precision. We believe that preferable indications for using this system are to perform surgery in narrow spaces (pelvic surgery) or when precise dissection is mandatory (Heller myotomy). (J GASTROINTEST SURG 2004;8:720–726)

KEY WORDS: Robotic surgery, Da Vinci, rectal prolapse, genital prolapse, Heller myotomy, adrenalectomy

The development of minimally invasive surgical techniques has reduced patients' morbidity. Performing surgical interventions through small incisions or ports reduces infection rates, the need of pain medication, and recovery times.[1,2] One of the disadvantages of conventional laparoscopic technique is that instruments are long and inflict trauma as they are manipulated through fixed entrance sites, with limited degrees of freedom. Moreover, the operative field is watched on a two-dimensional video monitor, which is relatively immobile and hence not always in the working axis. Robotic technology has recently been introduced to gastrointestinal laparoscopic surgery to facilitate or aid in the process of performing endoscopic surgery, [3–5] but only a few reports have been published on the results of this new approach.[6–8]

In September 2000, we have adopted the Da Vinci robotic system (Intuitive Surgical Inc., Sunnyvale, CA) in our institution (Fig. 1). The Da Vinci robotic system facilitates in the process of performing endoscopic surgery. This system consists of two major components: (1) the surgeon's console equipped with a three-dimensional optic system and two manipulator handles and (2) a movable cart with three articulated robot arms. Although usually still in the operating room, the surgeon has no direct contact with the patient, and the first assistant stands at the bedside. The surgical team (assistant surgeon and nurse) participate in the operation and watch the procedure on a video endoscopic unit while the surgeon is comfortably seated at the console and manipulates handles. The system translates the surgeon's hand movements to the robotic arms containing specific

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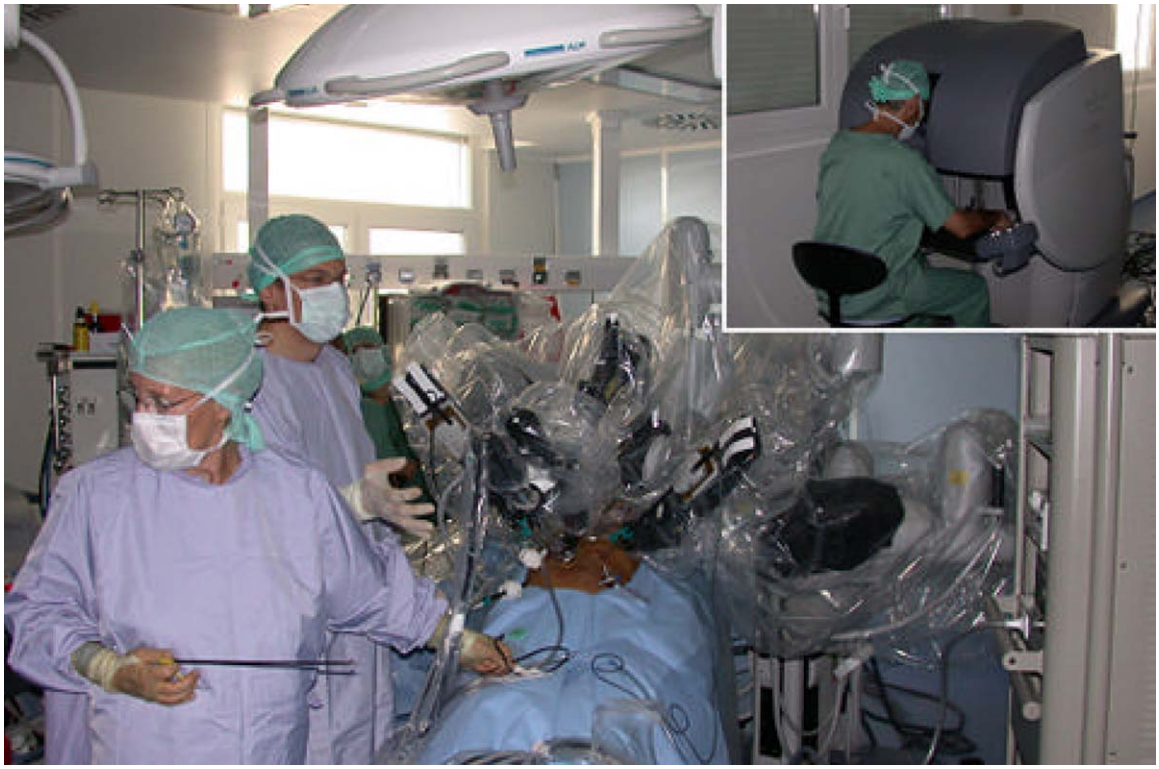

Fig. 1. The Da Vinci surgical system in the operating room.

surgical tools inside the body with great precision. Elsewhere, the tools (hook, scissors, forceps. and needle holder) are multiarticulated intracorporally, which allows several degrees of freedom (Fig. 2).

The aim of this prospective study was to report the preliminary results of 1 year of robotic surgery with the Da Vinci robotic system in clinical practice in our department of general surgery.

MATERIAL AND METHODS

Between September 2000 and September 2001, we performed laboratory training on pigs to make the surgical team familiar with the device. After this training period, we started to use the Da Vinci robotic system in clinical practice. In our institution, this robotic system is installed in a dedicated operating room and used by cardiac surgeons, urologists, gynecologists, and general surgeons. One hundred twenty-six patients underwent endoscopic procedures assisted by the Da Vinci system at our institution from September 2001 to September 2002. During this period, 32 procedures were performed by cardiac surgeons, 46 by urologists, 8 by gynecologists, and 40 by general surgeons. These latest patients are studied in this report. Patients were selected according to criteria currently used for conventional laparoscopic surgery. All patients were fully counseled about the risks, benefits, and alternatives to robotic surgery. We extensively discussed the novelty of the robotic system, and the procedures were performed in all cases after obtaining an informed consent. None of the patients refused robotic approach. All procedures were performed by senior surgeons (L.B., P.B.). All procedures were scheduled, and none of them were emergent or performed at night. All data were collected prospectively by an independent observer, who was a nurse dedicated to the robotic system evaluation. Patient demographics, operative indications, operative time, dissection time, complications, and hospital stay were recorded. In our data, the operative time includes all phases of setup, induction of pneumoperitoneum, placement of ports, and overall surgical time; the dissection time was the surgeon's active time at the console. The setup time included the time for wrapping and positioning the robot cart and ports.

For a comparison, we analyzed results from patients who underwent laparoscopic procedures at our department during the same period. These procedures were also performed by surgeons previously mentioned. Operative times, postoperative morbidity and mortality, and length of postoperative hospital stay were compared for adrenalectomies and anterior

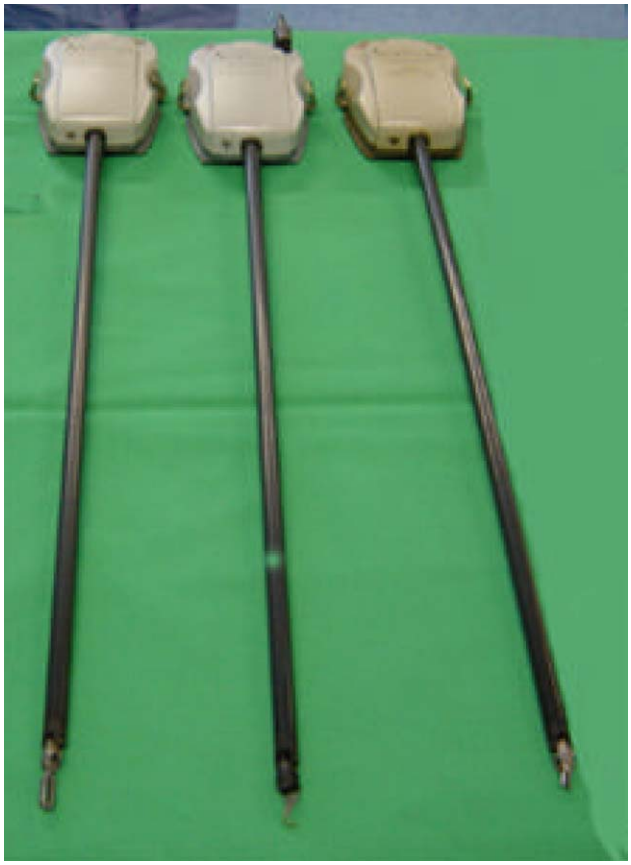

Fig. 2. The Da Vinci robotic system's specific tools (hook, scissors, forceps and needle holder).

fundoplications for gastroesophageal reflux disease (GERD). The reason why these latest procedures were not performed robotically was the unavailability of the robotic system, because it is used in one dedicated room by several surgical teams. Data for these patients were also recorded prospectively by the same independent nurse who collected data for robotic procedures.

Statistical Analysis

For description of continuous variables, the median and range values were calculated, and the Mann-Whitney test was used to compare these continuous variables. Results were considered significant at $P < 0.05$.

RESULTS

Between September 2001 and September 2002, 40 patients (28 women and 12 men; mean age, 48 years; age range, 17–81 years) underwent a robot-assisted procedure in our department of general surgery. We performed 3 cholecystectomies, 10 anterior fundoplication for GERD, 17 transperitoneal adrenalectomies, 2 Heller myotomies, 3 Frykman-Goldberg and 2 Orr-Loygue procedures for rectal prolapse, and 3 hysteropexies for genital prolapse.

Cholecystectomy

We operated on three women for symptomatic gallbladder lithiasis and performed cholecystectomy. This procedure was the first we performed in human practice. The age of these patients were 75, 78, and 81 years. The operative times were 80, 90, and 100 minutes, and the dissection times were 60, 70, and 80 minutes, respectively. There was no postoperative morbidity. The postoperative stay was 3 days for each patient.

Gastroesophageal Reflux Procedure

We performed 10 procedures for GERD in 6 men and 4 women (median age, 48 years; age range, 28–58 years). The indication for surgery was the presence of a pathologic gastroesophageal reflux, as documented by 24-hour pH-metry, gastroscopy, barium swallow, and esophageal manometry. We performed a Dor-Watson procedure (anterior fundoplication) as we proceed in all cases of gastroesophageal reflux in our institution. We encountered two perioperative complications that consisted of minor bleeding from the hepatic caudate lobe. These bleedings did not require conversion and were treated conservatively by electrocoagulation. The postoperative course of these patients was uneventful. We retrospectively compared robotic and laparoscopic Dor-Watson procedures (Table 1). The two groups were comparable in term of age, sex, and body mass index. The median operative time was significantly longer in the robotic group: 177 minutes (range, 100–245 minutes) for the robotic approach and 113 minutes (range, 65–170 minutes) for the laparoscopic approach ($P = 0.01$). The main reason for this longer time probably was the additional setup time, which was about 30 minutes (range, 25–40 minutes) for wrapping and positioning the robot. On the other hand, if we compare the surgeon's active time at the console during robotic approach with the laparoscopy time, this difference became nonsignificant ($P = 0.35$). No patient was converted to laparotomy in both groups. The median postoperative stay and morbidity rate were similar for the robotic (5.8 days; two pulmonary infections) and laparoscopic (5.5 days; one pulmonary infection) groups. At 6-month follow-up, all patients of both groups were free of reflux disease.

Table 1. Retrospective comparison of robotic and laparoscopic procedures

	N	Age, median (range) (yr)	Operative time, median (range) (min)	Dissection time, median (range) (min)	Conversion rate (n)	Morbidity (n)	Mortality (n)	Postoperative stay, median (range) (days)
Adrenalectomy								
Robotic	17	47 (31–75)	105 (65–165)	50 (25–125)	1 (6%)	2 (12%)	0 (0%)	6 (4–9)
Laparoscopic	14	43 (23–62)	84 (45–120)*	84 (45–120)†	1 (7%)	2 (14%)	0 (0%)	5.7 (3–10)
Gastroesophageal reflux disease								
Robotic	10	48 (28–58)	177 (100–245)	143 (75–210)	0 (0%)	2 (20%)	0 (0%)	5.8 (3–10)
Laparoscopic	10	41 (31–53)	113 (65–170)‡	113 (65–170)§	0 (0%)	1 (10%)	0 (0%)	5.5 (4–7)

Comparison with use of Mann-Whitney test:
*$P = 0.05$.
†$P = 0.07$.
‡$P = 0.01$.
§$P = 0.35$.

Adrenalectomy

We performed 17 adrenalectomies via the transperitoneal approach (15 women and 2 men; median age, 47 years; age range, 31–75 years). The indications for adrenalectomy are listed in Table 2. The procedure was performed in lateral decubitus position as in conventional laparoscopy (right lateral decubitus position for left adrenalectomy and left lateral decubitus position for right adrenalectomy). The median operative time was 105 minutes (range, 75–165 minutes), whereas the median active time was 50 minutes (range, 25–140 minutes). The median setup time, which was 40 minutes (range, 20–110 minutes), was probably the main reason for explaining this difference. If we compare the eight first cases with the latest nine cases, the median setup time decreased significantly from 67 minutes (range, 50–110 minutes) to 35 minutes (range, 20–45 minutes) ($P = 0.001$). We experienced one complication, which was bleeding of the right adrenal vein that required conversion to laparotomy. This patient was obese (body mass index = 40 kg/m^2) and presented with Cushing disease. One other patient was converted to standard laparoscopy because of failure of the camera system.

Table 2. Characterization of removed adrenal glands with robotic or laparoscopic approach

	Robotic (n = 17)	Laparoscopic (n = 14)
Mean tumor size (cm)	3.3	3.1
Tumor type (n)		
Aldosteronoma	6	4
Pheochromocytoma	3	6
Incidentaloma	3	3
Cushing	5	1
Right/left (n)	7/10	6/8

Postoperative morbidity occurred in two patients and consisted of one wound infection and one pulmonary infection. The median postoperative hospital stay was 6 days (range, 4–9 days). During the same period, we operated on 14 patients for adrenalectomy via the standard laparoscopic approach (Table 2). The two groups were comparable in term of age, sex, body mass index, tumor size, and side of the tumor. There also were no differences in terms of conversion rate (one conversion to laparotomy for bleeding in each group) and postoperative morbidity (one pulmonary and one wound infection in each group) (Table 1). The only significant difference was operative time, which tended to be longer in the robotic group ($P = 0.05$). However, as for GERD, this difference was not significant if we compare the surgeon's active time at the console with the laparoscopy time ($P = 0.07$).

Heller Myotomy

We performed Heller myotomy procedures for two patients (one man and one woman; 17 and 44 years old, respectively) presenting with achalasia, which was confirmed on esophageal manometry. The gastroesophageal junction was dissected, and the retroesophageal space was opened under direct vision, identifying and protecting the posterior vagus nerve. An incision was made in the distal esophageal musculature just above the gastroesophageal junction and carried cranially for 6 to 7 cm using the electrocautery knifes. The myotomy was extended onto the stomach for 1 to 1.5 cm. After careful inspection, a Dor-Watson–type fundoplication was performed. We observed no perioperative or postoperative complications. The operative times were 140 and 150 minutes; the dissection time was 90 minutes in both cases. The patients were discharged at postoperative day 7. Both patients were free of symptoms at 6 months.

Rectopexy for Rectal Prolapse

We operated on five women presenting with rectal prolapse. We performed two Orr-Loygue procedures and three Frykman-Goldberg procedures for patients presenting with a history of constipation associated with rectal prolapse.

Posterior mobilization of the rectum was carried out to the level of the levator ani muscles. In the pelvis, the peritoneum was incised 1 cm lateral to either side of the rectum and dissection was carried distally with preservation of the lateral stalks. Anterior dissection was extended to the upper third of the vagina. In the Orr-Loygue procedure, the rectum was suspended by two pieces of mesh that were sutured inferiorly along the lateral aspects of the rectum and superiorly to the promontory. In the Frykman-Goldberg procedure, the posterior dissection was the same; the rectum was elevated and its lateral peritoneal attachments were sutured to the presacral fascia, beginning just below the sacral promontory. The peritoneum was then closed and the sigmoid resection was performed through a small incision either suprapubic or in the left iliac fossa. The median age of these patients was 46 years (age range, 31–71 years). We observed one perioperative complication that was bleeding in front of the sacrum that necessitated a conversion to laparotomy. The median operative time was 265 minutes (range, 180–240 minutes); the median dissection time was 165 minutes (range, 48–270 minutes). In these cases, the robot positioning was excessively long (almost 70 minutes) because it had to be positioned between the patient's legs, which was unusual at the beginning of our experience. The postoperative course was uneventful. The median postoperative stay was 7 days (range, 4–13 days).

Colpohysteropexy for Genital Prolapse

We performed three hysteropexy procedures in three women (44, 49, and 54 years old) presenting with a genital prolapse. The posterior dissection between the anterior wall of the rectum and the posterior wall of the vagina was performed toward the pelvic floor. The first mesh was then sutured to the levator ani muscles and to the posterior wall of the vagina. Anterior dissection was carried out between the bladder and the anterior wall of the vagina, and then a second piece of mesh was sutured to the vagina with nonabsorbable stitches. This mesh was brought through the broad ligament of the uterus, and then both pieces of mesh were sutured to the promontory with two nonabsorbable stitches, and additional takers if necessary, in the prevertebral ligament. The operative times were 290, 310, and 340 minutes, and the dissection times were 200, 240, and 280 minutes. The setup time was as long as rectal prolapse surgery for the same reason. The postoperative morbidity was nil. The postoperative stay was 7 days in each case.

DISCUSSION

There are only a few reports demonstrating that completely endoscopic procedures assisted by the Da Vinci robotic system can be performed successfully and safely.[4–8] The morbidity due to the robotic system was minimal. Even though in our series two procedures (5%) required a conversion to laparotomy (one adrenal vein bleeding and one presacral vein bleeding), we do not believe that it is imputable to the robotic approach. We also encountered this kind of conversion in standard laparoscopic approach. The only event directly imputable to the device is probably the conversion to standard laparoscopy in one case (2.5%) because of the three-dimensional camera failure, which did not alter the postoperative course. These results seem to confirm the feasibility of robotic procedures.

The Da Vinci robotic system presents, in theory, many significant advantages.[3,4,9] The high-resolution three-dimensional optical system provides better depth perception and perhaps better definition of tissue planes than standard two-dimensional laparoscopic images. The operative field magnification on the console screen allows for more accurate identification of anatomic structures and for enhanced surgical precision and guarantees a natural orientation in the abdominal cavity. The navigator camera control system enables the surgeon to visualize the operative field, move to any site desired, change the view, and either zoom in or out without interrupting the procedure. Multiarticulated instruments that rotate 360 degrees increase the number of degrees of freedom and can allow sutures and other instruments to be applied easier in a variety of angles and orientations that would be difficult with the use of typical, rigid laparoscopic instrumentation. Due to the scaling motion function of the Da Vinci system, there was no physiologic trembling; the movements of the surgeon's wrist, hand, and fingers are transferred to the instrument with very good precision.

Nevertheless, there are some drawbacks to the Da Vinci system. (1) The robotic system needs a dedicated operating room specially designed and wired for these advanced technologies. (2) Precise positioning of the robot is essential for optimal operative outcome and to avoid robotic arm collision, as minor misplacements of the trocars may severely impede the performance of the operation. Therefore, the setup

of the robot takes time. Furthermore, we observed in this study that setup time (including wrapping and robot positioning) for the robotic system decreased with experience. When all patients were taken into account, the median setup time decreased from 60 minutes (range, 20–130 minutes) for the earlier cases to 30 minutes (range, 20–100 minutes) for the latest cases ($P = 0.006$). For this reason, the operative time for the latest patients was considerably diminished and was nearly similar to that for patients operated on with conventional laparoscopy. (3) Because the robot arms are not attached to the surgical table, during complex operations that require postural changes, the robot arms must be separated from the patient for each position change, which adds time to complex surgical procedures. (4) The current generation of Da Vinci system does not provide tensile feedback; therefore, the surgeon must rely on visual clues to estimate the tension placed on tissues, and he or she very soon learns to compensate with the three-dimensional vision. This is probably why we encountered two cases of minor bleeding on the hepatic caudate lobe in the beginning of our experience. (5) In the near future, the Da Vinci robotic system should have a fourth arm that would be helpful to perform more complex operations.

We performed three cholecystectomies in the beginning of our experience in human practice. Cholecystectomy seems to be easily and safely performed via the robotic approach.[4,6] Even though we have not compared the outcomes of robotic cholecystectomies with those of laparoscopic cholecystectomies, we did not perform any more of these procedures via the robotic approach because we do not believe it offers any advantages in this indication. Nevertheless, the goal of these earlier procedures was to make the operating staff familiar with the dedicated operating room.

In our series, the Dor-Watson antireflux procedures were safely performed with the Da Vinci robotic system. Like Melvin et al.,[10] we did not report any clear advantages in operative outcomes by performing robotic antireflux procedures compared with standard laparoscopic approaches. For this reason, we initiated a prospective study comparing long-term outcomes and quality of life in patients undergoing laparoscopic or robotic antireflux surgery.

Laparoscopic adrenalectomy is the preferred approach for the removal of most adrenal tumors. Only a few studies have reported the feasibility of robotic adrenalectomy.[11,12] We report our experience with 17 adrenalectomies (7 left and 10 right adrenal glands) with no major morbidities. We experienced one bleeding complication that required conversion to laparotomy; this occurred at the beginning of our experience in a very obese patient (body mass index = 40 kg/m^2) with Cushing disease. We do not believe that this complication is attributable to the robotic approach.

Laparoscopic Heller myotomy via a transabdominal route is a safe and effective modality for the treatment of achalasia, and generally good results have been reported.[13] Potential complications are failure secondary to undivided circular muscle fibers, perforation of the esophageal mucosa, or progression of disease. The robotic procedure may help improve the treatment of achalasia by eliminating these potential complications; the extra magnification and excellent three-dimensional imaging can help prevent esophageal perforation and identify residual circular muscle fibers. Even though there are only a few reports that deal with the feasibility and the outcomes of robotic Heller myotomy,[5,7,8] we believe that such a procedure is probably one of the best indications for robotic surgery because of the ease and safety of the dissection. In our series, both patients were free of symptoms at the week 6 outpatient visit. This has to be verified with more patients and a longer follow-up.

To our knowledge, we report the first cases of rectal or genital prolapse treated with robotic surgery. We performed three colpohysteropexies, three Frykman-Goldberg procedures, and two Orr-Loygue procedures. The use of the three-dimensional optical system and multiarticulated instruments that rotate 360 degrees allows a very fine dissection of the rectum and/or the vagina toward the levator ani plane. This dissection seems to be easier and safer than the traditional laparoscopic approach. After this dissection, the robotic system allows safe knot realization in this narrow area, especially for suturing mesh to the rectum and/or to the vagina, while the surgeon is comfortably seated at the console. Even though we encountered one conversion to laparotomy because of bleeding, we do not believe it is caused by the robotic approach.

In conclusion, we demonstrate the feasibility of advanced laparoscopic procedures using the Da Vinci robotic system. However, significant superiority in the performance and outcome of the procedures was not shown. Nevertheless, we believe that this robotic system allows easier and safer dissection and enables surgeons to better perform procedures due to the high quality of visualization and enhanced precision. This has to be proved with larger series in the near future. Elsewhere, this system is probably underused regarding its possibilities. In our experience, one of the main advantages of the Da Vinci system seems to be performing dissection in narrow spaces such as pelvic dissection in the case of rectal or genital prolapse surgery and when precise dissection is mandatory, such as the Heller myotomy procedure, but this

has to be evaluated with larger series. We believe that in the near future, the system will be technically improved, which may allow more difficult procedures like gastric, colonic, hepatic, biliary, or pancreatic surgery, as described by Giulianotti et al.[14]

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Gastric Cancer Surgery Without Drains: A Prospective Randomized Trial

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Prophylactic drain placement during major abdominal surgery has been widely practiced without clear scientific evidence to support it. We hypothesized that prophylactic drain placement is not necessary in gastric cancer surgery. A randomized prospective trial was conducted between February 1, 2001, and July 30, 2001. Patients were randomly assigned to either the drain group or the no-drain group. One hundred seventy patients completed the study by undergoing either subtotal or total gastrectomy with D2 lymph node dissection. Surgical outcome between the two groups was compared within the subtotal and total gastrectomy subgroups. Postoperative complication within 30 days was the primary end point of the study. No significant difference was noted in the incidence of postoperative complication between the drain group and the no-drain group. The results of this study suggest that prophylactic drain placement does not offer additional benefit for patients undergoing gastric cancer surgery with extended lymph node dissection.
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Key words: Gastric cancer, surgery, drains, prospective randomized trial

Prophylactic placement of drains during major abdominal surgery has been widely practiced since the 1800s despite the lack of scientific evidence or prospective study results to support the practice.[1] In gastric cancer surgery, drains have been used for the removal of blood, lymph, and other exudates that may have accumulated after surgery as well as for the early detection of hemorrhage or anastomotic leakage.[2–4] However, intraoperative use of drains in itself can cause complications such as organ damage, infection, and pain.[1–4] Advances in surgical technique, anesthesia, and perioperative patient care have consistently decreased the complication rates after gastric cancer surgery, especially in regions such as Korea and Japan, where gastrectomy with D2 lymph node dissection is the standard of care.[5, 6] Moreover, several studies have questioned the use of drains in other abdominal surgeries.[7–9] The aim of this study was to assess the value of drain use in gastric cancer surgery through a randomized prospective trial.

PATIENTS AND METHODS

The study was approved by the Clinical Trial Ethics Committee of Yonsei University College of Medicine. Two hundred fifteen patients who were diagnosed with gastric cancer and were scheduled to undergo surgery at the Department of Surgery, Yonsei University College of Medicine, between February 1, 2001, and July 31, 2001, were evaluated for eligibility. Patients without significant past medical history and without previous abdominal surgery who were eligible to undergo radical subtotal or total gastrectomy without organ resection other than splenectomy were eligible to participate in the study. One hundred seventy patients were randomly assigned to the drain group on the no-drain group in the operating room, at the beginning of the procedure, after determination that the primary tumor was resectable and the surgery was curative. The 170 patients underwent either total or subtotal gastrectomy with D2 or more lymph node dissection depending on the extent and location of the primary tumor. Surgical outcome of patients in the drain group was compared with that of patients in the no-drain group to assess the value of drain use in gastric cancer surgery.

Operative Technique

All procedures were performed by a single surgeon (S.H.N.). Operative protocol generally followed the

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guidelines of the Japanese Research Society for Gastric Cancer[10] and consisted of D2 or more lymph node dissection and a tumor-free margin of greater than 2 cm for T1 tumor and greater than 5 cm for T2-3 tumor. Subtotal gastrectomy was performed whenever these resection margins were achieved; otherwise, total gastrectomy was performed. During total gastrectomy, distal pancreatectomy and/or splenectomy was not performed unless there was suspicion of cancer involvement. Distal pancreatectomy was not performed for any of the patients in this study. Preoperative nasogastric tube insertion was not done except for patients with gastric outlet obstruction. When a distended stomach, small intestine, or colon was encountered during surgery, needle decompression was used to improve exposure of the surgical field.[11]

A two-armed closed suction drain (Sewoon Medical Co., Seoul, Korea) was used for patients in the drain group. One drain was placed in the right upper quadrant via the foramen of Winslow below the hepatoduodenal ligament during subtotal gastrectomy. Two drains were placed after total gastrectomy. One drain was placed in the right upper quadrant as in a subtotal gastrectomy, and the other drain was placed in the vicinity of the esophagojejunal anastomosis below the left diaphragm in the left upper quadrant.

Postoperative Care

Postoperative pain control was achieved with epidural or intravenous patient-controlled anesthesia (PCA) for the first 2 postoperative days. Tridol 50 mg intramuscularly (Tramadol HCl; Yuhan Corp., Seoul, Korea) was administered as needed from postoperative day 3 after removal of PCA. Nasogastric tubes, if inserted preoperatively, were discontinued on postoperative day 1. Drains were removed when the total output was less than 100 ml in 24 hours.

Patients were allowed sips of water from the evening of postoperative day 2. Liquid diet was started after confirmation of return of bowl function with passage of flatus and advanced to soft diet as tolerated. Patients were discharged from the hospital after tolerating soft diet for 3–4 days.

Surgical Outcome Assessment

Baseline patient characteristic assessment of each group included the American Society of Anesthesiologists (ASA) classification[12] and cancer stage according to the Fifth International Union Against Cancer (UICC) TNM classification.[13]

Surgical outcome in this study was measured in terms of the incidence of postoperative complications, operating time, frequency of analgesic use per day after PCA removal, number of days after surgery until passage of flatus, number of days after surgery until initiation of soft diet, and length of hospital stay after surgery. *Postoperative complication* was defined as any adverse event that required a surgical or medical intervention within 30 days of undergoing surgery and was the primary end point of this study. Operating time was measured from the time of skin incision until the closure of skin.

Surgical outcomes were compared between the drain and no-drain groups within the subtotal gastrectomy and total gastrectomy subgroups to assess the value of drains while controlling for the extent of surgery.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 10.0 (SPSS Inc., Chicago, IL). The intergroup comparisons were made using Student's t test for continuous variables and two-tailed χ^2test for discrete variables. Statistical significance was set at $P < 0.05$.

RESULTS

One hundred seventy patients entered the trial and underwent either total or subtotal gastrectomy between February 1, 2001, and July 31, 2001. Eighty-six patients had either subtotal or total gastrectomy with drains, and 84 patients had surgery without drains (Fig. 1). There were no deaths or complications that required reoperation throughout the duration of the study.

Patient Characteristics

The difference in primary tumor location among patients in the subtotal gastrectomy subgroup reached statistical significance. There were no other significant differences in demographic and clinical characteristics between patients in the drain group and those in the no-drain group for both subtotal gastrectomy and total gastrectomy subgroups (Tables 1 and 2). The majority of patients in both groups had no significant underlying disease preoperatively (ASA Classes I and II) and had surgery at an early stage (stages I and II).

Surgical Outcome

Drains were completely removed 5.3 days (range, 3–8 days) after surgery in patients with drains in the subtotal gastrectomy subgroup and 5.5 days (range, 4–7 days) after surgery in the total gastrectomy subgroup. No significant difference in the

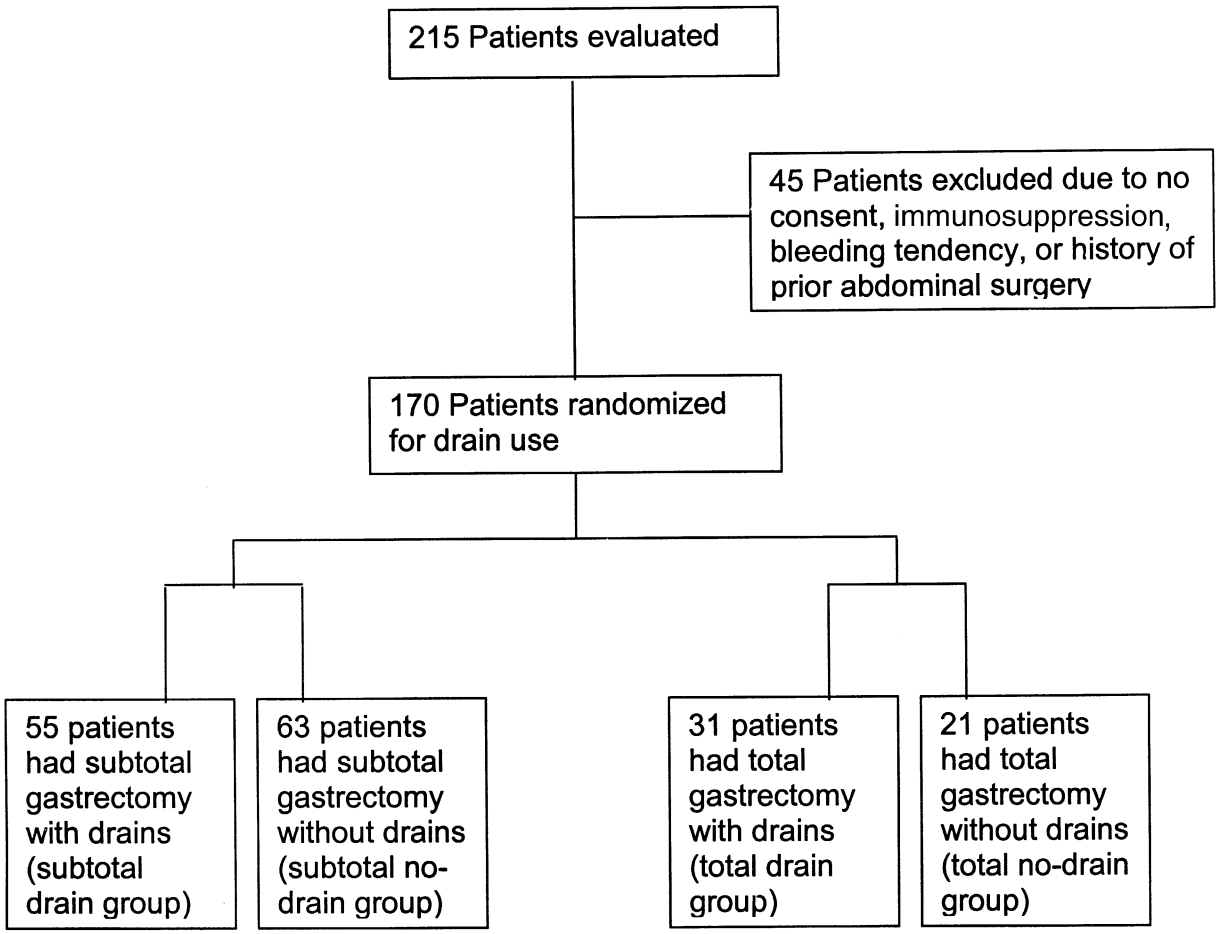

Fig. 1. Trial profile.

incidence of complications was noted between the drain group and the no-drain group in both the subtotal and total gastrectomy subgroups. Patients who developed intra-abdominal abscess had no evidence of leakage and were treated conservatively with ultrasound-guided percutaneous drainage.

Analysis of surgical outcome within the subtotal gastrectomy subgroup showed a significant difference in operating time between the drain group (143 ± 28 minutes) and the no-drain group (132 ± 27 minutes) ($P = 0.034$). No other significant difference in surgical outcome between the drain and no-drain groups was noted in the subtotal gastrectomy subgroup (Table 3). One patient in the drain group developed an intra-abdominal abscess without evidence of leakage.

Analysis in the total gastrectomy subgroup showed a increased analgesic use after surgery in the drain group (3.9 ± 3.6 doses per day) compared to with the no-drain group (1.6 ± 1.8 doses per day) ($P = 0.012$). Analgesic use in the drain group ranged between 0 and 11 doses per day. Three patients required analgesics at more than 8 doses per day, which was over the recommended maximum dosage of 400 mg/day. No adverse effects from medication were noted among the three patients, and they did not require analgesics on discharge from the hospital. Analgesic use in the no-drain group ranged between 0 and 5 doses per day. Patients with drains in the total gastrectomy subgroup passed flatus later (4.4 ± 0.7 days after surgery) than did patients without drains (4.0 ± 0.9 days after surgery) ($P = 0.048$). However, no significant difference was noted in initiation of soft diet and length of hospital stay after surgery (Table 4).

DISCUSSION

The results of our study suggest that the use of drains does not offer any additional benefit for patients undergoing gastric cancer surgery with extended lymph node dissection. Various studies on the use of drains after other abdominal operations, such as

Table 1. Demographic and clinical characteristics of patients in the subtotal gastrectomy subgroup

Patient characteristic	Drain group (n = 55)	No-drain group (n = 63)	*P*
Age, mean (SD) (yr)	58.5 (7.5)	54.9 (11.4)	0.051
Sex			0.847
Male	36 (33.3)	41 (35.9)	
Female	18 (66.7)	23 (64.1)	
ASA class			0.321
I	33 (61.1)	42 (65.6)	
II	21 (38.9)	20 (31.3)	
III	0 (0)	2 (3.1)	
Tumor location			0.039
Lower third	32 (59.3)	27 (42.2)	
Middle third	22 (40.7)	32 (50)	
Upper third	0 (0)	5 (7.8)	
Tumor size, mean (SD) (cm)	2.9 (2.1)	3.0 (2.1)	0.857
Depth of invasion			0.269
T1	29 (53.7)	36 (56.3)	
T2	8 (14.8)	15 (23.4)	
T3	17 (31.5)	12 (18.8)	
T4	0 (0)	1 (0.5)	
Nodes retrieved (SD)	34.6 (11.4)	36.7 (11.6)	0.336
Nodes involved			0.753
0	38 (70.4)	46 (71.9)	
1–6	11 (20.4)	13 (20.3)	
7–15	4 (7.4)	5 (7.8)	
⩾16	1 (1.9)	0 (0)	
Stage			0.854
I	33 (61.1)	44 (68.8)	
II	10 (18.5)	10 (15.6)	
III	10 (18.5)	9 (14.1)	
IV	1 (1.9)	1 (1.6)	

ASA = American Society of Anesthesiologists.
Values are given as number of patients (percentage) unless otherwise indicated.

Table 2. Demographic and clinical characteristics of patients in the total gastrectomy subgroup

Patient characteristic	Drain group (n = 31)	No-drain group (n = 21)	*P*
Age, mean (SD) (yr)	56.1 (10.1)	55.9 (12.5)	0.946
Sex			0.512
Male	24 (77.4)	15 (71.4)	
Female	5 (16.1)	6 (28.6)	
ASA class			0.514
I	19 (61.3)	16 (76.2)	
II	11 (35.5)	5 (23.8)	
III	1 (3.2)	0 (0)	
Tumor location			0.722
Lower third	4 (12.9)	4 (19.0)	
Middle third	14 (45.1)	8 (38.1)	
Upper third	13 (41.9)	9 (42.9)	
Tumor size, mean (SD) (cm)	5.8 (3.5)	4.2 (3.3)	0.130
Depth of invasion			0.737
T1	5 (9.1)	5 (23.8)	
T2	5 (9.1)	3 (14.3)	
T3	21 (38.2)	13 (67.7)	
T4	0 (0)	0 (0)	
Nodes retrieved (SD)	48.4 (16.7)	42.2 (10.6)	0.151
Nodes involved			0.057
0	8 (25.8)	7 (33.3)	
1–6	8 (25.8)	10 (47.6)	
7–15	11 (35.5)	1 (4.8)	
⩾16	4 (12.9)	3 (14.3)	
Stage			0.101
I	7 (22.6)	7 (33.3)	
II	6 (19.4)	2 (9.5)	
III	14 (45.2)	11 (52.4)	
IV	4 (12.9)	1 (4.8)	

ASA = American Society of Anesthesiologists.
Values are given as number of patients (percentage) unless otherwise indicated.

liver resection, pancreatectomy, and colon resection, have reported that the prophylactic use of drains is not recommended except in special situations, because drains can cause postoperative complications.[7–9] However, to our knowledge no study has been reported on the use of drains after gastric cancer surgery.

Although it remains controversial whether postoperative complications after gastric cancer surgery are indeed related to the extent of lymph node dissection, the current incidence of severe complications after gastric cancer surgery, such as anastomotic leakage, has been reported to be extremely low.[5, 6] In our study, the incidence of postoperative complications among patients in the no-drain group was comparable to that of patients in the drain group in both subgroup analyses, bringing into question the prophylactic value of intraoperative drain placement.

Experiences in some institutions suggest a high risk of pancreas-related complications after gastrectomy with D2 or more extended lymph node dissection, thus advocating prophylactic use of drains in gastric cancer surgery to avoid a reoperation.[14] However, we did not experience any pancreas-related complications or other major complications that required a reoperation among the 170 patients in our study, making the above argument questionable.

Moreover, drainage via use of interventional radiology has reduced the number of multiple laparotomies for surgical complications and thus supported abdominal surgery without the use of drains.[15] All patients who required drainage in our study were treated by ultrasound-guided percutaneous drainage.

To further validate our results, we minimized the risk of confounding in our trial by studying the patients in both groups under the same perioperative

Table 3. Surgical outcome in the subtotal gastrectomy subgroup

Surgical outcome	Drain group (n = 55)	No-drain group (n = 63)	*P*
Operating time, mean (SD) (min)	143 (28)	132 (27)	0.034
Analgesic use, mean (SD) (doses/day)	1.7 (2.2)	1.7 (3.3)	0.948
Patient reporting flatus, mean (SD) (POD)	3.8 (1.0)	3.8 (1.0)	0.690
Initiation of soft diet, mean (SD) (POD)	5.3 (1.1)	5.1 (0.9)	0.203
Complications, No. (%)			0.268
None	48 (87.2)	60 (95.2)	
Pneumonia	0 (0)	1 (1.6)	
Wound infection	2 (3.6)	0 (0)	
Intra-abdominal abscess	0 (0)	1 (1.6)	
Other*	4 (7.3)	2 (3.3)	
Hospital stay after surgery, mean (SD) (days)	8.9 (2.8)	8.6 (2.3)	0.540

POD = postoperative day.
*Other complications were joint pain, transient nausea and vomiting (24–48 hr), and rash.

Table 4. Surgical outcome in the total gastrectomy subgroup

Surgical outcome	Drain group (n = 31)	No-drain group (n = 21)	*P*
Operating time, mean (SD) (min)	161 (17)	159 (30)	0.755
Splenectomy, No. (%)			0.509
Spleen preserved	21 (67.7)	16 (76.2)	
Spleen removed	10 (33.3)	5 (23.8)	
Analgesic use, mean (SD) (doses/day)	3.9 (3.6)	1.6 (1.8)	0.005
Patient reporting flatus, mean (SD) (POD)	4.4 (0.7)	4.0 (0.9)	0.048
Initiation of soft diet, mean (SD) (POD)	5.7 (2.0)	5.6 (2.8)	0.704
Complications, No. (%)			0.747
None	26 (83.9)	18 (85.7)	
Pneumonia	3 (9.7)	1 (4.8)	
Wound infection	0 (0)	1 (4.8)	
Intra-abdominal abscess	1 (3.2)	1 (4.8)	
Other*	1 (3.2)	0 (0)	
Hospital stay after surgery, mean (SD) (days)	10.4 (5.1)	11.3 (6.6)	0.599

POD = postoperative day.
*Other complications were joint pain, transient nausea and vomiting (24–48 hr), and rash.

and intraoperative conditions. One surgeon performed all surgeries and one surgical team delivered perioperative care for patients in both the drain group and the no-drain group.

We also compared the surgical outcome between the drain group and the no-drain group within the subtotal and total gastrectomy subgroups to assess the value of drains in gastric cancer surgery without the potential confounding by the difference in the extent of surgery. Although the difference in primary tumor location among patients in the subtotal gastrectomy subgroup reached statistical significance, it should not have been a significant confounding factor in the study, because the extents of gastric resection and lymph node dissection were similar as evidenced by the similar number of retrieved lymph nodes.

Analysis of patients in the total gastrectomy subgroup revealed less analgesic use among patients in the no-drain group. The burden of having two drains may have lowered the patients' tolerance for pain. The duration of drain use was essentially the same for the subtotal gastrectomy (5.3 days) and total gastrectomy (5.5 days) subgroups, whereas there was no significant difference in analgesic use in the subtotal gastrectomy subgroup between patients with drains (who had one drain) and patients without drains.

Based on the results of this study, we believe that avoiding the use of drains prevents complications due to the drain itself, lessens patient discomfort, and does not compromise the overall surgical outcome. We do not recommend routine prophylactic placement of drains in gastric cancer surgery except in special situations such as after intraperitoneal chemotherapy, bowel perforation, and extended organ resection.

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Pancreaticoduodenectomy

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PREOPERATIVE MANAGEMENT

Although many patients with pancreatic malignancies will have lost substantial body weight, there is no evidence that preoperative nutritional repletion with total parenteral nutrition reduces perioperative complications or mortality. In the now uncommon case in which high-grade jaundice is associated with coagulation defects, preoperative administration of vitamin K and intraoperative fresh-frozen plasma are used as needed. Bowel preparation is unnecessary unless colonic resection is anticipated. Broad-spectrum antibiotics germane to biliary flora are given prior to skin incision and continued for one dose postoperatively.

PANCREATICODUODENECTOMY: GENERAL CONSIDERATIONS

This operation, whether performed as a classic Whipple procedure or as a pylorus-preserving variation, should incur a 30-day in-hospital mortality rate of less than 5%. Although the majority of surgeons worldwide may, at present, favor the pylorus-preserving modification of pancreaticoduodenectomy, it has been our experience that the postoperative length of hospital stay is significantly longer with the pylorus-preserving operation because of a higher incidence of delayed gastric emptying in approximately one third of patients. Because there is neither a nutritional advantage conferred nor any difference in cure rates between the two operations, we have favored the traditional antrectomy.

There has been recent interest in extending the operation to include tissues outside the standard field of dissection, retroperitoneal lymph nodes, and the nerve plexuses along the superior mesenteric artery. Popularized in Japan, this extended dissection has shown no benefit in clinical trials in Europe and the United States. In addition, circumferential dissection of the nerve plexuses around the artery frequently leads to debilitating diarrhea and gastrointestinal dysfunction.

Lateral or segmental resection of the portal or superior mesenteric vein may allow completion of the pancreaticoduodenectomy but has not convincingly increased the rate of cure even if an R0 resection (negative margin) is accomplished.

OPERATIVE TECHNIQUE

Step 1. Either a vertical midline incision, our preference, or a bilateral subcostal transverse incision can be used with equal access. The liver and peritoneal surfaces are examined for unexpected extrapancreatic metastases. Intraoperative ultrasonography of the liver may be used selectively when the findings are suspicious but indeterminate by palpation. Routine biopsy of apparently normal regional lymph nodes is unnecessary, but suspicious lesions and enlarged lymph nodes outside the planned field of dissection should be biopsied and examined by frozen section and the resection aborted if positive for metastatic cancer. Positive lymph nodes within the planned field of resection are not considered a contraindication to pancreaticoduodenectomy.

Step 2. The hepatic flexure of the colon is mobilized from its retroperitoneal attachments to access the third and fourth portions of the duodenum. Extensive mobilization of the entire right colon and small bowel mesentery (Cattell-Braasch maneuver) is unnecessary except for lesions involving the fourth portion of the duodenum or for the approach to mobilization and resection of a segment of the superior mesenteric vein. The duodenum and head of the pancreas are separated from the retroperitoneal bed medially past the aorta and distally to the ligament of

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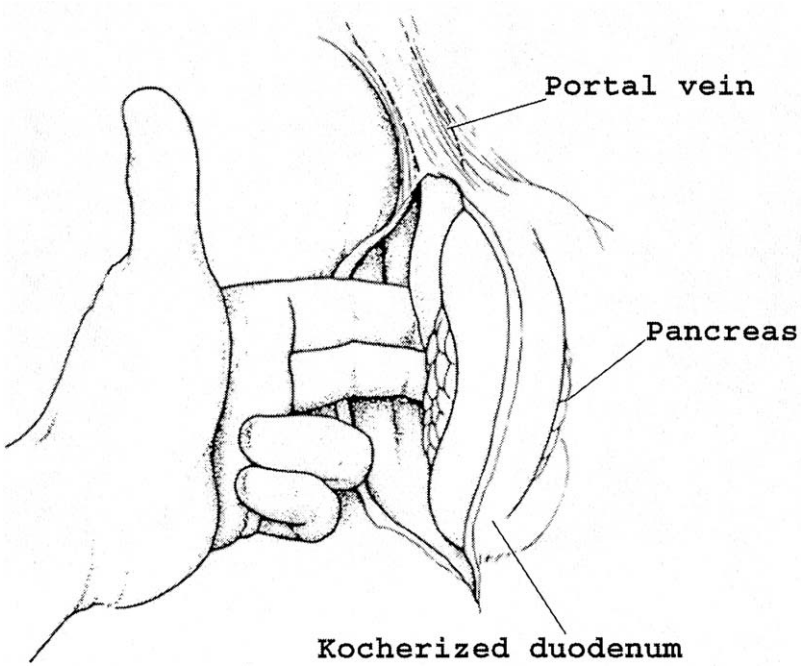

Fig. 1. The duodenum and head of the pancreas are extensively mobilized and medially rotated away from the inferior vena cava and aorta. Posterior extension of the tumor is rare. The relationship between the tumor and the superior mesenteric artery is established by palpation.

Treitz. It is now possible to palpate the superior mesenteric artery posteriorly as it originates from the aorta and to establish that the cleft between the artery and uncinate process of the pancreas is not obliterated by tumor (Fig. 1). A silk suture placed in the duodenum to mark the junction of the third and fourth portions is particularly helpful for identification of the proximal point of devascularization of the duodenum later when working back from the transected jejunum (step 7).

Step 3. The gallbladder is removed if still present. The bile duct is dissected free from the adjacent portal

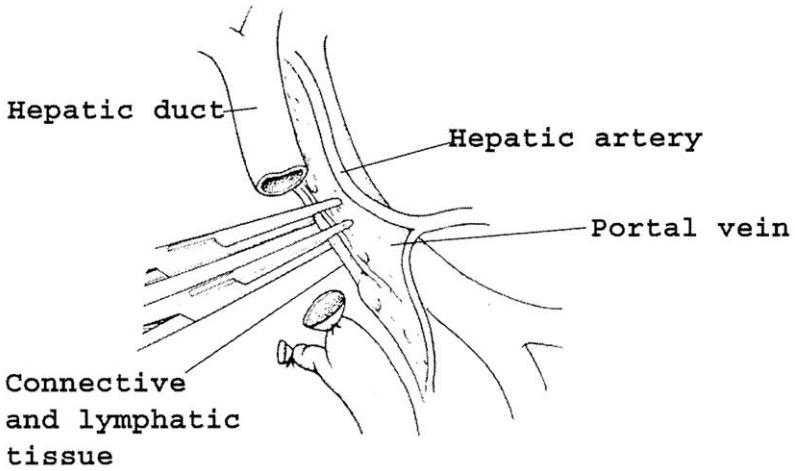

Fig. 2. After removal of the gallbladder, the bile duct is transected above the cystic duct. The distal bile duct is sutured to limit cancer spillage. The proximal duct is left unclamped to avoid crush injury. The lymphatic vessels and connective tissue lateral to the portal vein are divided and swept caudally with the specimen. Care must be taken not to injure an aberrant right hepatic artery originating from the superior mesenteric artery that, if present, will be found in this area.

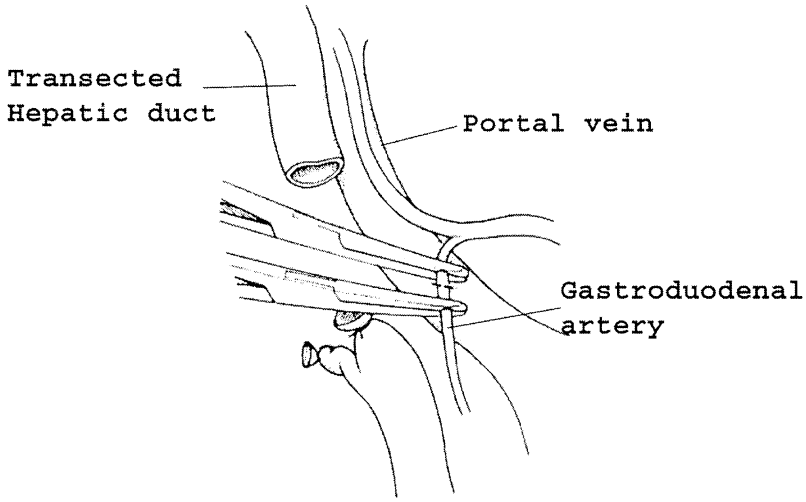

Fig. 3. Division of the gastroduodenal artery. The gastroduodenal artery should be doubly ligated or suture ligated. Division of the gastroduodenal artery exposes the anterior surface of the portal vein and greatly facilitates the dissection of the portal vein behind the pancreatic neck.

structures and divided above the cystic duct entry across the common hepatic duct. This proximal point of division minimizes the risk of a positive biliary resection margin consequent to the tendency of periampullary cancers to infiltrate cephalad along the submucosal lymphatic channels of the bile duct. The proximal bile duct is left unclamped to avoid trauma to the duct, but the distal bile duct orifice is sutured to minimize spillage of tumor cells. If evidence of unresectable cancer is discovered subsequently, the proximal bile duct is used for palliative bypass. The tissues lateral to the portal vein are carefully separated, divided, and ligated with care

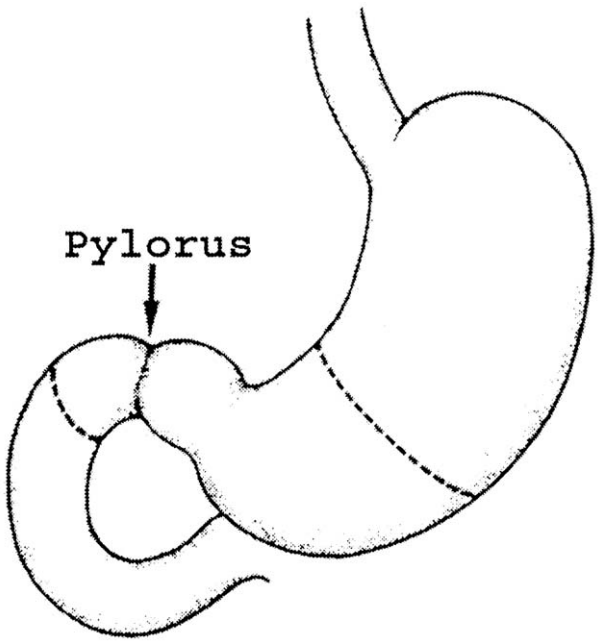

Fig. 4. Line of division of the stomach or duodenum. In a standard Whipple procedure, an antrectomy is performed. If pylorus preservation is desired, the duodenum is divided 2 cm distal to the pylorus.

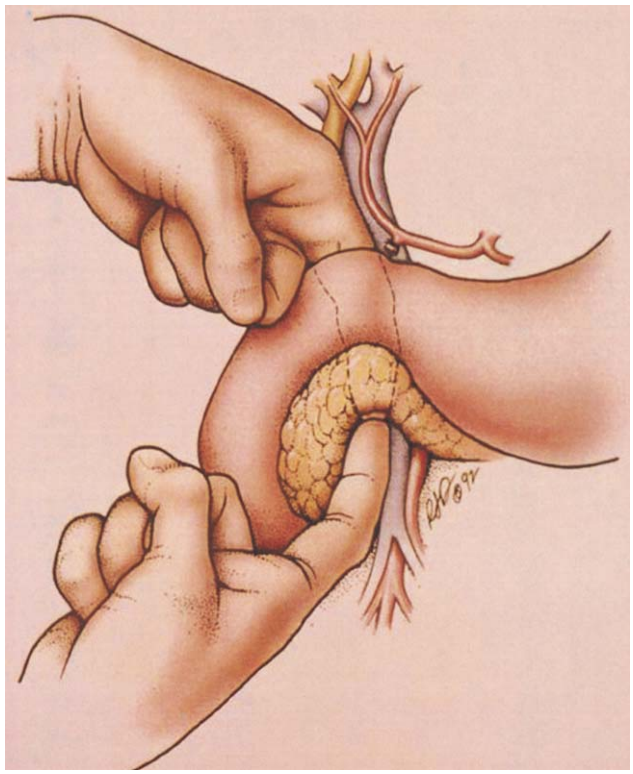

Fig. 5. The portal vein is identified above the pancreatic neck and the superior mesenteric vein is identified inferior to the pancreatic neck. The anterior surface of the vein is separated by blunt dissection from the pancreas, creating a tunnel behind the pancreatic neck.

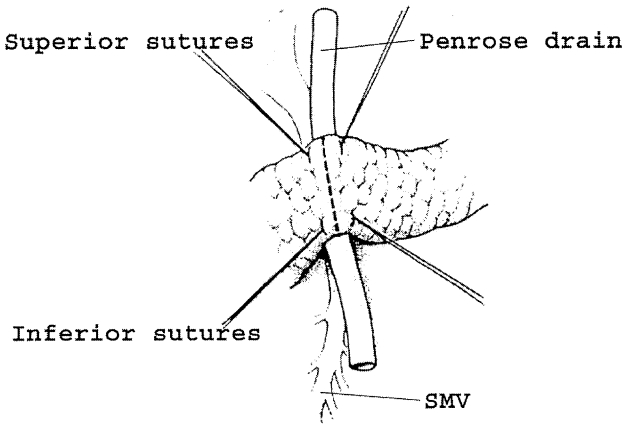

Fig. 6. Transection of the pancreatic neck. After the pancreatic neck has been separated from the anterior surface of the portal mesenteric vein, a Penrose drain is passed behind the pancreatic neck to elevate and protect the vein during division. Four hemostatic sutures are placed on either side of the transection line. The pancreas is now ready to be divided with electrocautery. SMV - superior mesenteric vein

taken that a replaced right hepatic artery off the superior mesenteric artery is not included (Fig. 2).

Step 4. The portal dissection is continued down the anterior aspect of the portal vein, with beginning development of the tunnel in front of the vein and behind the neck of the pancreas. Division of the right gastric artery and gastroduodenal artery greatly enlarges this window and facilitates access to the portal vein behind the pancreas (Fig. 3). The gastroduodenal artery should be doubly ligated or suture ligated to minimize the chance of subsequent erosion and bleeding. Lymph nodes anterior to the proper hepatic artery are taken with the specimen. Although there are no direct anterior branches to the portal vein, there are significant branches at the upper and lower

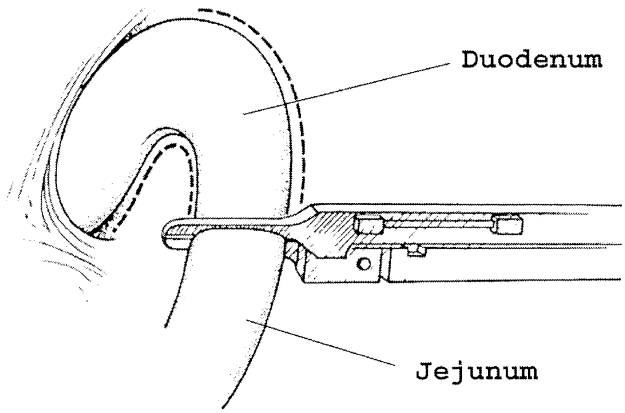

Fig. 7. The ligament of Treitz is taken down, and the jejunum is divided with a stapler 6 to 10 cm past the ligament of Treitz. The jejunal vascular branches are divided at the bowel wall.

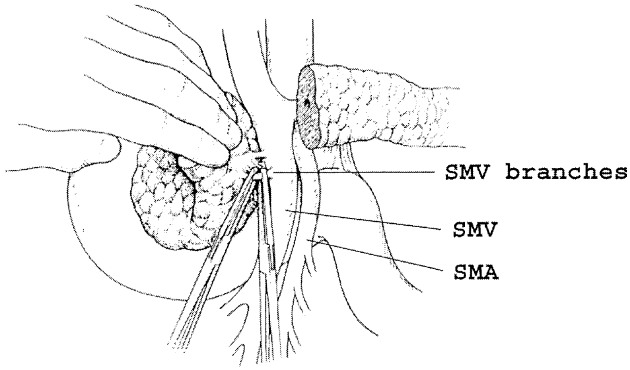

Fig. 8. The final step of the dissection requires isolation, division, and ligation of the vascular supply and retroperitoneal attachments at the head of the pancreas. The venous tributaries to the superior mesenteric vein (*SMV*) are readily identified by retracting the pancreatic head gently to the right and the vein to the left. SMA = superior mesenteric artery.

margins of the pancreas that enter the anteromedial aspect of the portal/mesenteric vein, and these can be easily damaged during dissection of the tunnel.

The approach to the mesenteric vein below the neck of the pancreas is facilitated by dividing the gastrocolic omentum outside the gastroepiploic vessels down to

Fig. 9. After dividing venous tributaries from the uncinate process to the superior mesenteric vein portal vein, the vein is retracted to the left with instruments or vessel loops to identify and expose the superior mesenteric artery behind and to the left. The lymphatic, neural, and arterial branches are cleared from the anterolateral surface of the artery. If, in the rare instance it is necessary to retract the vein to the *right* to expose the artery, division of the splenic vein may also be required for adequate exposure.

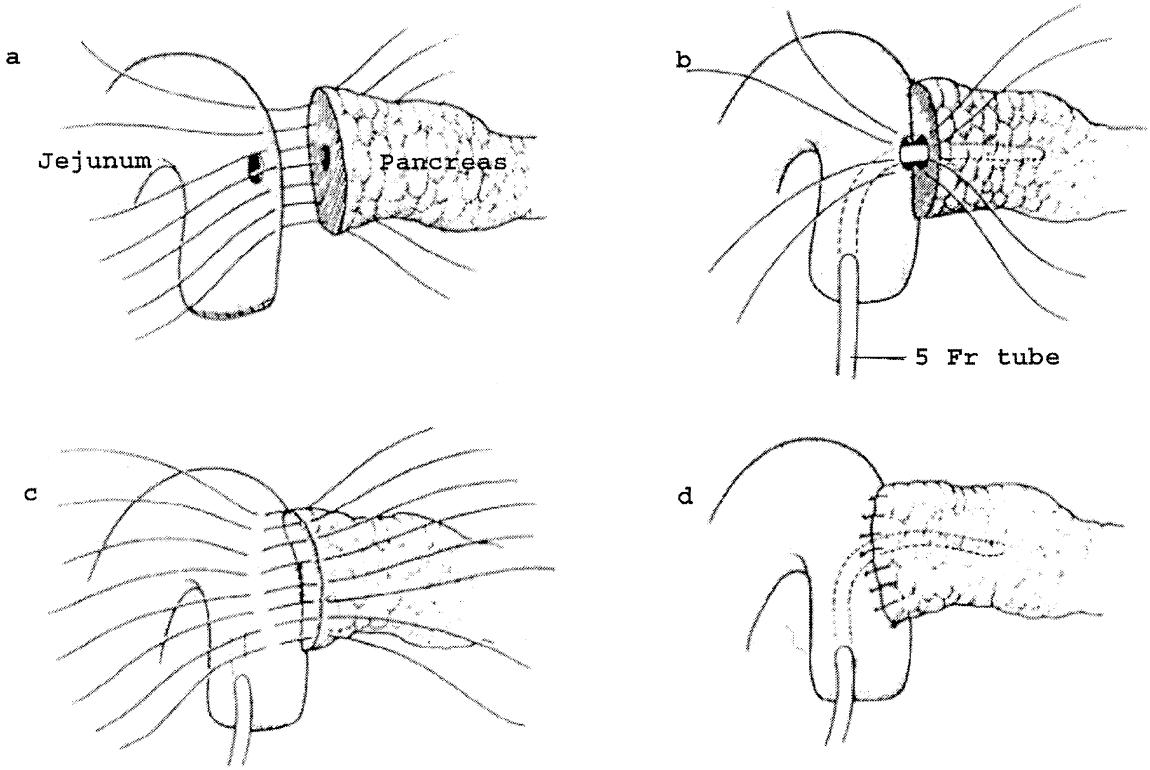

Fig. 10. Pancreaticojejunostomy. A two-layer end-to-side duct-to-mucosa pancreaticojejunostomy is preferred.

the level of the head of the pancreas and further mobilizing the hepatic flexure caudally. The middle colic vein and gastroepiploic vein can be traced down to the superior mesenteric vein for rapid identification.

Step 5. After the left gastric and gastroepiploic vessels are divided at the gastric wall, the stomach is divided across the proximal antrum with a stapler (Fig. 4). Alternately, the duodenum 2 cm past the pylorus may be divided with the stapler. The lesser curvature portion of the stomach is turned in with nonabsorbable sutures over the staple line in Hofmeister fashion, leaving a sufficient portion of the staple line for a 4 cm anastomosis.

Step 6. Transection of the pancreas in front of the portal vein is next. The dissection of the tunnel behind the pancreatic neck should be completed by blunt dissection under direct vision (Fig. 5). Although traditional descriptions cite this maneuver as critical to proving resectability, it is only relevant to cancers in the neck and body of the pancreas. Periampullary tumors are much more likely to involve the lateral and posterior aspects of the portal/mesenteric vein. Evaluation of this area can be uncertain at this point in the operation, and the disappointing finding of involvement of the vein may not be possible until much later in the operation, after division of the pancreas and attempted dissection of the uncinate process. A soft Penrose drain is passed behind the pancreas both for elevation of the pancreatic neck and protection of the portal vein. Sutures are placed at the four quadrants of the transection line for guidance and for ligation of the vascular arcades, which run along the cephalad and caudad margins of the pancreatic parenchyma (Fig. 6). The pancreas is divided with electrocautery, and additional bleeding points on the cut margins are controlled. Suture closure of the pancreatic duct on the side of the specimen may help to reduce spillage of tumor cells during subsequent manipulation.

Step 7. The transverse colon and its mesentery are elevated cephalad, and the entire small bowel is eviscerated to facilitate exposure and the dissection of the distal duodenum proximal to the ligament of Treitz. The jejunum is divided with a stapler 6 to 10 cm past the ligament of Treitz at a point that will provide sufficient mobility of the distal jejunum to reach easily to the right upper quadrant for the biliary and pancreatic anastomoses (Fig. 7). The feeding vessels to the proximal jejunum and distal duodenum are divided at the enteric wall back to the previously

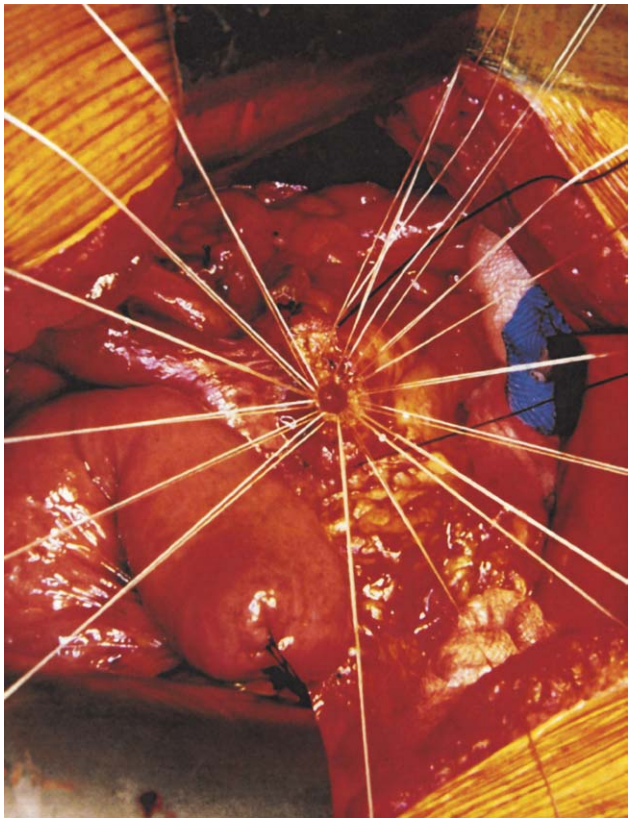

Fig. 11. Interrupted synthetic absorbable sutures are placed circumferentially through the margins of the pancreatic duct and laid aside until after the posterior row of nonabsorbable sutures between the pancreas and jejunum are in place. This sequence allows precise suture placement even in small, normal pancreatic ducts without risk of lacerating injury to a soft gland.

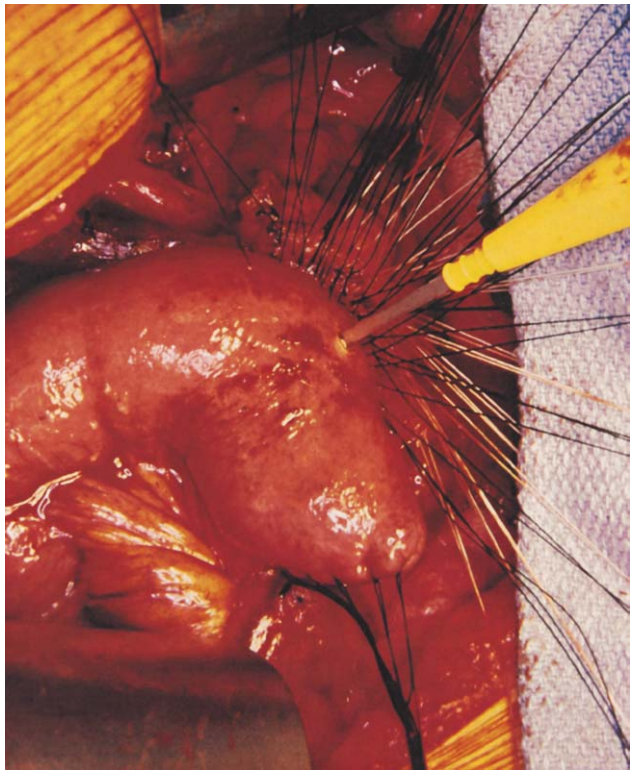

Fig. 12. Before fixation of the jejunal loop to the pancreas by tying the posterior rows of sutures, an opening is made in the jejunum to match the size and location of the pancreatic duct.

placed marker suture. This suture is particularly valuable in order to ensure that the duodenal dissection is adequate to allow subsequent freedom to complete the resection of the uncinate process but that it is not carried too far proximal into the cancer field.

Step 8. The final step in removal of the specimen is to divide the venous tributaries of the uncinate process to the portal and mesenteric veins and to dissect along the lateral margin of the superior mesenteric artery, taking both the arterial branches and the anterolateral periarterial soft tissues, which include both lymphatics and nerve plexuses that can contain tumor (Fig. 8). The plane between the pancreas and the mesenteric vessels is opened by retracting the specimen to the right and the mesenteric vein to the left. The safety of this dissection may be increased by passing vessel loops around the portal vein and superior mesenteric vein for retraction. This is of particular value if there is an inflammatory reaction or tumor in the region of the dissection. In the event of laceration of the vein or the need for venous resection, an additional vessel loop must be placed around the splenic vein proximal to the splenoportal junction. Traction on the vessel loops and vascular clamps are used for venous control as necessary. Lateral venorrhaphy with a running fine nonabsorbable suture may suffice for repair or reconstruction, as long as the lumen is not unacceptably narrowed. Segmental resection and reconstruction, either end to end or with interposition of a graft (jugular or iliac vein, or polytetrafluoroethylene may be necessary in some cases, but it is debatable whether this contributes to cure. As noted previously, extensive mobilization of the right colon and small bowel mesentery may facilitate access to and mobilization of the superior mesenteric vein. Further mobility can be obtained by dividing the splenic vein proximal to the splenoportal junction.

Traction of the portal/mesenteric vein to the left exposes the groove lateral to the superior mesenteric artery. The tissues overlying the artery anteriorly are divided and the dissection is carefully carried down the lateral wall of the artery, skeletonizing it (Fig. 9). If there is a right hepatic artery originating at the

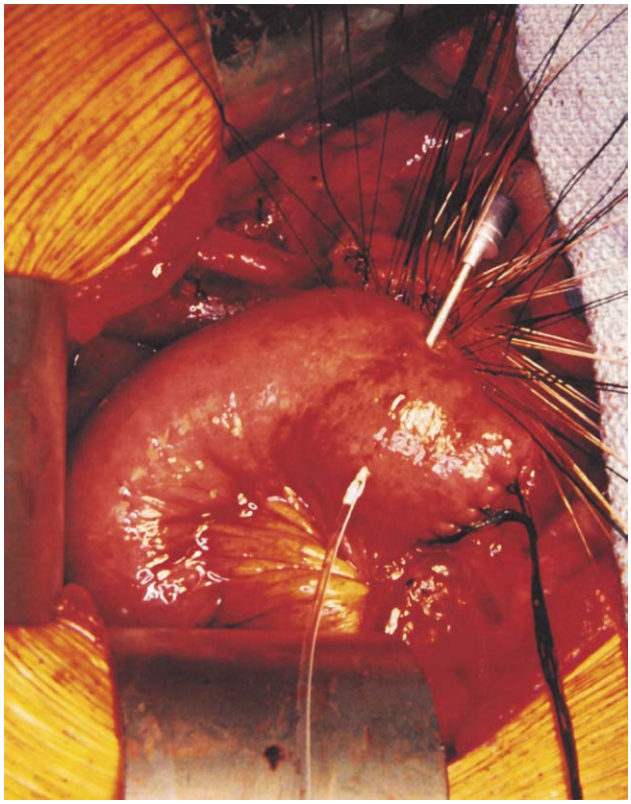

Fig. 13. A no. 5 pediatric feeding tube is introduced into the lumen through a 14-gauge needle and laid aside until the outer and inner posterior rows of sutures have been tied.

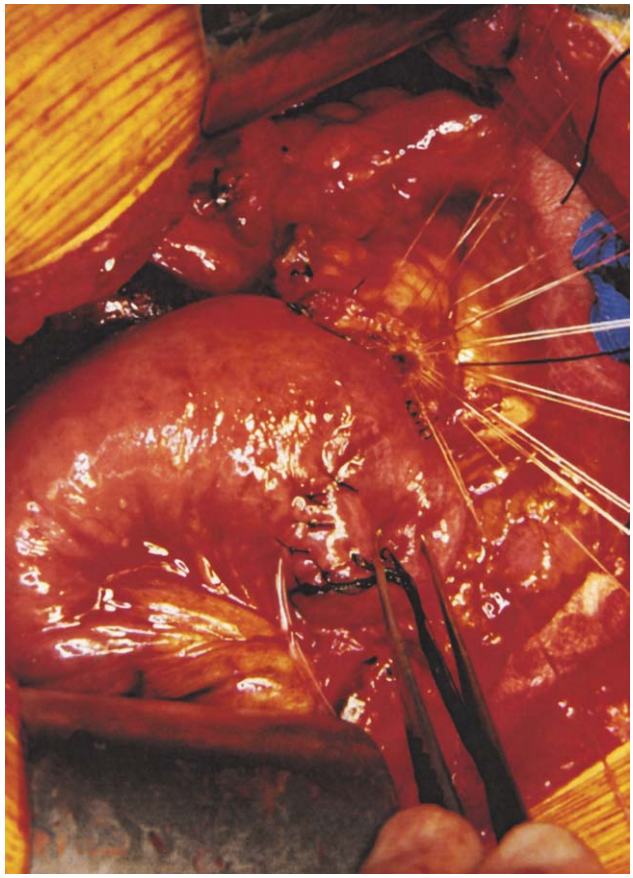

Fig. 14. After the feeding tube has been threaded into the pancreatic duct, it is fixed in position by a purse-string chrome catgut suture, and the jejunal entry is buried in a Wetzel tunnel to prevent leaking.

superior mesenteric artery, care must be taken to avoid injuring it. The attachments of the uncinate process, including the arterial branches, are then taken sequentially along the lateral margin of the superior mesenteric artery. After removal of the specimen, metal clips are placed at the margins of the resection field to target postoperative radiation therapy.

It is helpful to the pathologist to orient the specimen before handing it off the field. We consistently place a safety pin in the uncinate margin and a long suture on the posterior soft tissue margin, and communicate this to the pathologist directly.

Step 9. The colon and mesocolon are once again elevated, and the small bowel is eviscerated to facilitate closure of the ligament of Treitz with interrupted nonabsorbable sutures. The end of the jejunum is oversewn with nonabsorbable Lembert sutures over the staple line and it is brought through the right side of the transverse mesocolon. The pancreaticojejunostomy is performed first. Whenever possible, this anastomosis is created in two layers, end to side, using an outer row of interrupted nonabsorbable 3-0 sutures that includes most of the cut surface of the pancreas and an inner row of 4-0 interrupted synthetic absorbable sutures duct to mucosa (Fig. 10). It is almost always possible, even with a small/normal pancreatic duct, to perform the anastomosis with this technique. When the duct is very small, we place a no. 5 pediatric feeding tube into the lumen and place a minimum of eight sutures circumferentially through the cut edge of the duct. All of the inner layers of duct sutures, anterior and posterior rows, are placed first and arrayed carefully to avoid entanglement (Fig. 11). The outer posterior sutures are then laid in between the pancreas posterior to the duct and the seromuscular layer of the bowel. Before they are tied, a duct-sized incision is made in the jejunum opposite the pancreatic duct lumen (Fig. 12). The no. 5 pediatric feeding tube is then brought through the jejunal wall via a no. 14 needle (Fig. 13). The posterior row of sutures is tied, and the posterior row of duct sutures is placed through the full thickness of the jejunum. The feeding tube is then placed into the pancreatic

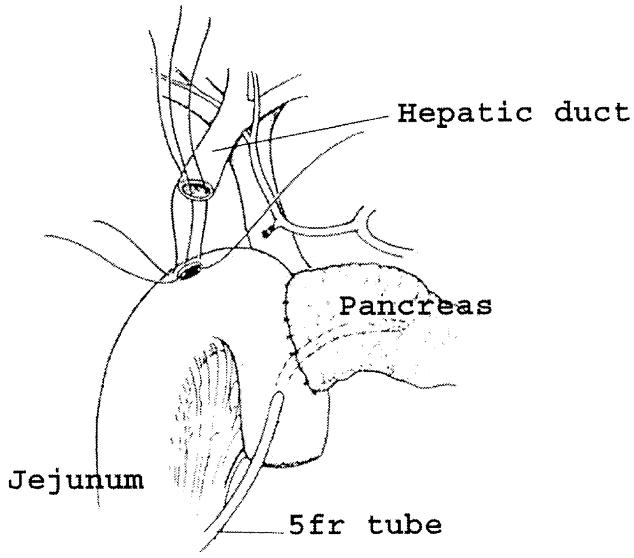

Fig. 15. The hepaticojejunostomy is made with a single layer of interrupted closely placed 3-0 or 4-0 absorbable sutures and is placed several centimeters distal to the pancreaticojejunostomy. It is preferable that all duct sutures be placed first and carefully arranged to avoid entanglement. The posterior row is then sewn and tied prior to sewing the anterior row.

duct, and its exit point in the jejunal wall is fixed with a purse-string chromic catgut suture and a Witzel tunnel of interrupted silk Lembert sutures (Fig. 14). The anterior row of duct sutures is then placed in the full thickness of the jejunal orifice and tied. The anastomosis is completed with an anterior row of silk sutures. It is desirable to have the outer anterior and posterior rows of sutures include 1 cm of the pancreas to create a wider surface of apposition. The pancreatic drainage tube will later be brought through the omentum and out through the right side of the abdominal wall. If there is a very dilated pancreatic duct, the pancreatic tube is not necessary.

Step 10. Distal to the pancreatic anastomosis, an end-to-side hepaticojejunostomy is made with a single layer of interrupted closely spaced synthetic absorbable sutures (Fig. 15). Unless the bile duct is small or fragile, no transanastomotic drainage tube is necessary. In the event it is needed, a small (no. 8 pediatric feeding tube) catheter can be left through the anastomosis and brought out distally through the jejunum and through the abdominal wall. If there has been preoperative placement of a transhepatic drain, this can be left in place instead of a retrograde tube placed from the jejunum.

Step 11. After fixing the jejunal loop to the transverse mesocolon with interrupted nonabsorbable sutures, gastrointestinal continuity is restored with a retrocolic Hofmeister-type Billroth II gastrojejunostomy (Fig. 16). This anastomosis is made with running absorbable sutures as an inner layer and interrupted nonabsorbable sutures as an outer layer. The anastomosis is fixed below the mesocolon with interrupted silk sutures.

If a pylorus-preserving operation has been chosen, it has been suggested that placement of the duodenojejunostomy in an antecolic position may reduce the incidence of delayed gastric emptying.

Step 12. Soft closed-suction drains are placed in the right upper quadrant, anterior and posterior to the biliary and pancreatic anastomoses. These are brought out through separate incisions in the right side of the abdomen. Neither gastrostomy nor feeding jejunostomy tubes are necessary, but a gastrostomy may be advisable after pylorus preservation because of the problem of delayed gastric emptying. The abdominal wall is closed according to surgeon preference.

POSTOPERATIVE CARE

The nasogastric tube is typically discontinued on postoperative day 1, and clear liquids may be allowed

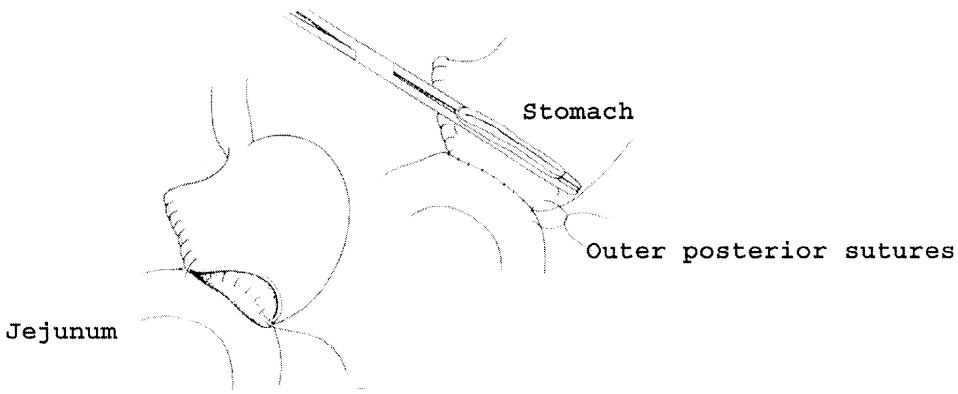

Fig. 16. The gastrojejunostomy is preferably a retrocolic Hofmeister anastomosis with the efferent limb to the left, using an outer layer of silk Lembert stitches and an inner layer of running absorbable sutures and fixed below the mesocolon.

on day 2. The diet is advanced to low-fat soft solids in frequent small feedings as tolerated. Blood glucose should be monitored and diabetes treated as appropriate. The concentration of amylase in the drainage is measured on day 5 or 6 when the patient is eating. If there is no indication of an anastomotic leak, the drains are removed individually on day 5, 6, or 7. The pancreatic (and biliary) stents are removed at one of the postoperative office visits, generally at 3 weeks.

Pancreatic fistula remains the most common serious complication of this operation. The mainstay of treatment is complete drainage, either by closed-suction drains placed at operation or by percutaneously placed catheters if necessary. The catheters should be left in place long enough to ensure formation of a secure tract and then withdrawn in segments to allow the tract to close behind as drainage diminishes. In the case of low-volume fistulas (<200 ml/day), patients may eat and be discharged to home. High-output fistulas may require a more aggressive approach with fasting, maintenance of fluid and electrolyte balance, and parenteral nutrition. Octreotide, 200 U subcutaneously 3 times a day, has been used an adjunct to reduce the volume of fistula output, but there is no conclusive evidence that closure is accelerated.

In the event of delayed gastric emptying for more than 7 to 10 days, a Gastrografin contrast upper gastrointestinal study should be performed to rule out mechanical obstruction. The condition resolves spontaneously, although the gastroparesis can persist as long as 3 to 4 weeks. Management consists of supportive measures. Prokinetic agents such as erythromycin (200 mg intraveneously 3 times daily, 30 minutes before meals) have been used with a modicum of purported success.

Review Article

Current Management of Gastrointestinal Carcinoid Tumors

Kenneth J. Woodside, M.D., Courtney M. Townsend, Jr., M.D., B. Mark Evers, M.D.

Gastrointestinal carcinoid tumors are rare neuroendocrine tumors arising from the embryologic primitive gut. Depending on the location in the gastrointestinal tract, these tumors may secrete a variety of hormonally active substances. However, many of these tumors are found incidentally, or the diagnosis is made postoperatively. Also, there is a significant incidence of multicentric carcinoid tumors and synchronous noncarcinoid malignancies in these patients. Treatment is usually based on the size of the tumor. Surgical resection remains the cornerstone of therapy. For advanced metastatic disease, somatostatin analog therapy and surgical debulking provide the best symptomatic relief and may improve survival. Recent studies have demonstrated a benefit from radiolabeled somatostatin analogs for carcinoid tumor localization. In contrast, radiolabeled somatostatin analogs have shown little therapeutic benefit. Future directions include somatostatin receptor profiling of carcinoid tumors, with somatostatin analog therapy targeting the specific receptors. (J GASTROINTEST SURG 2004;8:742–756)

KEY WORDS: Carcinoid tumor, neuroendocrine tumor, carcinoid syndrome, gastrointestinal tract, somatostatin, review

Carcinoid tumors, relatively rare neuroendocrine neoplasms arising from enterochromaffin cells found in the crypts of Lieberkühn,[1,2] were initially described by Lubarsch in 1888.[3] Almost 20 years later, Oberndorfer[4] coined the term *Karzinoide* to represent the carcinoma-like appearance and the relative indolent nature. Although there are reports of carcinoid tumors arising from almost every organ of the embryonic primitive gut, including the liver and pancreas, they most commonly appear in the pulmonary system and gut. These tumors secrete vasoactive substances and hormones. From midgut derivatives of the gastrointestinal tract, serotonin (5-hydroxytryptamine [5-HT]) and its precursors are the most common secreted products[5–16] (Table 1).

Controversy exists regarding the true incidence of carcinoid tumors. The incidence of clinically detected carcinoid tumors is approximately two cases per 100,000 patients.[17] However, because the tumor grows slowly with few symptoms, the actual incidence is thought to be higher. A series of 16,294 autopsies by Berge and Linell[18] found the incidence of carcinoid tumors to be approximately 1.2%, whereas a study by Moertel et al.[2] of 14,852 autopsies found the incidence of small bowel carcinoid tumors to be 0.65%. The most common site of carcinoid tumors in the adult gut is the appendix, followed by the ileum and rectum[17,19] (Table 2). Recent studies, however, suggest that appendiceal carcinoid tumors may occur less frequently than small intestinal tumors.[20] Up to one fourth of small bowel carcinoid tumors are multicentric, and approximately one fifth are associated with synchronous malignancies of another histologic type, such as colonic adenocarcinoma.[2,20–22] The incidence of pulmonary carcinoid tumors appears to be increasing,[17] although these differences may result from the limitations of registry data such as reporting bias or changes in detection rates. This review will specifically focus on carcinoid tumors of gastrointestinal origin.

EMBRYOLOGY AND PATHOLOGY

Carcinoid tumors are classified by the embryologic origin within the primitive gut[23] (Table 3). Foregut

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Table 1. Secretory products of carcinoid tumors

Amines	Tachykinins	Peptides	Other
5-Hydroxytryptamine	Kallikrein	Pancreatic polypeptide (40%)	Prostaglandins
5-Hydroxyindoleacetic acid (88%)	Substance P (32%)	Chromogranins (100%)	
5-Hydroxytryptophan	Neuropeptide K (67%)	Neurotensin (19%)	
Histamine		Human chorionic gonadotrophin-alpha (28%)	
Dopamine		Human chorionic gonadotropin-beta	
		Motilin (14%)	

Values in parentheses represent percentage frequency.
Adapted from Evers BM. Small bowel. In Townsend CM Jr, ed. Sabiston Textbook of Surgery, 16th ed. Philadelphia: WB Saunders, 2001, pp 873–916.

tumors arise from the respiratory tract or from the esophagus, stomach, upper duodenum, or pancreas. These tumors typically produce low levels of serotonin but may secrete 5-hydroxytryptophan (5-HTP), histamine, or adrenocorticotropic hormone.[5–9] Midgut tumors may arise from the distal duodenum, jejunum, ileum, appendix, ascending colon, or liver. These tumors are more likely to produce serotonin at high levels and may cause classic carcinoid syndrome.[10,11] Hindgut tumors, arising from the distal portion of the colon and rectum, are much less likely to produce serotonin but may produce somatostatin, peptide YY, 5-HTP, or other hormones.[12–15]

On gross examination, carcinoid tumors are usually firm submucosal nodules. Invasion of the serosa elicits an intense desmoplastic reaction that often leads to intestinal kinking and partial or intermittent bowel obstruction (Fig. 1). The cut surface of these lesions is usually yellow, with the majority of gastrointestinal carcinoid tumors less than 1 cm in diameter. Although the malignant potential is a function of location, depth of invasion, and growth pattern, tumor size is the most influential determinant. Intestinal carcinoid tumors (except in the appendix) less than 1 cm in diameter are associated with a 2% incidence of metastasis, whereas tumors 1 to 2 cm in size are associated with a 50% incidence of metastasis and those larger than 2 cm are associated with an 80% to 90% incidence of metastasis.[24] The low rate of metastasis for carcinoid tumors of the appendix may be due to the early onset of obstructive symptoms (i.e., appendicitis) associated with a relatively small tumor size when compared to other gastrointestinal locations. Small bowel carcinoid tumors are multicentric in approximately one fourth of the patients.[2,21] Carcinoid tumors may be associated with a synchronous malignancy of another histologic type elsewhere, most commonly colonic adenocarcinoma, in 10% to 20% of patients.[22] In addition, gastric carcinoid tumors can be associated with multiple endocrine neoplasia type I (MEN-I).[25,26]

Microscopically, carcinoid tumors are composed of small, round, well-differentiated neuroendocrine cells with regular nuclei. Typical carcinoid tumors have one of five growth patterns: insular, trabecular, glandular, undifferentiated, or mixed.[27] Atypical or anaplastic tumors have increased nuclear atypia, increased mitotic activity, or necrotic areas and are more likely to behave aggressively. Classification systems based on location, size, tissue and vascular invasiveness, differentiation, and functional status have been proposed.[28,29] However, a defined classification system has yet to be consistently embraced.

Table 2. Location and distribution of carcinoid tumors

Site and embryonic origin	Site distribution (%)
Foregut	
Esophagus	<1
Stomach	2–30
Duodenum	2–5
Pancreas	<1
Bronchopulmonary complex	10–25
Midgut	
Jejunum	1–2
Ileum	15–20
Appendix	19–35
Ascending colon	1–5
Liver	<1
Ovary	<1
Hindgut	
Transverse colon	<1–5
Descending colon	2–5
Rectum	10–12
Unknown	<1–2

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CARCINOID MANIFESTATIONS, DIAGNOSIS, AND LOCALIZATION

There is a considerable variability in the clinical presentation of patients with carcinoid tumors[30] depending on the anatomic location, tumor size, and

Table 3. Characteristics of foregut, midgut, and hindgut gastrointestinal carcinoid tumors

Foregut	Midgut	Hindgut
Site of primary tumor		
Esophagus	Distal duodenum	Descending colon
Stomach	Jejunum	Sigmoid colon
Proximal duodenum	Ileum	Rectum
Liver	Appendix	
Gallbladder	Right colon	
Bile ducts	Transverse colon	
Pancreas		
Cell of origin		
Epithelial endocrine cell	Epithelial endocrine cell	Epithelial endocrine cell
Enterochromaffin-like cell in stomach	Subepithelial endocrine cell in appendix	
Typical histologic findings		
Well differentiated, often multiple, occurs in MEN-1	Well differentiated, often multiple	Well differentiated
Often invasive in sporadic carcinoid	Nodal metastases very common except from appendix	Nodal metastases common
Usual syndrome		
Atypical with prolonged purple flush headache, lacrimation, bronchoconstriction	Typical short pink/red flushes with diarrhea, cardiac fibrosis, wheezing, dyspnea, pellagra	Syndrome very rare
Possible mediators		
5-Hydroxytryptophan, histamine, others	Serotonin, kinins others	

From Sutton R, Doran HE, Williams EM, et al. Surgery for midgut carcinoid. Endocrinol Relat Cancer 2003;10:469–481. Reproduced by permission of the Society for Endocrinology.

metastasis (Table 4). Most carcinoid tumors are found incidentally or are thought to be of a different tumor type prior to histologic examination. Patients with incidentally identified lesions have a better prognosis than those with symptomatic lesions and are less likely to have advanced disease.[30–32] Nonfunctional carcinoid tumors may present as any other tumor for that region of the gut. Esophageal tumors may produce obstructive symptoms such as dysphagia or vomiting. Gastric tumors may present with abdominal pain or may be discovered only on esophagogastroduodenoscopy. Duodenal and intestinal tumors may present with partial or complete obstruction, caused by mass effect, intussusception, or local desmoplastic reaction resulting in kinking or adhesive bands (Fig. 1). Appendiceal tumors often present as appendicitis and are often found incidentally. Patients with a functioning metastatic carcinoid tumor may present with carcinoid syndrome.

Specific laboratory diagnosis is dependent on the embryologic origin of the tumor and is detailed below. In addition, lesions may be identified by routine screening endoscopy (e.g., gastric, duodenal, colonic, or rectal lesions) or other screening or diagnostic tests (e.g., metastases in the liver found incidentally by computed tomography (CT) or primary lung lesions detected by screening chest radiography) (Figs. 2 and 3). Occasionally an additional workup for associated tumors or syndromes may be required (e.g., patients with gastric carcinoid tumors may require workup for MEN-I). Also, many of these carcinoid tumors are associated with metachronous and synchronous lesions, indicating the need for further screening (e.g., colonoscopy in patients with small bowel carcinoid tumors).

If the carcinoid tumor is diagnosed preoperatively, a metastatic workup is indicated. CT can be used to assess hepatic or large lymph node metastases. Angiography and high-resolution ultrasonography can provide useful information regarding mesenteric involvement but are not used routinely because the findings can be nonspecific. Endoscopically accessible lesions can be further defined by endoscopic ultrasound imaging, delineating invasion and local lymph node involvement. There has been an enthusiasm for positron emission tomography (PET),[33,34] but results can be equivocal and do not seem to warrant the expense in most patients when compared to somatostatin receptor scintigraphy.[35,36] As such, this modality has not been vigorously embraced, although recent advances using new octreotide analogs may promote a resurgence of interest.[37]

Radiolabeled somatostatin analog scintigraphy is the staging technique of choice and can be used to

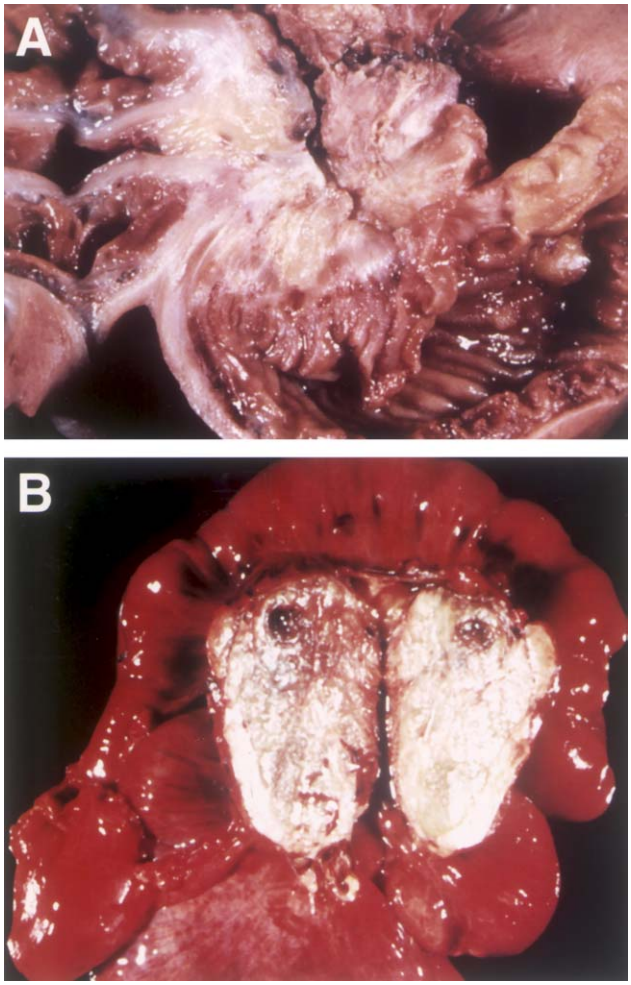

Fig. 1. Gross pathologic characteristics of a small bowel carcinoid tumor. **A**, Carcinoid tumor of the distal ileum with an intense desmoplastic reaction and fibrosis of the bowel wall. **B**, Mesenteric metastases from a carcinoid tumor of the small bowel. (From Evers BM, Townsend CM Jr, Thompson JC. Small intestine. In Schwartz SI, ed. Principles of Surgery. New York: McGraw-Hill, 1999, pp 1217–1263.) Current management of gastrointestinal carcinoid tumors. Reprinted with permission.

localize both primary and metastatic tumors, with sensitivities approaching 90%.[38–43] These techniques can localize both primary and metastatic tumors, increase the accuracy of staging, and assist in operative planning. In addition, intraoperative localization of the radiolabeled probe can be useful, as described in the "Surgical Treatment" section. Most commonly, ^{111}In-labeled octreotide or pentetreotide is used, although the longer acting ^{111}In-labeled lanreotide has shown similar sensitivity.[36] In addition, ^{123}I-MIBG has shown some benefit in localization of primary and metastatic carcinoid tumors.[44,45] However, ^{111}In-labeled pentetreotide is usually more sensitive for the detection of metastatic lesions when compared to

Table 4. Clinical presentation of carcinoid tumors

Carcinoid tumors	
Foregut	
Bronchial carcinoid tumors	Cough, hemoptysis, postobstructive pneumonia, Cushing's syndrome Carcinoid syndrome rare
Gastric carcinoid tumors	Usually asymptomatic and found incidentally
Midgut	
Small intestine carcinoid tumors	Intermittent bowel obstruction or mesenteric ischemia Carcinoid syndrome common when metastatic
Appendiceal carcinoid tumors	Usually found incidentally. May cause carcinoid syndrome when metastatic
Hindgut	
Rectal carcinoid tumors	Either found incidentally or discovered due to bleeding, pain, and constipation. Rarely cause hormonal symptoms, even when metastatic

From Kulke MH. Neuroendocrine tumours: Clinical presentation and management of localized disease. Cancer Treat Rev 2003;29:363–370. Reprinted with permission.

^{123}I-MIBG. For lesions that were detectable by conventional radiologic studies, such as CT or magnetic resonance imaging (MRI), sensitivity for ^{111}In-labeled pentetreotide was 67%, compared to 50% for ^{123}I-MIBG, and for those not detected by such studies sensitivities were approximately 38% and 13%, respectively.[45] These data suggest that radiolabeled somatostatin analogs are superior to ^{123}I-MIBG.

CARCINOID SYNDROME

Because carcinoid tumors can produce and secrete multiple active peptides, systemic sequelae may result from excessive circulating levels of biologically active hormones. Classical or "typical" carcinoid syndrome results from systemic circulation of serotonin and its precursors and derivatives (Table 5). Atypical carcinoid syndrome results from other carcinoid-derived hormones such as adrenocorticotropic hormone. Foregut carcinoid tumors produce low amounts of serotonin and are usually associated with atypical carcinoid syndromes. Adrenocorticotropic hormone–producing tumors may result in Cushing's syndrome, whereas growth hormone–releasing hormone–producing tumors may result in acromegaly and diabetes.[8,46,47] Similarly, hindgut carcinoid tumors may result in an atypical carcinoid syndrome. Atypical manifestations of these carcinoid tumors depend on

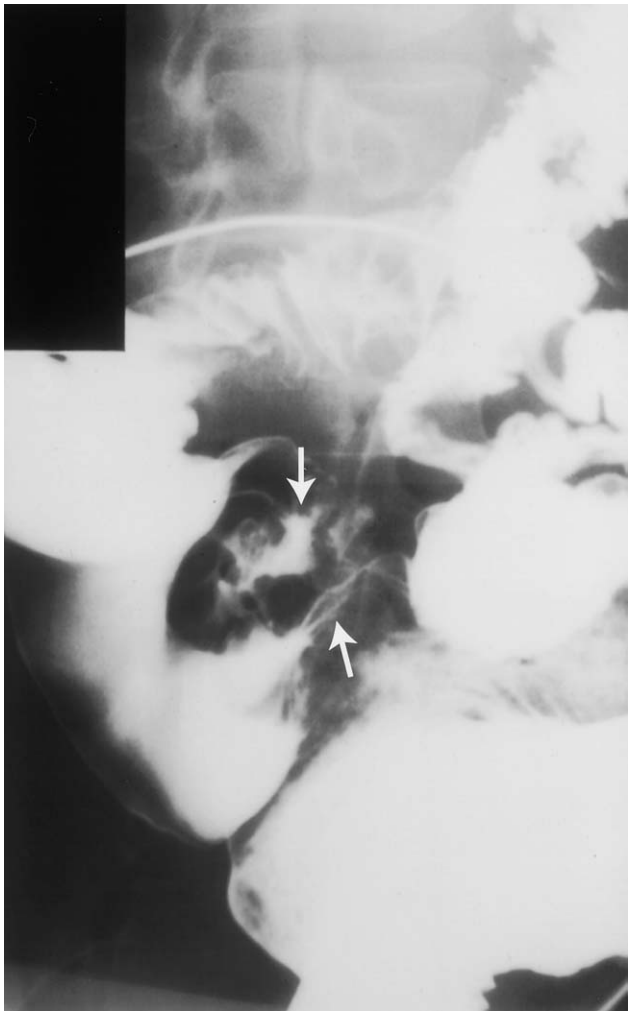

Fig. 2. Barium radiograph of a carcinoid tumor of the terminal ileum demonstrating fibrosis with multiple filling defects and high-grade partial obstruction. (From Evers BM. Small bowel. In Townsend CM Jr, ed. Sabiston Textbook of Surgery, 16th ed. Philadelphia: WB Saunders, 2001, pp 873–916.) Reprinted with permission.

the exact profile and metabolism of the secreted hormones. Typically foregut and hindgut tumors drain, at least partially, to the systemic circulation, thus avoiding hepatic metabolism and clearance of the hormones.

Secreted products of midgut carcinoid tumors usually drain into the porta hepatis, resulting in hepatic metabolism. Carcinoid syndrome from midgut tumors is more likely to be observed in patients with metastatic disease, and results from serotonin, 5-HTP, histamine, dopamine, kallikrein, substance P, and prostaglandin release. Typical midgut carcinoid syndrome presents with the classic symptoms of flushing, diarrhea, and abdominal cramping pain. There are four variations of cutaneous flushing: diffuse erythematosus (short-lived flushing of the face, neck, and upper chest), violaceous flushing (similar to diffuse erythematosus flushing but with a longer duration and with possible permanent cyanotic flush, watery eyes, and injected conjunctiva), prolonged flushing (may last up to 3 days and involve the entire body, and may be associated with profuse lacrimation, hypotension, and facial edema), and bright red patchy flushing (usually associated with gastric carcinoid tumors). Carcinoid syndrome–associated diarrhea results from increased circulating serotonin,[48,49] and is episodic, watery, and explosive. Treatment is largely based on the presenting signs and symptoms. In particular, somatostatin analog therapy is described in the "Medical Treatment" section.

In addition, hepatomegaly, asthma, and right-sided heart valve disease may be present with carcinoid syndrome. Hepatomegaly may be related to tumor burden in the liver. Asthmatic episodes are often temporally associated with flushing symptoms and can be treated with β_2-adrenergic agonists. Two thirds of patients with carcinoid syndrome will develop carcinoid heart disease manifesting as fibrous endocardial thickening of the right heart, with retraction

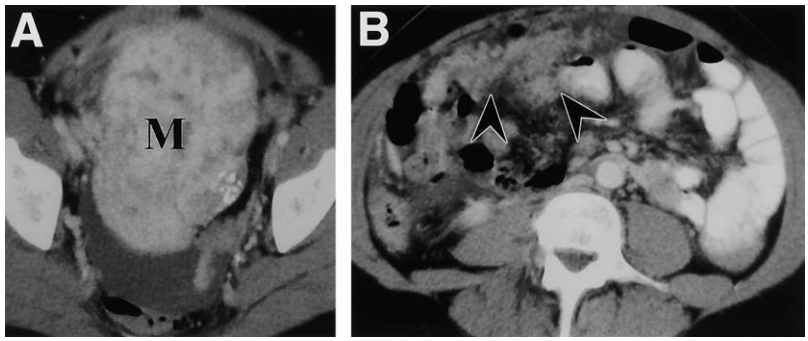

Fig. 3. A, CT scan showing a large, enhancing pelvic mass (*M*) that encases the ovaries from a metastatic goblet cell carcinoid tumor of the appendix. **B**, CT scan obtained cephalad to *A* demonstrating intraperitoneal spread (*arrowheads*). (From Pickhardt PJ, Levy AD, Rohrmann CA Jr, Kende AI. Primary neoplasms of the appendix: Radiologic spectrum disease with pathologic correlation. Radiographics 2003;23:645–667.) Reprinted with permission.

Table 5. Clinical characteristics of carcinoid syndrome

Clinical symptoms	Frequency (%)	Characteristics	Supposed mediators
Flushing	85–90	*Foregut*: Purple, prolonged, involves most often face and neck, sometimes whole body *Midgut*: Pink/red, short time	Kallikrein, histamine, 5-hydroxytryptamine, prostaglandins, substance P
Diarrhea	70	Secretory	Gastrin, 5-hydroxytryptamine, histamine, prostaglandins, vasoactive intestinal peptide
Abdominal pain	35	Long history	Small bowel obstruction due to tumor or tumor products, mesenteric ischemia, hepatomegaly
Bronchospasm	15	Wheezing	Histamine, 5-hydroxytryptamine
Pellagra	5	Dermatitis, diarrhea, dementia	Niacin deficiency
Heart disease			
Right side	30	Dyspnea	5-Hydroxytryptamine, substance P
Left side	10		
Telangiectasia	25	Face	Unknown

From Schnirer II, Yao JC, Ajani Ja. Carcinoid—a comprehensive review. Acta Oncol 2003;42:672–692. Reprinted with permission.

and fixation of the right-sided valves (Fig. 4), resulting in valvular stenosis and regurgitation.[10,50–52] Valve replacement may be required. In addition, pellagra (i.e., dementia, dermatitis, and diarrhea) may be present, resulting from reduced nicotinic acid pools caused by excessive tumor diversion of dietary tryptophan.

SURGICAL TREATMENT

Surgical resection is the mainstay of carcinoid treatment (Table 6). As detailed below, larger tumor size is associated with locally advanced or metastatic disease for most anatomic locations. Generally, for tumors smaller than 2 cm without lymph node involvement, local resection is adequate. For larger tumors (>2 cm), more extensive resections should be considered. Certain locations, such as the small bowel, are associated with multicentricity, and care should be taken to ensure adequate resection. Metachronous lesions should also be dealt with appropriately.

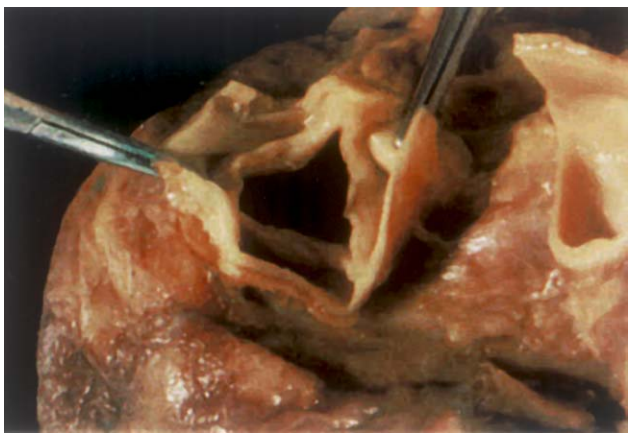

Fig. 4. Fibrotic pulmonary valve from a patient with carcinoid heart disease. (From Kulke MH, Mayer RJ. Carcinoid tumors. N Engl J Med 1999;340:858–868.) Reprinted with permission.

Intraoperative localization can be accomplished using traditional surgical, radiographic, and endoscopic techniques, including palpation, CT scanning, endoscopic tattooing, and intraoperative ultrasound imaging. In addition, tumors can be detected with radiolabeled somatostatin analogs and a gamma-detecting probe.[53–59] A radiolabeled somatostatin analog, such as that used for scintigraphy, is administered prior to surgery. Intraoperatively, the gamma probe can be used to detect the primary tumor, lymph node involvement, or metastatic disease. Postoperatively, scintigraphy can be repeated to detect residual disease. In fact, a single dose of radiolabeled octreotide can be used for preoperative scintigraphy, intraoperative localization, and postoperative scintigraphy.[56] Surgical treatment of carcinoid tumors in specific locations in the gastrointestinal tract is described below.

Stomach

Gastric carcinoid tumors are relatively rare and are separated into the following three categories: type I gastric carcinoid tumors are associated with chronic atrophic gastritis type A; type II tumors are associated with Zollinger-Ellison syndrome and MEN-I; and type III tumors are sporadic gastric carcinoid tumors. Type I and II tumors are associated with hypergastrinemia, which results in hyperplasia of the enterochromaffin cells in the gastric mucosa. In addition, they may be associated with pernicious anemia. These lesions are generally small (<1 cm in diameter), indolent, and often multifocal. Treatment of smaller

Table 6. Summary of surgical recommendations for treatment of midgut carcinoid tumors

Size	Nodes	Treatment
Jejunum and ileum		
<1 cm	40%	Segmental resection with nodal clearance
1–2 cm	60%	Segmental resection with nodal clearance
>2 cm	85%	Segmental resection with nodal clearance
Appendix		
<1 cm	<0.1%	Appendectomy
1–2 cm	<2%	Appendectomy or right hemicolectomy*
>2 cm	50%	Right hemicolectomy with nodal clearance
Right and transverse colon		
<1 cm	40%	Hemicolectomy† with nodal clearance
1–2 cm	60%	Hemicolectomy with nodal clearance
>2 cm	85%	Hemicolectomy with nodal clearance
Mesenteric metastases		
Up to SMA/SMV		Resection of mesenteric nodal mass
Surrounding SMA/SMV		Nodal resection not possible
Hepatic metastases		
<50% Replacement		Liver resection if >25% normal liver preserved
Unsuitable for resection		Consider transplantation‡

SMA/SMV = superior mesenteric artery/superior mesenteric vein.
*Depending on operative findings/histology; if hemicolectomy, wide nodal clearance.
†Right hemicolectomy or extended right hemicolectomy depending on site.
‡If no extrahepatic disease and poor response to other treatments.
From Sutton R, Doran HE, Williams EM, et al. Surgery for midgut carcinoid. Endocr Relat Cancer 2003;10:469–481. Reproduced by permission of the Society for Endocrinology.

lesions is usually accomplished with endoscopic resection and close endoscopic surveillance,[60] whereas larger lesions sometimes require more extensive resection. Interestingly, antrectomy removes the source of gastrin and may result in tumor regression.[61,62]

Sporadic (type III) carcinoid tumors are usually more aggressive and are associated with poor outcome because they are often metastatic at the time of presentation. Type III carcinoid tumors are usually solitary and greater than 1 cm in diameter at presentation.[63] They may be associated with flushing, probably mediated by histamine release.[25] If resection is feasible, a subtotal or radical gastrectomy is usually required. Endoscopic resection is less than ideal, even for smaller lesions.[60]

Duodenum

Duodenal carcinoid tumors are rare and may be classified as either foregut or midgut tumors, depending on the particular portion of the duodenum from which they are derived. A recent retrospective study by Zyromski et al.[64] described 27 patients with duodenal carcinoid tumors identified over a 23-year period. In this series, patients presented with symptoms suggestive of duodenal partial obstruction such as abdominal pain or vomiting. Pancreatitis or bleeding was somewhat less common. Most of these tumors originated in the foregut and were localized to the first or second portion of the duodenum. Treatment was based on the size of the lesion. Endoscopic excision was used for lesions smaller than 1 cm, whereas transduodenal excision should be employed for lesions between 1 and 2 cm. For larger lesions (>2 cm) pancreaticoduodenectomy or segmental resection should be employed, although all patients with these larger lesions developed recurrent tumor. Consistent with the behavior of other carcinoid tumors, larger lesions were associated with more aggressive behavior, as was invasion of the muscularis propria or a periampular location.

Small Intestine

Carcinoid tumors of the small intestine occur more frequently in the distal ileum and are often multicentric.[2] Most patients present with small bowel obstruction, as malignant carcinoid syndrome is relatively rare, even in patients with metastatic disease. Although there is a characteristic kinking of the small bowel caused by the intense desmoplastic reaction (see Figs. 1 and 2), these findings are nonspecific and a diagnosis is usually not accomplished preoperatively. Elevated 5-hydroxyindoleacetic acid (5-HIAA) levels, a breakdown product of serotonin, in a 24-hour urine collection indicate a probable carcinoid tumor. Serum chromogranin A levels are elevated in 80% of these patients.[65,66]

Unlike other gastrointestinal carcinoid tumors, size is a less reliable predictor of malignant potential, with a significant metastatic rate identified even with smaller (<2 cm) lesions.[30,67] Treatment is based on site, size, and metastatic status.[68,69] Small (<1 cm) primary tumors without regional lymph node involvement may be removed with segmental intestinal resection. For a larger lesion (>1 cm), multicentric disease, or regionally metastatic disease, wide excision of the bowel and mesentery is indicated. Lesions of the terminal ileum may require a right hemicolectomy. Five-year survival is approximately 65% in patients with local or regional disease but decreases to approximately 35% in patients with metastatic disease.[17] Palliative resection and debulking operations are also indicated in patients with severe desmoplastic reactions and obstruction.

Appendix

Carcinoid tumors of the appendix often cause partial or complete occlusion of the appendiceal lumen (Fig. 5) and are most often found after operation for acute appendicitis. In adults, most are asymptomatic until the development of appendicitis and are usually smaller than 2 cm.[70–72] The average age of presentation is in the fifth decade of life, with a slight female predominance.[73] Approximately three fourths of appendiceal carcinoid tumors are in the distal third of the appendix.[74] Metastatic disease is relatively rare with small lesions. However, in lesions larger than 2 cm, distant metastatic disease is significantly more common.[75] As with any midgut tumor, hepatic metastasis is a possibility and may result in carcinoid syndrome.

Lymph node metastasis is rare (~0.1%) in tumors smaller than 1 cm; therefore simple appendectomy is the treatment of choice.[76] Carcinoid tumors larger than 2 cm are treated by right hemicolectomy because lymph node metastasis occurs in approximately 25% to 50% of patients.[75,76] The treatment of intermediate-sized tumors (1 to 2 cm) is somewhat controversial. The incidence of nodal spread for these intermediate-sized tumors is exceedingly low and approaches that of smaller lesions. Therefore simple appendectomy alone is considered adequate by many surgeons, particularly if the tumor is in the midappendix or tip.[75,76] In contrast, other studies suggest that tumors at the appendiceal base or those with a more aggressive behavior, such as invasion of the mesentery, should be treated with a right hemicolectomy,[77] because this procedure is well tolerated and achieves improved locoregional control. In our clinical practice, we perform a simple appendectomy as long as surgical margins are clear of tumor. Modlin et al.[17] have shown that 5-year survival is 94% for patients with local disease, 85% for patients with regional invasion, and 34% for patients with distant metastatic disease.

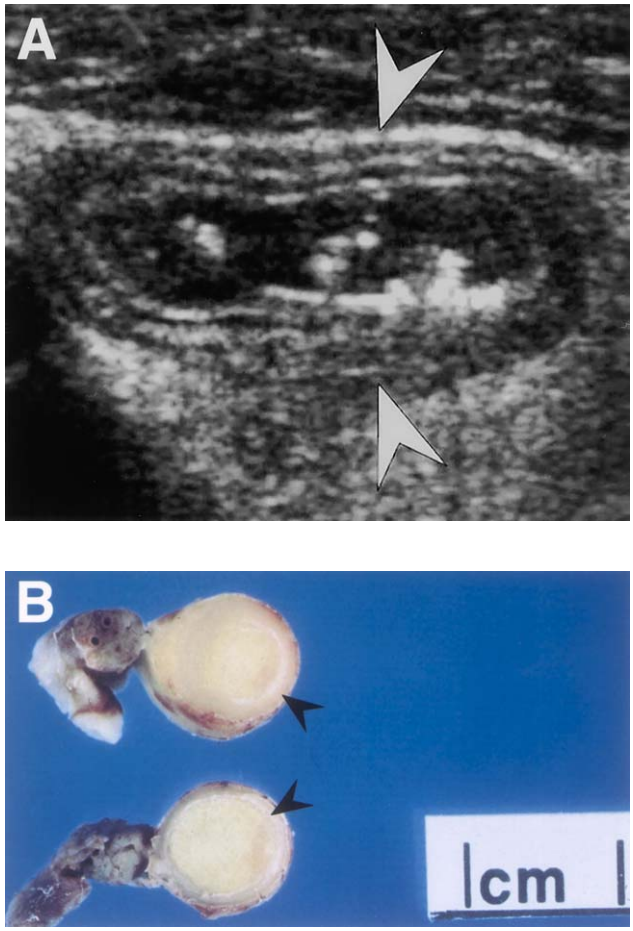

Fig. 5. A, Longitudinal ultrasound image of the right lower quadrant showing a dilated, noncompressible appendix (*arrowheads*) with striated wall-thickening and intraluminal gas echoes in a 6-year-old boy with clinical symptoms of obstructive appendicitis. **B**, Photograph of the gross specimen sectioned at the appendiceal base demonstrating a rounded, subcentimeter carcinoid tumor (*arrowheads*), which produced the luminal obstruction. (From Pickhardt PJ, Levy AD, Rohrmann CA Jr, Kende AI. Primary neoplasms of the appendix: Radiologic spectrum disease with pathologic correlation. Radiographics 2003;23:645–667. Reprinted with permission.)

Colon

Colonic carcinoid tumors are rare, with most of these tumors occurring in the right colon. Patients with colonic carcinoid tumors usually have more nonspecific symptoms and present at a later stage than those with small bowel or appendiceal carcinoid tumors. The luminal diameter is greater in the colon;

therefore these lesions are often quite large (>5 cm) or metastatic when found.[78,79] Because screening for colonic cancer now includes full colonoscopy, more of these tumors may be diagnosed at an earlier stage. Selected patients who are diagnosed with small carcinoid tumors may be treated with endoscopic resection. However, most patients require colonic resection with locoregional lymphadenectomy.[79] Patients with local disease have a 5-year survival of 70%, whereas regional and distant spread decreases survival to 44% and 20%, respectively.[17]

Rectum

Rectal carcinoid tumors usually are of hindgut origin and rarely secrete serotonin. Approximately half of patients with rectal carcinoid tumors present with rectal bleeding, pain, or constipation, whereas the other half are asymptomatic and are diagnosed during screening colonoscopy. Metastatic disease is rare in lesions smaller than 1 cm and common in lesions larger than 2 cm. Small lesions are managed with local excision or endoscopic resection, whereas larger (>2 cm) lesions or lesions that invade the mucosa muscularis are usually treated by a low anterior resection or abdominoperineal resection. However, several retrospective studies concluded that major resection may not confer a survival advantage over local excision,[80–82] suggesting that high-risk patients may be managed with lesser procedures. Specifically these studies found that survival was dependent on resection of smaller tumors (<2 cm) and those not associated with metastasis.

Metastatic and Advanced Disease

The management of locally advanced and metastatic disease requires a multidisciplinary and multimodality approach. Surgical debulking of metastatic carcinoid tumors is recommended, both for relief of symptoms and, because these lesions are relatively indolent, for prolonged survival.[71,83–89] Somatostatin analog scintigraphy should be included for assessment of disease extent. A suggested treatment algorithm is shown in Fig. 6. In particular, for metastatic disease to the liver, surgical resection (e.g., wedge resection or formal lobectomy) or radiofrequency ablation has resulted in symptomatic relief or improvement in most patients, and a prolongation of 5-year survival from approximately 18% to 30% to 50% to 80%.[71,83,85-87,89–91] For diffuse hepatic metastasis, hepatic artery ligation or percutaneous embolization may reduce biochemical tumor markers in 65% of patients and provide some symptomatic relief,[84,86,89] although survival benefits are unclear. Resection of the primary tumor with mesenteric lymph nodes, even in the presence of liver metastases, results in symptomatic relief.[88] Frequently treatment of metastatic disease is improved when combined with chemotherapy or somatostatin analog therapy (described in the "Medical Treatment" section), although results vary widely. Orthotopic liver transplantation for unresectable hepatic metastatic disease has shown some promise in patients without evidence of extrahepatic disease or concurrent noncarcinoid tumors,[91–93] with 5-year survival approaching 70% in one series.[93]

Anesthetic Considerations

Anesthesia may precipitate a carcinoid crisis, which is characterized by hypotension, bronchospasm, flushing, tachycardia, and arrhythmias.[77] The perioperative management of patients with metastatic carcinoid disease has significantly improved with the use of octreotide, which is given intravenously during the perioperative period and reduces the incidence of carcinoid crisis. Intraoperative complications occur in 11% of patients without perioperative octreotide, with few complications in those receiving octreotide. However, episodic bronchospasm can occur, which is often treated with albuterol. The patient must be monitored for sudden hypotension or hypertension. Intravenous antihistamines and steroids may also be beneficial. In addition, arrhythmias can occur, especially in patients with carcinoid-related valvular disease. In fact, carcinoid heart disease and high urinary 5-HIAA levels are significant risk factors for perioperative morbidity and mortality.[94]

MEDICAL TREATMENT

Chemotherapy and External-Beam Radiation Therapy

Chemotherapy has only limited value for unresectable disease. Single-agent therapy has proved ineffective; multiagent regimens have had some limited success. The Eastern Cooperative Oncology Group (ECOG) noted that streptozocin and either fluorouracil or cyclophosphamide resulted in a median survival of 28 months in patients with primary small bowel carcinoid tumors. Furthermore, there was a 44% and 37% objective response rate, respectively, among patients with small bowel carcinoid primary tumors.[95] Additional regimens, such as doxorubicin, differing cycles of streptozocin and fluorouracil, lomustine and fluorouracil, or fluorouracil, doxorubicin, cyclophosphamide, and streptozocin, have not significantly improved survival.[96–98] In addition, external-beam radiation is not beneficial for local control, although it remains the standard for palliation of

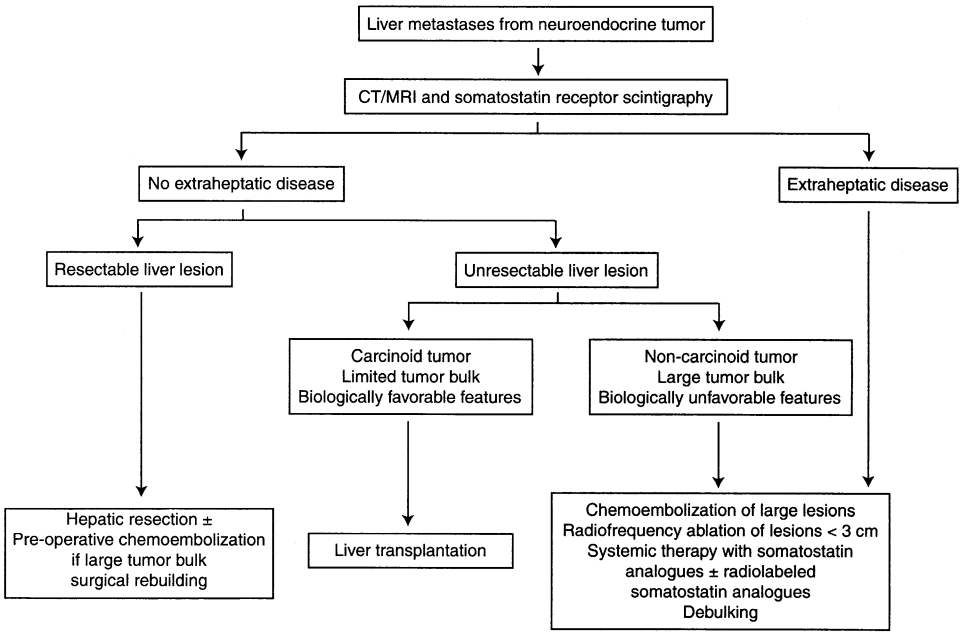

Fig. 6. Management algorithm for patients with neuroendocrine liver metastases. (Adapted from Sutcliffe R, Maguire D, Ramage J, Rela M, Heaton N. Management of neuroendocrine liver metastases. Am J Surg 2004;187:39–46. Reprinted with permission.)

brain and bone metastases as well as for spinal cord compression.[99]

Hormone Analog Therapy

Somatostatin has a relatively short half-life, limiting its clinical utility. However, somatostatin analogs with longer half-lives, such as octreotide and lanreotide, have been used for treatment of advanced disease. As with somatostatin, these analogs inhibit the release and action of multiple endocrine hormones and exocrine secretions in the gastrointestinal tract, as well as gastrointestinal motility and hepatic blood flow (reviewed in references 100 and 101), theoretically reducing tumor function and growth. Octreotide can be given subcutaneously and will relieve or improve the symptoms of carcinoid syndrome in almost 90% of patients.[72,100,102] Lanreotide, a long-acting analog given every 10 to 14 days, and depot octreotide, given once a month, are thought to have similar effects.[103–106] A number of studies have reported improved biochemical profiles with somatostatin analogs (reviewed in reference 101). In fact, tumor stabilization may occur in approximately half of the patients treated with somatostatin analogs, especially in those patients with slower growing tumors.[107] However, actual tumor shrinkage is rare. Complications that can occur with chronic somatostatin therapy include biliary sludge, steatorrhea, hyperglycemia, and cardiac conduction abnormalities, which may require additional treatment.[108]

Synergistic effects may occur when somatostatin analogs are combined interferon-α, which enhances T-cell–mediated (i.e., cellular) immunity.[109–112] However, clinical trials have been limited in size. When combined with octreotide, 5-year survival for disseminated midgut carcinoid tumors is 57%, compared with 37% for those treated with octreotide alone.[111] Interferon-α, when combined with the polyamine biosynthesis inhibitor α-difluoromethylornithine, has shown promise in animal models, but clinical trials are lacking.[113] Interferon-α alone has some clinical utility, with up to 40% of patients demonstrating a biochemical response (e.g., decreased 5-HIAA) and approximately 12% of patients demonstrating an objective tumor response (e.g., radiographically proved tumor shrinkage) in multiple trials (reviewed in reference 108). In contrast, interferon-γ does not seem to have any significant effect on tumor progression, either alone or in combination with interferon-α.[114,115]

Although radiolabeled somatostatin has proved useful for diagnosis and localization of tumor, less benefit has been noted with therapeutic applications. Theoretically the internalized radiolabel will induce tumor cell death. Yttrium^{90}-labeled and ^{111}In-labeled somatostatin analogs, as well as ^{131}I-MIBG, have shown some clinical benefit in a limited number of patients,[116–120] although significant responses were somewhat lacking. Usually the radiolabeled analog

is given over a prolonged period lasting several weeks. Although it is well tolerated, significant clinical benefit has yet to be definitively shown. However, 83% of patients with malignant carcinoid syndrome had a significant reduction in symptoms after treatment with ^{90}Y-labeled octreotide.[119] Overall, treatment with ^{111}In-labeled pentetreotide resulted in the most promising results, with 70% of patients showing some benefit at 6 months after therapy and 31% with sustained benefit at 18 months.[118] Despite symptomatic benefit, almost 70% of these patients had disease progression by 18 months.

FUTURE DIRECTION

Octreotide binds somatostatin receptors-2 and -5 with high affinity. Somatostatin receptor-2 is the more common receptor subtype found on carcinoid tumors.[121,122] Future therapy, based on hormone analogs with high affinities for the specific subtype of somatostatin receptor expressed on the individual tumors, may improve these outcomes.[122–125] In addition, somatostatin analogs may be coupled to cytotoxic drugs for somatostatin receptor–expressing tumors.[126,127] In addition, modulation of somatostatin receptor levels with gene therapy may be beneficial. Specifically, converting somatostatin receptor–deficient tumors into high somatostatin receptor–expressing or specific somatostatin receptor–expressing tumors may increase the efficacy of somatostatin analog therapy.[127,128]

Other hormone analogs, such as the gastrin-releasing peptide bombesin or cholecystokinin analogs, may have similar diagnostic and therapeutic roles as somatostatin analogs.[127,129,130] Although these therapies may have less specificity for carcinoid tumor cells than somatostatin, they raise the intriguing possibility of combination therapy with a hormonal cocktail customized to the receptor profile of the individual tumor. Furthermore, inhibitors of polyamine biosynthesis, with or without concurrent treatment with interferon-α and somatostatin analogs, have shown promise in experimental models[113,131] and may potentially be used as adjuvant therapeutic agents for advanced carcinoid disease. Such studies suggest that inhibition of protein synthesis, an essential process for rapidly growing tumors, combined with hormone analog therapy, may have an impact on tumor growth and survival.

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Intrapancreatic True Arterial Aneurysm Mimicking Pancreatic Tumor

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A 75-year-old female smoker presented with a 2-week history of mild epigastric pain. Her medical history, apart from mild hypertension and Raynaud's syndrome, was unremarkable. Nothing abnormal was found on abdominal examination, and results of routine laboratory tests were normal. She was evaluated initially with an ultrasound scan, which showed a mass in the proximal tail of the pancreas. Results of computed tomographic (CT) and magnetic resonance imaging, which followed, confirmed the presence of a solid mass, 2.8 cm in longest diameter, in the proximal portion of the pancreatic tail (Fig. 1).

At laparotomy the mass proved to be entirely intrapancreatic, with no correlation with the splenic artery and no obvious peripancreatic lymph node involvement. A typical distal pancreatectomy and splenectomy were performed (Fig. 2). On postoperative day 11, the patient had sustained myocardial ischemia and underwent emergency coronary angiography and angioplasty. She recovered without further incident. Results of histologic examination showed an arterial aneurysm within the pancreatic parenchyma (Fig. 3). A well-defined wall of the aneurysm was documented (Fig. 4). Considering the location of the aneurysm, its likely origin would be the great pancreatic artery (magnapancreatic artery—branch of the splenic artery) (Fig. 5).

A comprehensive search of the literature of the past 25 years revealed only one report of aneurysm

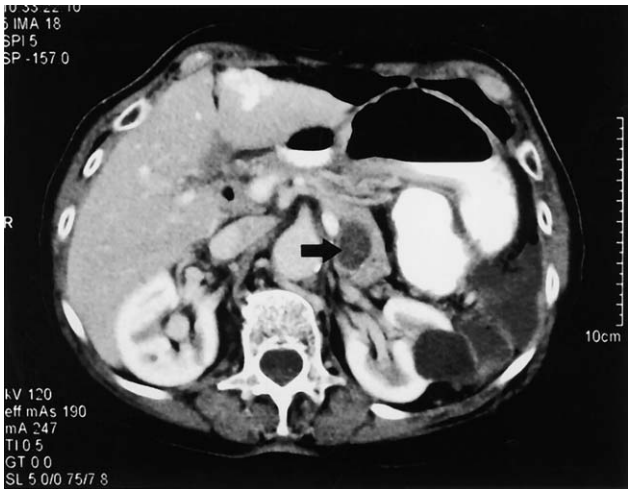

Fig. 1. CT scan demonstrating solid mass (*arrow*) in the proximal portion of the pancreatic tail.

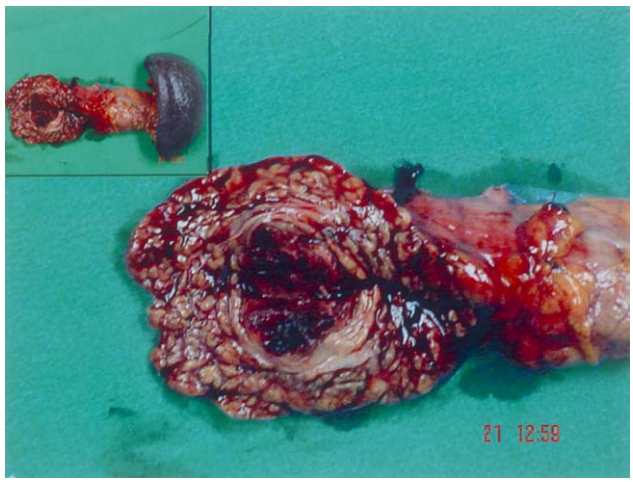

Fig. 2. Photograph of gross specimen showing arterial aneurysm in pancreatic tail.

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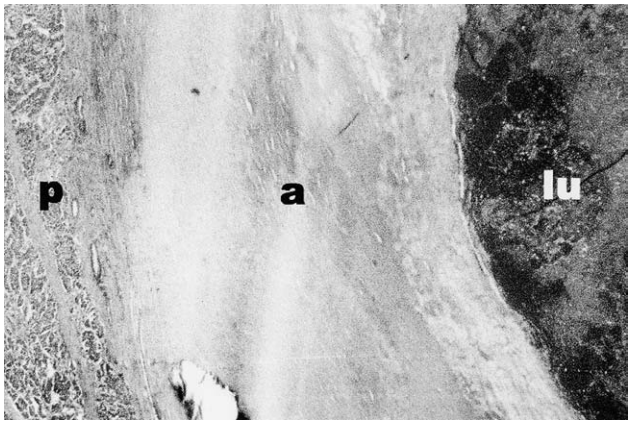

Fig. 3. Arterial aneurysm within the pancreatic parenchyma. p = pancreas; a = wall of the aneurysm; lu = lumen. (Hematoxylin and eosin stain; original magnification ×50.)

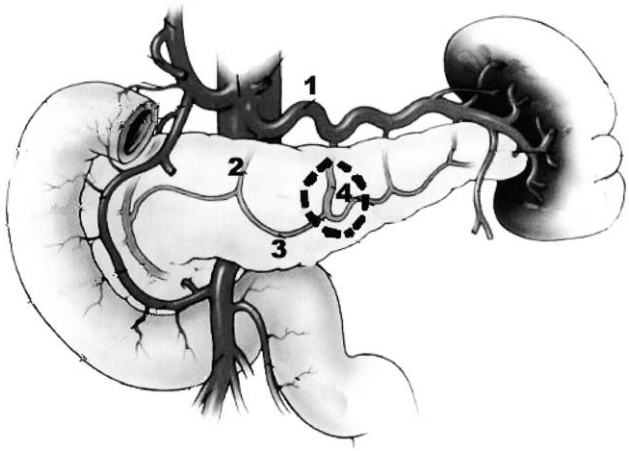

Fig. 5. Because of the location of the aneurysm, its origin was presumed to be the great pancreatic artery (i.e., magnapancreatic artery branch of the splenic artery). 1 = splenic artery; 2 = dorsal pancreatic artery; 3 = transverse pancreatic artery; 4 = magnapancreatic artery).

of the magnapancreatic artery (a postpancreatitis pseudoaneurysm).[1] Reports of true aneurysms of pancreatic arteries, other than pancreaticoduodenal artery aneurysms, are lacking. True aneurysms of pancreaticoduodenal arteries are rare and account for only 2% of all splanchnic artery aneurysms.[2] More than 60% of the reported patients presented after rupture, thus carrying a high mortality rate.

The etiology of true aneurysms of the magnapancreatic artery is unknown. Evidence suggests that local hemodynamic events play a more important role than atherosclerosis, as in the development of pancreaticoduodenal artery aneurysms (stenosis of the celiac axis)[3] and splenic artery aneurysms (multiparity and portal hypertension).[4] Abnormalities of the vessel wall, such as medial fibrodysplasia, arteritis, or Raynaud's syndrome (as in our patient), may also contribute to the development of these aneurysms.

The natural history of pancreatica magna aneurysms is obscure. They probably remain asymptomatic unless they rupture into the retroperitoneal space. The likelihood of rupture and the correlation between size and propensity to rupture are unknown, but it seems sensible to presume that they are likely to resemble those characteristics in splenic artery aneurysms. Accordingly, elective treatment of aneurysms exceeding 2 cm and of any sized aneurysms in women of childbearing age and during pregnancy is recommended.

Because of the intrapancreatic location of these lesions, distal pancreatectomy and splenectomy is a reasonable approach. Selective catheterization and embolization of the aneurysm may be an alternative.

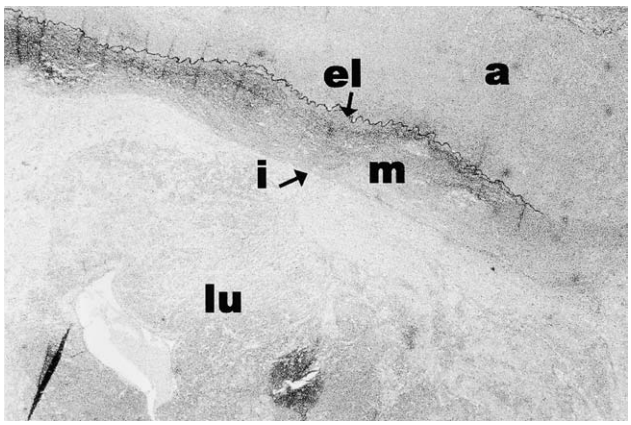

Fig. 4. Well-defined wall of the aneurysm. i = intima; m = media; el = elastic layer; a = adventitia; lu = occluded lumen. (Elastic stain; original magnification ×50.)

Dedicated to Michael Trede, our teacher, the giant of pancreatic surgery, on his seventy-fifth birthday.

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Book Review

Nutritional Considerations in the Intensive Care Unit
Scott A. Shikora, Robert G. Martindale, and Steven D. Schwaitzberg (eds.). Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; and Dubuque, IA: Kendall/Hunt Publishing Co., 2004. Pages: 432. Price: $206.

Drs. Scott A. Shikora, Robert G. Martindale, and Steven D. Schwaitzberg edited this book on nutrition in the intensive care practice at the request of the American Society for Parenteral and Enteral Nutrition. Several worldwide experts have contributed to the 36 chapters included in 432 pages (also available on a single CD-ROM). The book is divided into four sections. The first section covers the interrelationship between critical illness and nutritional status. The second section deals with traditional nutritional issues such as determining macronutrient and micronutrient requirements, fluids and electrolytes, acid-base disorders, and access issues. The third section addresses specific nutritional approaches related to a wide range of critical care conditions such as trauma, severe burns, and abdominal sepsis, as well as common preexisting comorbidities such as diabetes, chronic organ dysfunction, obesity, immunosuppressive disorders, and transplantation. Age-related topics such as pregnancy, neonatal, and pediatric patients are also covered. The final section examines the cost of nutritional support and the use of novel nutritional approaches such as designer formulas, probiotics, and anabolic agents.

The book has successfully fulfilled its purpose to provide a comprehensive state-of-the-art manual regarding feeding all of the major types of critically ill patients and different feeding scenarios encountered in intensive care units. The book is also a useful study guide and a valuable reference for all health care providers involved in the care of the critically ill. However, as a practice guide, the book offers many expert opinions that remain to be validated in appropriate randomized clinical studies, for which that particular field is deficient.

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