Summary of Proceedings of the 38th Annual Meeting of the Pancreas Club

Panelists: Juan Sarmiento, M.D., Gregory Tsiotos, M.D., Kevin Behrns, M.D., Michel Murr, M.D., Jose Eduardo Cunha, M.D., William H. Nealon, M.D.

The 38th Annual Meeting of the Pancreas Club took place during Digestive Disease Week in New Orleans on Sunday, May 16, 2004. The papers presented during the oral presentations are summarized. The Pancreas Club has four sessions. One of these is known as "How I Do It," and the summary of this session is published separately. The other three sessions were entitled, "Pancreatitis (basic and clinical studies)," "Basic Science Studies in Pancreatic Cancer," and "Clinical Studies in Pancreatic Cancer." The summaries were prepared by the moderators. The moderators for the first session were Juan Sarmiento, M.D., from Atlanta, Georgia and Gregory Tsiotos, M.D., from Athens, Greece. The moderators for the second session were Kevin Behrns, M.D., from Chapel Hill, North Carolina and Michel Murr, M.D., from Tampa, Florida. The moderators for the third session were Jose Eduardo Cunha, M.D., from Sao Paulo, Brazil and William H. Nealon, M.D., from Galveston, Texas.

SESSION I—PANCREATITIS

FAS/FASL Interactions Play a Central Role in Pancreatitis-Induced Liver Injury

Gallagher and colleagues from the University of South Florida Health Science Center in Tampa, Florida, previously reported that Fas ligand derived from Kupffer cells mediated liver injury during acute pancreatitis. With this new experiment, they aimed to characterize the role of such ligands in hepatic cellular apoptosis in the same setting. For that they induced pancreatitis with CDE diet in FAS knock-out mice and measured liver FAS, FASL, p38-MAPK, PARP, and cytochrome *c*. Also, apoptosis was determined by DNA fragmentation and TUNEL staining. All measured values (including apoptosis determination) were significantly higher in the pancreatitis group. In knock-out mice (FAS−/−, FASL−/−), the response of those markers was significantly attenuated; even pancreatitis-induced DNA fragmentation was reduced by 60% in the latter group. This study confirmed that pancreatitis-induced liver apoptosis by up-regulation of FAS/FASL ligands. The authors speculate that manipulation of those ligands could play an important role in decreasing the hepatocellular injury seen in pancreatitis.

Randomized Controlled Trial of Pylorus-Preserving Whipple Versus Duodenum-Preserving Pancreatic Head Resection in Chronic Pancreatitis

The second paper of the session was presented by Makoweic and colleagues from the University of Freiburg, Germany. Regarding the background of two underpowered trials on the subject, this group randomized 87 patients with head-dominant changes of chronic pancreatitis to Whipple (n = 44) vs. Beger (n = 43) procedures. Pain was the dominant symptom in this population (62%). Operative results were comparable between the groups, although the Whipple procedures took longer than their counterparts (435 versus 368 minutes, mean values). Although the results in terms of pain control, quality of life, and weight gain were improved significantly by each operation, there was no difference between the groups. Even the incidence of postoperative diabetes was similar. The authors concluded that for patients with head-dominant chronic pancreatitis, both operations (pylorus-preserving Whipple and the Beger procedure) were equally effective and had similar postoperative outcomes.

Surgical Management of the Complications Associated With Percutaneous and/or Endoscopic Management of Pseudocysts of the Pancreas

Nealon and colleagues from the University of Texas Medical Branch, Galveston, describe the surgical management of complications resulting from the

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use of nonoperative measures for decompression of pancreatic pseudocysts spanning 11 years (up to 2003). Seventy-nine patients underwent either percutaneous or endoscopic decompression. In general, complications of nonoperative therapy (sepsis, 91%; bleeding, 20%; hypotension, 65%; renal failure, 20%; need for ventilatory support, 24%; persistent fistula, 84%; ICU stay, 46%) document the magnitude of such complications. The magnitude of complications in a separate group managed with operative treatments alone was significantly reduced. This paper emphasizes the importance of preoperative imaging (MRCP, ERCP) to select the patients who will benefit from primary surgical therapy. The authors also again make a correlation between ductal anatomy and the complications in pseudocysts.

Bile-Pancreatic Juice Exclusion Exacerbates Stress Kinase Activation and Cytokine Production in Ligation-induced Pancreatitis in Rats

Samuel and colleagues from the University of Iowa College of Medicine, Iowa City, Iowa, have shown that biliopancreatic (BP) exclusion from gut exacerbates acute pancreatitis, possibly mediated via cytokine production. Three groups of rats were studied: one sham, one with BP exclusion, and a third with BP exclusion and re-infusion of juice after ligation of the pancreatic duct. All cytokines studied (P38, JNK, TNF, IL-1) increased significantly after ligation of the pancreatic duct; this effect was clearly ameliorated by replacement of BP secretions. The authors concluded that BP exclusion from gut exacerbates acute pancreatitis induced by ligation in rats, and opens the door for new therapies involving the role of enteral nutrition in this model.

Nonciception in Acute Pancreatitis is Partially Mediated by TRPV-1 Receptor

Wick and colleagues from the University of California San Francisco, San Francisco, California, demonstrate that the transient receptor potential vanilloid-1 (TRPV-1) is a nonselective cation channel present on nociceptive neurons. After inducing pancreatitis in male Sprague-Dawley rats with L-arginine, the activation of nociceptive pathways was measured in the dorsal horn and also by abdominal wall contractions. There was a two-fold increase in staining of the spinal cord c-Fos expression (as an objective measure of nociceptive activity) 24 hours after induction of pancreatitis, seen especially in T9, T11, and L1, having a direct correlation with the number of abdominal wall contractions. After antagonistic effect of capsazepine in the treated group, there was a significant decrease in the amount of Fos-like reactivity in T9-L1, although it did not exert any effect on the serum amylase. The authors conclude that nociceptor in this model of pancreatitis depends partially upon activation of TRPV-1 and that antagonistic agents could be useful to treat pain in patients with pancreatitis.

Quality of Life After Total Pancreatectomy. Ten-Year Experience

Salvia and colleagues from Verona, Italy, sent questionnaires (EORTC QLC-C30) to patients after total pancreatectomy procedures performed between 1994 and 2003. Reviewing a 66% response rate, the median use of insulin was 30 U/day, with most patients claiming daily (30%) and weekly (70%) hypoglycemic episodes. These episodes and steatorrhea were prominent in this population.

Endothelial Injury Induced by Neutrophils in Acute Pancreatitis. Role of Endothelins

De Souza and colleagues have collected blood from controls and patients with acute pancreatitis (19 in each group) and cocultured their neutrophils with endothelial cell monolayers to assess its integrity through detachment. This was also measured after treatment with antagonists for endothelin types A and B separately. There was a significant increment in the level of detachment in the neutrophils of patients with acute pancreatitis; also, antagonists to the endothelin receptors failed to inhibit detachment on the same group (as opposed to neutrophils coming from controls). The authors conclude that endothelins play an important role in the endothelial injury that is seen in acute pancreatitis and speculate that distant organ damage could be attenuated by antagonists of endothelins receptors.

SESSION II—BASIC SCIENCE STUDIES IN PANCREATIC CARCINOMA

PGE_2 Enhances Pancreatic Cancer Invasiveness Through an ETS-1–Dependent Induction of MMP-2

Ito and colleagues from Brigham and Women's Hospital, Harvard University, Boston, Massachusetts, tested the hypothesis that PGE_2 enhances cancer invasiveness by inducing MMP-2 expression in two pancreatic cell lines in the presence or absence of rofecoxib, a selective COX-2 inhibitor. Rofecoxib significantly attenuated the PGE_2-induced increase in the binding of the transcription factor ETS-1 as well

as MMP-2 promoter activity, and reduced cellular invasiveness as determined by Matrigel assay. Furthermore, silencing of ETS gene by siRNA reduced baseline expression of MMP-2, as did administration of an MMP antibody. The authors conclude that COX-2–derived PGE_2-mediated pancreatic cancer cell line attains invasiveness through an ETS-1–dependent induction of MMP-2 expression. This study demonstrates the complex interplay of MMP and COX-2 in cell invasiveness and cancer cell metastasis. These data are important and should be validated by further examination of upstream regulators and in full animal models.

SKI Overexpression Attenuates the Induction of p21 by TGF-β in Human Pancreatic Cancer

TGF-β plays an important role in cellular growth and proliferation. Heider and Behrns from the University of North Carolina Chapel Hill, North Carolina, sought to determine whether overexpression of SKI, which is an upstream cell signaling system, attenuates TGF-β signaling in human pancreatic cancer specimens and human pancreatic cell lines. SKI overexpression was very common in human pancreatic cancer specimens, as demonstrated by immunohistochemistry or Western blotting, and in Panc-1 cells, as demonstrated by immunohistochemistry or Western blotting. Manipulating SKI expression with siRNA significantly increased the TGF-β–induced activity of the p3TP/luciferase reported and induction of p21 in Panc-1 cells. The investigators concluded that the transient inhibition of SKI through RNA interference results in increased activity at the TGF-β promoter and enhanced transcription of p21 in response to TGF-β treatment, supporting the role of SKI as a suppressor of TGF-β signaling in pancreatic cancer. These findings are very interesting as we learn more about the role of SKI in TGF-β signaling. The small discrepancy in detecting SKI overexpression using immunochemistry and Western blots may be overcome with a larger number of specimens.

Potential Involvement of the ERK Pathway in the Resistance of Pancreatic Cells to Anoikis. A Central Step in the Development of Metastatic Disease

Cancer cells are resistant to anoikis, a special programmed mode of cell death dependent upon loss of cell–cell and cell–matrix interaction. This resistance is thought to play a role in metastatic potential. Galante and Bold from the University of California Davis, Sacramento, California, hypothesized that pancreatic cell lines are resistant to anoikis via upregulation of ERK and overexpression of the antiapoptotic protein BCL-2. In two cell lines, MIA-PACa-2 and BxPC-3, the percentage of anoikis as detected by flow cytometry inversely correlated with levels of phosphorylated ERK and BCL-2, suggesting that these may confer resistance to anoikis in pancreatic cell lines. These are interesting findings. The emerging field of anoikis warrants further investigation—specifically, the mechanistic link between anoikis and upstream cell signaling systems in nontransformed cell lines. Furthermore, the specificity of flow cytometry in detecting anoikis versus apoptosis needs to be validated.

Suramin Inhibits Not Only Tumor Growth and Metatasis But Also Angiogensis in Experimental Human Pancreatic Cancer

Porebski and colleagues from UCLA Medical Center, Los Angeles, California, examined the effect of an increasing doses of suramin on metastatic growth potential in an orthotopic model of pancreatic cancer in nude mice. They evaluated tumor volume, dissemination score, and microvascular density of subcutaneously grown tumors of three cell lines—MIA-PaCa-2, AsPC-1, and Capan-1—each of which has a spectrum of differentiation. Suramin at high doses (60 mg/kg), but not at low doses, significantly reduced tumor volumes and microvascular density in all three cell lines and reduced the dissemination score in MIAPcCa-2 cell line tumors only. These preliminary and descriptive data are important in furthering our understanding of the role that angiogenesis plays in the metastatic potential of cancer cells and should be used to explore the mechanism of suramin's effect on tumor growth and dissemination.

CEACAM6 Is a Novel Tumor Marker in Pancreatic Adenocarcinoma and PanIN Lesions

Matros and colleagues from Brigham and Women's Hospital, Harvard University, Boston, Massachusetts, presented work on the association of the novel pancreatic cancer tumor marker, carcinoembryonic antigen–related cell adhesion molecule (CEACAM6), and outcome from treatment. The investigators used the robust tissue microarray method to examine pancreatic cancer specimens from 89 patients who underwent a pancreatectomy with curative intent. In addition, 54 PanIN lesions from 44 patients were analyzed for expression of CEACAM6. Lack of expression was correlated with decreased lymph node involvement and lower disease stage. Multivariate analysis demonstrated that carcinomas with

CEACAM6 expression tended to have lower survival ($P = 0.09$). Furthermore, in PanIN lesions, CEACAM6 was expressed more frequently in high-grade lesions (PanIN III) compared with low-grade PanIN tumors. These findings suggest that the absence of CEACAM6 expression is associated with favorable histologic and clinical outcome, but that the expression of CEACAM6 was not definitely associated with poor prognosis. This study used the latest tissue array technology to perform an important translational study. With the use of this technology, the authors can examine other tumor markers and, more important, they can validate their CEACAM findings by providing altered regulation of downstream effectors of CEACAM6.

EGF Receptor Antagonism Produces Cell Death and an In Vivo Survival Benefit in a Murine Model of Pancreatic Ductal Adenocarcinoma

Because epidermal growth factor receptor (EGFR) is differently up-regulated in pancreatic carcinoma compared with normal pancreas, the role of this oncogene has been examined as a potential therapeutic target. Durkin and colleagues from the University of South Florida, Tampa, Florida, presented their data on inhibition of EGFR with erlotinib, a specific antagonist, on in vitro and in vivo growth of the pancreatic carcinoma cell line HPAC. The HPAC cell line expressed the EGFR transcript and protein and in the presence of erlotinib displayed decreased in vitro growth. Growth in vivo after treatment with EGFR inhibitor was also inhibited and survival was improved compared with control and compared with reference, matrix metalloproteinase inhibitor–treated animals. The animals treated with erlotinib also demonstrated decreased orthotopic implantation, tumor size, weight, and metastases compared with control and reference-treated animals. This study demonstrates proof of principle that EGFR antagonism decreases tumor growth and virulence in a mouse model of pancreatic carcinogenesis. The molecular mechanism of this growth inhibition was not clear, however, because decreased EGFR phosphorylation with erlotinib has not been demonstrated by the authors. Furthermore, because EGFR functions as a tyrosine kinase and multiple other growth-regulating tyrosine kinase pathways exist, the specificity and potential side effects of any eventual therapy against EGFR must be investigated rigorously. Nonetheless, this study displays the utility of tyrosine kinase inhibition in pancreatic cancer growth regulation and adds further insights into the important cell signaling pathways in this chemoresistant cancer.

A Novel Method of Metronomic Gemcitibine Dosing in a Murine Model of Pancreatic Adenocarcinoma Increases Efficacy Over Conventional Therapy

The current methods of delivery of chemotherapy are likened to a blast effect, in that the tumor cells see a high concentration of drug for a short period of time and the cells that survive this insult mutate to avoid further such insult. This pattern of drug delivery may result in chemoresistance. To avoid this potential phenomenon, metronomic dosing, or chronic low-dose therapy, has been proposed, and it presumably acts through destruction of endothelial cells and inhibition of angiogenesis. Barnett and Beck from University of Texas Southwestern Medical Center, Dallas, Texas, studied metronymic dosing of gemcitabine in an animal model, in which pancreatic cancer cells were implanted in one flank and, after the tumors were established, the mice were treated with intraperitoneal gemcitabine or contralateral flank implantation of gemcitabine in a polymer gel (GemGel) that permits slow release. With the use of this delivery system, the authors found decreased tumor size compared with conventional therapy. Furthermore, histology of the GemGel-treated group showed extensive necrosis and decreased expression of CD31, an endothelial cell marker. This work demonstrates the importance of investigating the benefit of existing drug administration regimens and re-thinking the mechanisms of carcinoma chemoresistance.

SESSION III—CLINICAL STUDIES IN PANCREATIC CARCINOMA

Intraductal Papillary Mucinous Neoplasms of the Pancreas (IPMN): An Updated Experience

Sohn and colleagues reported on 136 pancreatic resections performed at John Hopkins Hospital, Baltimore, Maryland, between 1987 and 2003 for patients with IPMNs. Pancreatoduodenectomy was performed in 71% of patients, total pancreatectomy in 15%, distal pancreatectomy in 12%, and central pancreatic resection in 2%. Pathology was reviewed to identify main duct or branch duct orgin of the tumors. No evidence of invasive cancer was found in 84 patients (62%) with IPMN. The remaining 52 patients (38%) had invasive cancer: tubular (60% of these), colloid (27%), mixed (7%), and anaplastic (6%). The patient ages of this study were 63 years for these with adenomas and 68 years for these with invasive cancer and suggest that there may be a 5-year time lag for an adenoma to develop into an invasive cancer. Final positive margins were found

in 15% of patients with invasive cancer, and 54% had positive nodes. In 24% of patients with noninvasive IPMNs, residual tumor was identified at the pancreatic neck or uncinate margin. The 5-year overall survival for patients without invasive cancer was 77%, with many deaths secondary to metachronous invasive cancer. The survival rate was significantly higher than the 43% survival rate in patients with an invasive component. No differences in survival were observed regarding adenomas, borderline tumors, and carcinomas in situ. Surprisingly, survival was statistically similar when comparing branch duct or main duct origin of the tumor. Fourteen patients with colloid carcinomas had a better 5-year survival rate (83%) compared with the 31 patients with tubular carcinomas (24%). IPMN recurrences and deaths from cancer occurred regardless of the benign or malignant nature of the lesion at initial resection. The genetic progression from IPMN adenoma to IPMN with invasive cancers appears to be distinct from the progression of PanINs to pancreatic adenocarcinomas. Dpc4 expression is lost in more than 50% of pancreatic ductal adenocarcinomas but only 16% of invasive IPMNs. Additionally, loss of heterozygosity of the *STK11/LKB1* gene was identified in 32% of IPMN patients, with subsequent germline and somatic mutations identified in remaining alleles. In addition, invasive IPMNs demonstrate much higher rates of methylation at multiple gene loci, including p16, E-cadherin, MGMT, and hMLH1, compared with pancreatic ductal adenocarcinoma.

Pancreaticoduodenectomy for Pancreatic Adenocarcinoma: Impact of Margin Status on Pattern of Failure and Survival

The importance of retroperitoneal (RP) margin status on pattern of failure and survival after pancreatoduodenectomy (PD) for pancreatic cancer was discussed in a paper by Raut and colleagues from the Surgical Oncology Department of The M. D. Anderson Cancer Center, Houston, Texas. From 258 consecutive patients who underwent PD for pancreatic adenocarcinoma from 1992 to 2002, 253 were studied with a minimum follow-up of 12 months (median, 12 months) The RP margin, defined as the soft tissue margin adjacent to the lateral wall of the superior mesenteric artery, was microscopically positive (R1) in 36 patients (14%) and negative (R0) in 222 (86%). There were no significant differences in the standard prognostic factors such as tumor size and lymph node metastases or in the preoperative and postoperative therapy between the R1 and R0 groups. Patterns of recurrence (local, regional, and distant), overall survival, and the disease-free interval were not statistically different in the R1 and R0 groups. Considering the unique findings of this study, the authors speculate on the possible influence of the technical aspects of the surgical resection and the frequent use of multimodal therapy in this study on the reversion of the biological disadvantage of microscopically positive RP margin.

18-FDG PET in Differentiating Malignant From Benign Pancreatic Cystic Lesions: A Prospective Study

A previous report from the University of Padua, Italy, demonstrated the usefulness of 18-FDG PET scan in discriminating malignant from benign cystic pancreatic lesions (Ann Surg 2001;134:675–680). The group of Sergio Pedrazzoli from the University of Padova, Padova, Italy, report on an additional 50 patients with suspected cystic neoplasms (n = 33) or IPMN (n = 17) who were prospectively investigated with 18-FDP PET scan, abdominal computed tomography (CT), serum CA 19-9, and, in some instances, magnetic resonance imaging (MRI). The final diagnosis was based on the pathologic findings in 33 operated patients and percutaneous biopsy in 3 but only on clinical follow-up in 14. Sixteen of 17 patients with malignant tumors (94%) showed 18-FDG uptake, including two patients with carcinoma in situ. Eleven patients (65%) were correctly identified as having malignancy by CT. Only 2 of 30 patients with benign tumors had FDG uptake. Although the authors concluded that 18-FDG PET is accurate and better than CT in identifying malignant pancreatic cystic lesions, the study did not point out how PET scan influenced the management of these patients.

Five-year Actual Survival Following Extended Lymphatic Clearance in Cancer of the Head of the Pancreas

A clinical study by Boggi and colleagues was carried out at the University of Pisa in Italy to determine the 5-year survival rates of extended versus standard lymphadenectomy in pancreatic head cancer. The authors reported on 87 pancreatectomies without neoadjuvant or adjuvant treatments performed for nonadvanced pancreatic cancer between 1987 and 1988, with a minimum follow-up of 5 years. Forty-four patients underwent extended lymphatic clearance (ELC) with a mean number of 25.3 $\pm$ 1.8 dissected nodes. In 43 patients who underwent standard lymphatic clearances (SLC), the mean number of dissected nodes was 9.8 $\pm$ 1.3. Postoperative length of stay was 21 $\pm$ 8.9 days for ELC patients and 20 $\pm$ 6.2 days after SLC. The morbidity and mortality rates after ELC were 47.6% and 2.3% compared

with 33.3% and 4.5% for SLC, respectively. Severe diarrhea, requiring medical treatment, was significantly more frequent after ELC than after SLC (33% versus 2%). Actual survival rate at 1, 3, and 5 years was 71%, 25%, and 14% after ELC and 57%, 15%, and 8% after SLC, respectively. The corresponding figures for patients with lymph node metastases were 61%, 24%, and 14% and 52%, 10%, and 0% for ELC and SLC respectively. The incidence and pattern of cancer recurrence were similar after the two types of operations, confirming that extended lymphadenectomy does not significantly enhance survival compared with the standard resection.

Distal Pancreatectomy for Resectable Adenocarcinoma of the Body and Tail of the Pancreas

The role of surgical resection of adenocarcinoma of the pancreatic body and tail has been questioned due to the low resectability rates and the poor long-term survival of these tumors. This issue was addressed in a retrospective review by Christein and colleagues of 93 patients undergoing distal pancreatectomy for adenocarcinoma of the body and tail of the pancreas at the Mayo Clinic, Rochester, Minnesota, from 1987 to 2003. Thirty-three (35%) of patients underwent an en bloc pancreatic resection (EDP), including at least one adjacent organ, and the other 60 (65%) underwent a standard distal pancreatectomy (SDP). Pathologic analysis demonstrated invasive ductal adenocarcinoma in 66 patients (71%), mucinous cystadenocarcinoma in 18 (19%), and invasive adenocarcinoma associated with intraductal papillary mucinous neoplasm (IPMN) in 9 patients (10%). An R0 resection was possible in 78 (84%) patients. The overall complication rate was 46%, with pancreatic stump leak being the most common morbidity (20%). There was no operatively induced mortality. Median survival was 19.6 months, and the 5-year survival rate was 11.8%. Survival of patients undergoing EDP did not differ from that of those who underwent SDP ($P = 0.26$). Survival also was not significantly affected by blood transfusion requirements ($P = 0.40$), adjuvant therapy ($P = 0.15$), lymph node status ($P = 0.11$), or margin status ($P = 0.08$) but correlated positively with tumor staging ($P < 0.004$). Patients with cystadenocarcinoma or with IPMN-associated adenocarcinoma had a median survival of 32.2 months, significantly better than the 15.4-month median survival for those with invasive ductal adenocarcinoma ($P < 0.003$).

Differences in Survival for Patients with Resectable Versus Unresectable Metastases From Pancreatic Islet Cell Cancer

From the Departments of Surgery of John Hopkins University, Baltimore, Maryland, and University of Indiana, Indianapolis, Indiana, House and colleagues reported on 31 patients with islet cell tumors with synchronous liver metastases at the time of initial presentation: 23 with nonfunctional tumors, 2 with gastrinomas, 2 with glucagonomas, 3 with VIP-omas, and 1 with an insulinoma. The patients were divided into two groups according to liver metastasis resection (group PL, n = 26) or no metastasis resection (group P, n = 5). In two patients of group PL, a combination of resection and ablation was applied. Multiple ($\geqslant$10) small bilobar metastases were found in all of the P group patients. There were no statistical differences between the PL and P groups in primary tumor size, lymph node metastases, and concomitant liver disease or adjuvant treatments. All patients underwent resection of the pancreatic primary by means of 12 pancreaticoduodenectomies—11 (42%) in the PL group and only 1 (20%) in the P group—or 19 distal pancreatectomies—15 (58%) in group PL and 4 (80%) in group L. The median overall survival for the respectable liver metastases group was 78 months versus 17 months for those with unresectable liver metastases ($P = 0.06$). This result indicates that patterns of liver metastases from islet cell tumors, specifically bilobar miliary metastases that are not amenable to resection or ablation, predict a poor outcome despite resection of the primary pancreatic tumor.

Phase III Trial of Radiosensitizer PR-350 Combined With Intraoperative Radiotherapy for the Treatment of Locally Advanced Pancreatic Cancer

Well-oxygenated cells are believed to be more sensitive to intraoperative radiotherapy (IOR) than hypoxic cells. Based on this theory, a prospective study to clarify the role of a novel radiosensitizer for hypoxic cells, PR-350 (doranidazole), combined with IOR was conducted in Sendai and Tokyo, Japan, and presented by Makoto Sunamura. PR-350 is a 2-nitroimidazole nucleoside analogue, less neurotoxic than etanidazole, that has the ability to sensitize radioresistant tumor cells to the lethal effects of ionizing radiation under extremely hypoxic conditions. Forty-eight patients treated with IOR for locally advanced pancreatic cancer were randomized, in a 3-year period, to PR-350 or placebo. Efficacy of the treatment, evaluated by CT examination, was reported in 47.4% of the PR-350 group, which was significantly better than the 21.7% effective response in the control group. Tumor mass reduction rate was also significantly improved in the PR-350 group at 6 months following therapy. Although there were little differences in median survival (318 days versus 303 days) and in the 1-year survival rate (36% versus 32%) between the treated and the control group, respectively, it is worth mentioning that four of the PR-350–treated patients lived longer than 2 years after the end of the trial compared with only one in the control group.

The Giuseppe Grassi Prize—Comments

Lloyd M. Nyhus, M.D., F.A.C.S.

The Grassi Prize presentations at the meeting of the International Society of Digestive Surgery in Yokohama, Japan in the fall of 2004 were of excellent, scientific quality. A few reminders of the late, beloved Dr. Grassi are in order. He was the first General-Secretary of the Collegium Internationale Chirurgie Digestivae (CICD). This college was formed in 1969 by Professors Grassi, Benedetti-Valentino of Italy and Hollender of France. This was the forerunner of the International Society of Digestive Surgery (ISDS). I would be remiss if I did not remind us that this past year, Professor Hollender was President of the renowned National Academy of Medicine of France.

I remember well the first Congress of the CICD, which was held in San Remo, Italy during 1970. Dr. Grassi was President of that meeting, and everyone attending recognized the excellence of the sessions in which he played such an important part.

We were all saddened by the sudden death of Dr. Grassi in 1981, while he was participating in patient care rounds. He was scheduled to depart from this important work to attend an Executive meeting of the CICD. You can imagine that this meeting was filled with reminiscences of Dr. Grassi and his important role in the founding of the CICD.

Congratulations to the current leaders of the ISDS for the recognition and support of younger, contributing surgeons in the world today through the Grassi Prize.

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Pharmacologic Preconditioning Effects: Prostaglandin E_1 Induces Heat-Shock Proteins Immediately After Ischemia/Reperfusion of the Mouse Liver

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Prostaglandin E_1 (PGE_1) has several potential therapeutic effects, including cytoprotection, vasodilation, and inhibition of platelet aggregation. This study investigates the protective action of PGE_1 against hepatic ischemia/reperfusion injury in vivo using a complementary DNA microarray. PGE_1 or saline was continuously administered intravenously to mice in which the left lobe of the liver was made ischemic for 30 minutes and then reperfused. Livers were harvested 0, 10, and 30 minutes postreperfusion. Messenger RNA was extracted, and the samples were labeled with two different fluorescent dyes and hybridized to the RIKEN set of 18,816 full-length enriched mouse complementary DNA microarrays. Serum alanine aminotransferase and aspartate aminotransferase levels at 180 minutes postreperfusion were significantly lower in the PGE_1-treated group than in the saline-treated group. The cDNA microarray analysis revealed that the genes encoding heat-shock protein (HSP) 70, glucose-regulated protein 78, HSP86, and glutathione *S*-transferase were upregulated at the end of the ischemic period (0 minutes postreperfusion) in the PGE_1 group. Our results suggested that PGE_1 induces HSPs immediately after ischemia reperfusion. HSPs might therefore play an important role in the protective effects of PGE_1 against ischemia/reperfusion injury of the liver. (J GASTROINTEST SURG 2005;9:758–768)

KEY WORDS: cDNA microarray, heat-shock protein, ischemia/reperfusion injury, preconditioning, prostaglandin E_1

Ischemia/reperfusion (I/R) injury is the main cause of hepatic damage resulting from temporary clamping of the hepatoduodenal ligament during liver surgery or graft failure following liver transplantation. This condition can lead to fatal liver failure, so it is important for surgeons to prevent or ameliorate I/R injury.

Several factors contribute to hepatic I/R injury. The lack of oxygen during the ischemic period causes mitochondrial deenergization, adenosine triphosphate (ATP) depletion, and alterations of H^+, Na^+, and Ca^{2+} homeostasis, which activate hydrolytic enzymes and impair cell-volume regulation.[1–4] On reoxygenation, the formation of reactive oxygen species (ROS) by uncoupled mitochondria promotes oxidative stress and mitochondrial membrane-permeability transition (MMPT).[5] Together, these events are responsible for cell death through necrosis or apoptosis.[1] Concomitantly, the activation of Kupffer cells releases ROS, nitric oxide, and several proinflammatory cytokines: tumor necrosis factor (TNF)-α,

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interleukin (IL)-6, IL-1β, monocyte chemotactic peptide 1 (MCP1), IL-12, and CXC chemokines.[6] The cytokines, together with the increased expression of adhesion molecules (intracellular adhesion molecule 1 [ICMA1] and E-selectin) by sinusoidal endothelial cells, promote liver neutrophil infiltration, which contributes to the progression of parenchymal injury.[6,7] Thus, several factors act in concert to enhance liver susceptibility to I/R injury, further increasing the patient risk during surgery. Efforts to ameliorate or prevent I/R injury have traditionally focused on blocking the events associated with irreversible liver damage.

Two powerful strategies have been developed for clinical use: ischemic preconditioning and hyperthermic preconditioning. Ischemic preconditioning consists of a brief period of ischemia, followed by a short interval of reperfusion before the surgical procedure, which involves prolonged ischemic stress.[8] Murry et al.[9] initially discovered this phenomenon in the myocardium in 1986. Although knowledge of the molecular mechanisms involved remains vague, several mediators have been suggested to play a critical role in these protective pathways, including adenosine[8], nitric oxide[10], oxidative stress and heat-shock proteins (HSPs) such as HSP72 and heme oxygenase 1/HSP32[11], and TNF-α.[12] In particular, HSP70[13] and HSP32[11] are believed to contribute to the protective mechanism of hyperthermic preconditioning, as overexpression of these molecules has been shown to increase the resistance of the liver and other organs to ischemic injury.

The discovery that PGE_1 was effective in the treatment of fulminant hepatitis and primary graft nonfunction after liver transplantation[14,15] led to considerable interest in identifying the underlying hepatoprotective mechanisms of this activity. PGE_1 is well known as a vasodilator that acts directly on vascular smooth muscle and attenuates the vasoconstrictive stimuli.[16,17] PGE_1 also improves microcirculation by inhibiting platelet aggregation.[18] A previous study of PGE_1 by our group[19] showed that pretreatment with PGE_1 reduces the intracellular concentration of calcium and decreases the production of superoxide anion. In addition, we revealed that PGE_1 protects the liver against I/R injury by reducing leukocyte-endothelial cell adhesion via the downmodulation of ICAM-1 expression in the endothelium.[7] However, the precise mechanisms by which PGE_1 protects against I/R injury have not yet been determined.

Recently, large-scale gene-expression analysis using complementary DNA (cDNA) microarray has been gaining importance as an investigational tool in biology and chemistry.[20] Our mouse cDNA microarray technology allows rapid large-scale screening of the expression of thousands of genes in a single experiment.[20] However, interpreting the vast amounts of data generated by analyzing the simultaneous expression of thousands of genes creates both unique opportunities and substantial challenges. Despite these difficulties, previous investigators have used cDNA microarrays to clarify the mechanism of I/R injury.[21,22]

In the present study, we applied the cDNA microarray technique to determine the relationship between liver preconditioning and the mechanisms by which PGE_1 protects against I/R injury in vivo, with a particular focus on the HSPs.

MATERIAL AND METHODS

Animals

This study was conducted in accordance with the Animal Protection Guidelines of Yokohama City University, Japan. Male C57BL/6J mice (CLEA Japan Inc, Tokyo, Japan) aged 8 weeks and weighing 18–25 g were used. The mice were housed in wood chip–bedded cages in an air-conditioned room (24 ± 1°C) with controlled 12-hour light/dark cycles. The animals were permitted free access to laboratory chow and tap water and were not fasted before surgery.

Surgical Procedures and Experimental Design

Mice were anesthetized with diethyl ether. They were then placed in the supine position, and a 24-gauge catheter (Terumo Co., Tokyo, Japan) was inserted into the right jugular vein for the continuous infusion of drugs. The position of the catheter was fixed using an adhesive agent (Aron alpha A; Sankyo Co., Tokyo, Japan). Perfusion was performed using a syringe pump (Terumo STC-531; Terumo Co.) and a polyvinyl chloride tube (SF-ET0525; Terumo Co.) connected to the catheter. The drugs were continuously infused via the right jugular vein, starting 15 minutes before the induction of ischemia. The liver was made ischemic by clamping the left branches of both the portal vein and the hepatic artery, which prevented portal congestion, using a microvascular clip for 30 minutes (approximately 70% ischemia of the whole liver). The clip was then released to allow reperfusion of the liver. Three groups of mice were included in the study: the PGE_1 group, which received infusions of PGE_1 at 3 μg/kg per minute (PGE_1 was provided as a gift by the Ono Pharmaceutical Co., Ltd., Osaka, Japan); the NS group, in which the mice were infused with saline solution at a volume equivalent to that used for PGE_1; and the sham group,

in which the mice were laparotomized for 5 minutes but did not receive drug infusions. The animals were killed 0, 10, or 30 minutes after the start of reperfusion, and the left ischemic lobe of the liver was removed and drained of blood. Blood samples were collected via the inferior vena cava 180 minutes post-reperfusion, and serum transaminase concentrations were measured.

cDNA Microarrays

The RIKEN set of 18,816 full-length enriched mouse cDNA arrays[23] was used in these experiments. The arrays consisted of 21,168 clones, which were spotted onto a glass slide and divided into three multiblocks, including clones of β-actin cDNA and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) cDNA as positive controls and plant cDNA as a negative control. After exclusion of the control spots, 18,816 clones were used for the data analysis.

RNA Extraction and Preparation of Probe cDNA

Total RNA was extracted from the frozen liver tissue via the improved acid-guanidium-phenol-chloroform (AGPC) method, as described previously.[24] RNA from the PGE_1 and NS groups was labeled with the red fluorescent dye Cy3-dUTP (Amersham Pharmacia Biotech) during reverse transcription (RT). RNA from the sham group was labeled with blue fluorescent dye Cy5-dUTP (Amersham Pharmacia Biotech). RT was performed using Oligo-dT primer and SuperScript II (GIBCO/BRL) for 1 hour at 42°C. After RT, probe cDNA was prepared using 100 μg of RNA, as reported previously.[23]

Hybridization and Data Scanning

Probe cDNA from the NS and sham groups was mixed and simultaneously hybridized to the cDNA microarray. After filtering, the separate images from each fluorescent signal were scanned using a ScanArray 5000 confocal laser scanner (GSI Lumonics, Ottawa, Canada). The scanning images were analyzed using Scannalyze2 software (available online at http://rana.lbl.gov/EisenSoftware.htm).[25] Composite color images of the hybridization results were made by representing the Cy3 fluorescent image as red and the Cy5 fluorescent image as green, and then merging the two images. The data for each signal were evaluated using Scannalyze2 software.

Microarray Data Analysis

To ensure the accuracy of the data, we carried out the same experiment twice and extracted the data that were consistent. The data were normalized by the global normalization method using the Preprocessing Implementation for Microarray (PRIM) filtering program.[26] Briefly, the process consisted of three steps: first, the removal of spots that were flagged during the visual inspection of the microarray images; second, the removal of spots that had signal intensities lower than the threshold value; and third, the removal of spots that were beyond the threshold distance from the least-means-square line in a plot comparing the data from the two duplicate experiments. After the data were filtered, inappropriate spots were excluded, and the final results were subjected to further analysis when the correlation coefficient value for the duplicate experiments was greater than 0.7. The final data were represented as the log ratio (base 2); that is, $\log_2$(Cy3/Cy5). We obtained one set of log-ratio data for the NS group/sham group and another for the PGE_1 group/sham group. The data were transformed by substracting the $\log_2$ NS group/sham group from the $\log_2$ PGE_1 group/sham group, according to the following equation: $\log_2 PGE_1$ group/sham group $-\log_2$ NS group/sham group $= \log_2(PGE_1$ group/sham group)/(NS group/sham group) $= \log_2$ PGE_1 group/NS group.

For example, when the clone expression of the PGE_1 group was four times that of the NS group, the final data for the gene were expressed as $2(\log_2 4)$. Clones that were upregulated by two times or more, or downregulated by 0.5 time or less, were analyzed further. We applied hierarchical clustering to both axes by the weighted pair-group method with a centroid average using the software program Cluster.[27] The results were expressed using the computer program TreeView (available online at http://rana.lbl.gov/EisenSoftware.htm).[28] The genes indicated in red and green were upregulated and downregulated, respectively, in the PGE_1-treated group. The clone annotation was in accordance with the functional annotation of a full-length mouse cDNA collection (FANTOM).[29]

Real-time Quantitative RT-PCR With the LightCycler

The reliability of the cDNA microarray results was assessed by real-time quantitative RT–polymerase chain reaction (PCR) analyses. Real-time quantitative RT-PCR analyses of *HSP70* mRNA and *HSP86* mRNA were performed with a single-step PCR using the LightCycler instrument (Roche Diagnostics, Mannheim, Germany), as described previously.[30] HSP70-specific oligonucleotide primers D and E (sense and antisense, respectively) spanning 107 bp of sequence, and two fluorescence probes hybridizing

to the target sequence, were used (Table 1). HSP86-specific oligonucleotide primers F and G (sense and antisense, respectively) spanning 118 bp of sequence, and two fluorescence probes hybridizing to the target sequence, were also used (Table 1). To correct for the variation in *HSP70* mRNA values, real-time RT-PCR analysis of GAPDH was also carried out using primers and hybridization probes that generate a 307-bp fragment of *GAPDH* mRNA (Table 1). All of the primers and probes were synthesized and purified by reverse-phase high-performance liquid chromatography (Nihon Gene Research Laboratories, Sendai, Japan). The real-time PCR assays were repeated three times and mean values were used for the analysis. *HSP70* mRNA values were corrected with reference to the ratio of *GAPDH* mRNA to *HSP70/GAPDH* mRNA. *HSP86* mRNA values were also corrected in the same way.

Statistical Analysis

All data are expressed as mean ± standard deviation. Student's *t* test was used to determine statistically significant differences in serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values. Values of $P < 0.05$ were considered to be statistically significant.

RESULTS

Hepatocellular Injury After Reperfusion

Serum transaminase concentrations 180 minutes after I/R are summarized in Figure 1. The serum ALT concentration was significantly lower in the PGE_1 group (307 ± 60 IU/L, n = 4) than in the NS group (654 ± 176 IU/L; n = 4; $P < 0.05$). The serum AST concentration in the PGE_1 group (305 ± 87 IU/L; n = 4) was also significantly lower than that of the NS group (520 ± 136 IU/L; n = 4; $P < 0.05$). Serum hyaluronic acid concentrations did not differ significantly between the two groups (data not shown).

Cluster Analysis of Altered Gene-Expression Patterns

After filtering for elementary unreliable data, we identified 7,859 complete clones that were present at all three time points (0, 10, and 30 minutes) of reperfusion after 30 minutes of ischemia in both groups. Of these, 160 clones were upregulated by a log ratio of 1 or more (two times or more) or downregulated by a log ratio of −1 or less (0.5 time or less). To investigate the early events after I/R, we examined 160 clones that showed different expression levels in the NS and PGE_1 groups. The hierarchical clustering of these clones 0, 10, and 30 minutes after I/R is shown in Figures 2 through 5.

Clones of the HSP family, including HSP86 1-kDa (*HSP86*), HSP DNAJ-like 2, HSP70 5-kDa protein (*HSP70*), and 78-kDa glucose-regulated protein (*GRP78*), were upregulated at the end of the ischemic period (0 minutes postreperfusion) (Figs. 2 and 5). In addition, the glutathione *S*-transferase clone was upregulated 0 minutes postreperfusion and the catalase clone was upregulated 10 minutes postreperfusion (Figs. 2, 4, and 5). These enzymes are involved in detoxifying free radicals. Clones encoding ATP

Table 1. Sequences of primers and hybridization probes

mRNA		Sequence (5′–3′)	Length (mer)
HSP70			
Primers	Sense (D)	CAAGTGGCTGTTTACTGCTTT	21
	Antisense (E)	ACACCCTGACCCACCTTT	18
Probes	Donor	TTTAAAATAGCCAATTCCTCCTCTCCCTG-**FL**	29
	Acceptor	**LC**-CCCCAAGACATGTGAGCAACTGCTAAT-**P**	27
HSP86			
Primers	Sense (F)	CAAGAGGTTGATAGAGCGTTT	21
	Antisense (G)	AGCCATCTTAATTTGGTCTCC	21
Probes	Donor	GACGTAACGTAACCTACTGTTCATGTTTGCTCT-**FL**	33
	Acceptor	**LC**-GTCTGAAGTGTTTAGCTGTTGAGCTGGATTC-**P**	31
GAPDH			
Primers	Sense	TGAACGGGAAGCTCACTGG	19
	Antisense	TCCACCACCCTGTTGCTGTA	20
Probes	Donor	TCAACAGCGACACCCACTCCT-**FL**	21
	Acceptor	**LC**-CACCTTTGACGCTGGGGCT-**P**	19

FL, fluorescein; LC, LightCycler-Red 640; P, phosphate group.

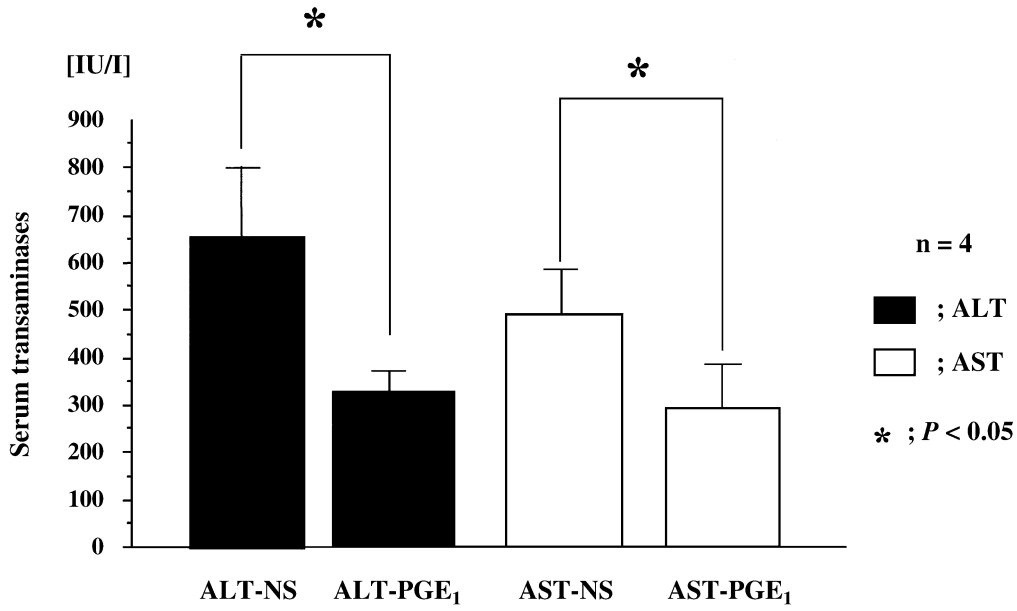

Fig. 1. Comparison of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels 180 minutes postreperfusion. The black box represents the prostaglandin E_1 (PGE_1) group, and the white box represents the NS group. ALT and AST levels in the PGE_1 group decreased significantly compared with the NS group. All data are expressed as mean ± SD ($n = 4$), $^*P < 0.05$ versus the value in the corresponding NS group.

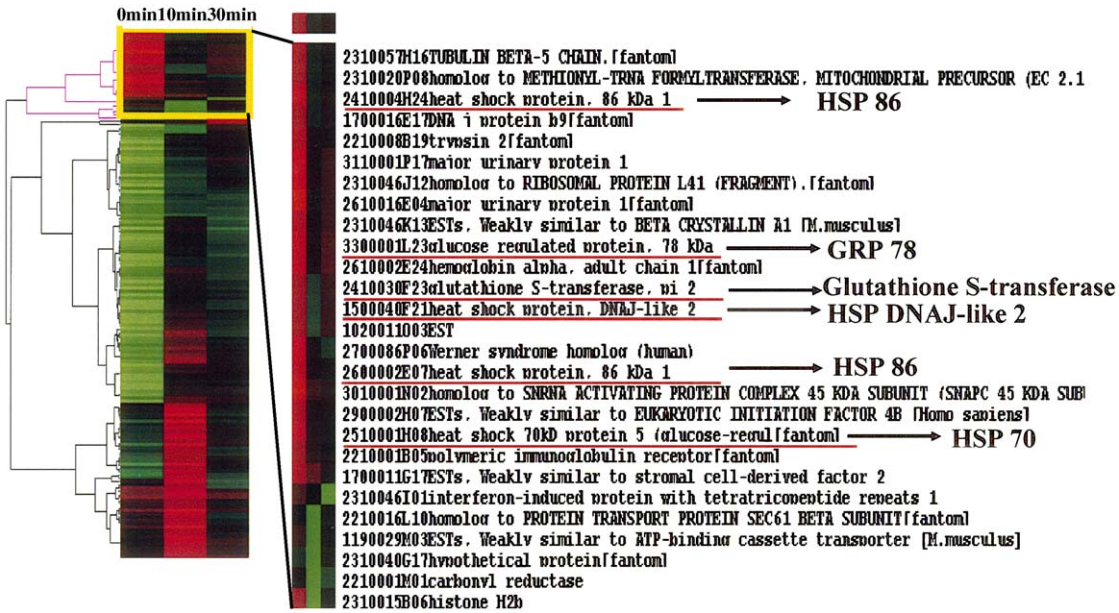

Fig. 2. Cluster analysis of altered gene expression in prostaglandin E_1 (PGE_1)-treated mice after liver reperfusion. The columns on the left show the gene-expression levels 0, 10, and 30 minutes postreperfusion. The portion highlighted in yellow is shown in greater detail in the column on the right. The genes indicated in red were upregulated in the PGE_1 group, whereas those shown in green were downregulated. The red section at the top of the 0 minutes column indicates a gene cluster that was upregulated in the PGE_1 group. This cluster includes the heat-shock protein (HSP) genes *HSP70*, *HSP86*, *GRP78*, and glutathione *S*-transferase (underlined in red).

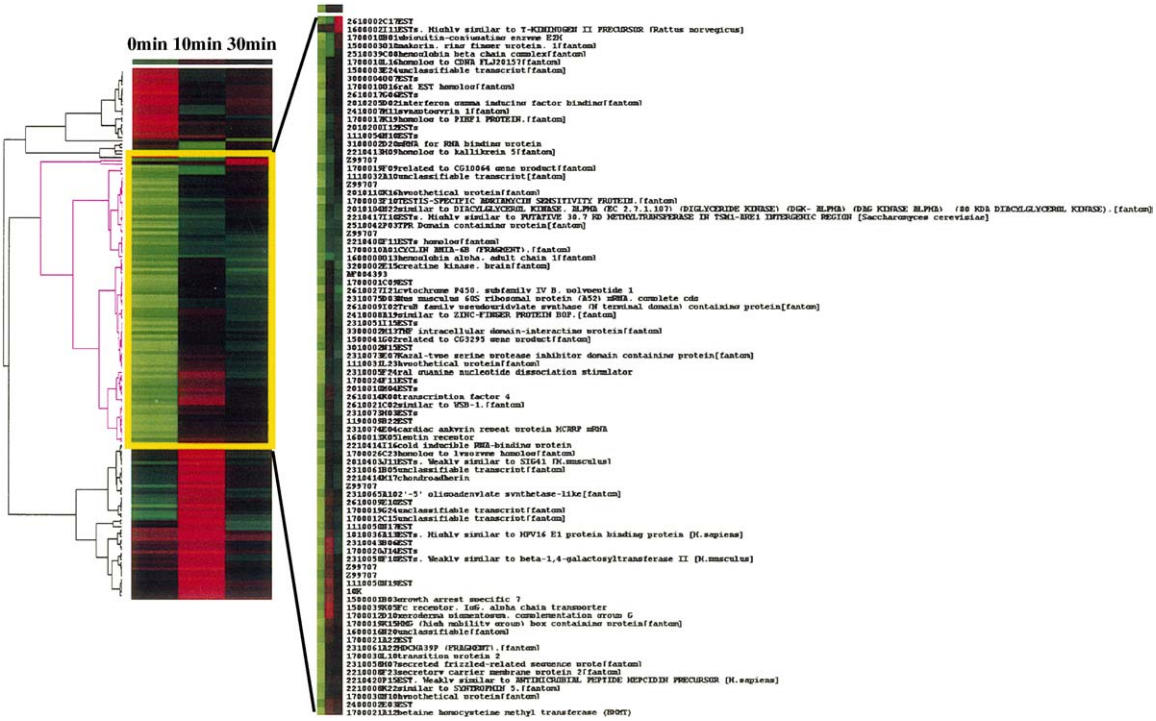

Fig. 3. Cluster analysis of gene-expression patterns that were altered ≤0.5-fold in the prostaglandin E_1 (PGE_1) group 0 minutes postreperfusion. The layout of the figure is as described in Figure 2. The green section in the middle of the 0 minutes column indicates a gene cluster that was downregulated in the PGE_1 group. This cluster did not include any heat-shock protein genes.

synthase (mitochondrial), apoptosis inhibitor, and scavenger receptor were all upregulated 10 minutes postreperfusion (Figs. 4 and 5).

The middle section of the left-hand column (0 min) in Figure 3 was green, indicating that this cluster (comprising 85 clones) was downregulated in the PGE_1 group. HSP clones were not contained within this cluster.

Verification of cDNA Expression Array Results of Real-time Quantitative RT-PCR With the LightCycler

The expression levels of *HSP70* and *HSP86* at 0 minutes postreperfusion were examined by real-time PCR. The corrected *HSP70* mRNA values (*HSP70/GAPDH* mRNA ratio) were 1.11×10^{-1} and 5.87×10^{-1} for the NS and PGE_1 groups, respectively. In addition, the corrected *HSP86* mRNA values (*HSP86/GAPDH* mRNA ratio) were 0.759×10^{-1} and 6.34×10^{-1} for the NS and PGE_1 groups, respectively. In general, these analyses showed results consistent with those obtained with cDNA arrays. Figure 6 shows real-time RT-PCR with the LightCycler analysis of *HSP70* and *HSP86*.

DISCUSSION

In the present study, as in many previous reports, PGE_1 ameliorated I/R injury to the liver, and serum AST and ALT levels 180 minutes after I/R in the PGE_1-pretreated group were significantly lower than those in the control group. The microarray analysis identified 160 clones, of which the expression patterns were notably altered by PGE_1 administration. HSPs, which were the particular focus of this study, showed significant changes in gene expression immediately after I/R.

The cytoprotective effects of PGE_1 against I/R injury in the liver have been well documented, as mentioned earlier.[7,16–19] In a clinical setting, Sugawara and colleagues[31] reported that the cytoprotective effect of PGE_1 against I/R-induced liver injury was the result of the regulation of IL-6 production. However, to our knowledge, no previous reports have considered the relationship between PGE_1 and HSPs. By contrast, several studies have investigated the relationship between preconditioning effects and HSPs, and geranyl-geranyl-acetone (GGA) has been reported to have a pharmacologic preconditioning effect.[32] Our results demonstrated that PGE_1 shows

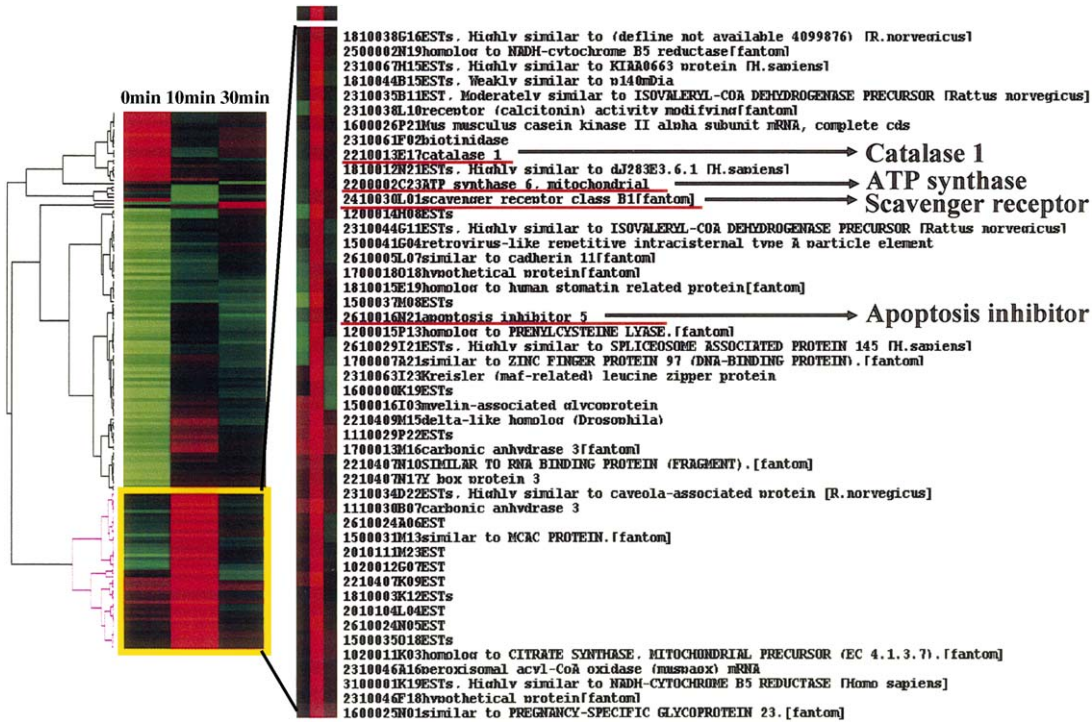

Fig. 4. Cluster analysis of altered gene-expression patterns in prostaglandin E_1 (PGE_1)-treated mice 10 minutes after liver reperfusion. The layout of the figure is as described in Figure 2. The red section at the bottom of the 10 minutes column indicates a gene cluster that was upregulated in the PGE_1 group. This cluster includes the genes encoding catalase, ATP synthase, scavenger receptor, and apoptosis inhibitor (underlined in red).

similar activity, which induces the expression of HSPs.

Kume and colleagues[33] reported that ischemic preconditioning of the rat liver could induce HSP production and attenuate liver damage, improving the restoration of hepatic function during reperfusion and resulting in 100% postischemia survival. HSPs might contribute to the correct folding of proteins following reperfusion and could therefore be crucial for cellular survival after I/R.[33] In the present study, we observed increased HSP gene expression in the PGE_1 group compared with the NS group during ischemia. Several HSP clones were upregulated by the end of the 30-minutes ischemic period before reperfusion, including the HSP70 family (*HSP70* and *GRP78*), *HSP86*, and HSP DNAJ-like 2 (Figs. 3 and 4) clones. These results clearly demonstrated that intravenous pretreatment with PGE_1 caused the liver to transiently overproduce HSPs. This priming effect (that is, pharmacologic preconditioning) might protect against subsequent injury from I/R.

HSPs are involved in the cellular stress responses that are induced by elevated temperature—hence the name "heat-shock" proteins.[34] In addition, other cellular stressors, including free radicals, TNF-α, I/R, sepsis, and acute inflammation, have also been shown to induce HSPs.[35] HSPs play an important role in the intracellular transport of proteins (chaperone function), the protection of protein structure, and the switching of certain receptors, and the heat-shock response seems to protect cells against various forms of stress.[36,37]

I/R injury induces MMPT prior to apoptosis, and the inhibition of MMPT prevents many apoptotic phenomena. Miyoshi and Gores[38] reported that MMPT causes the mitochondria to release cytochrome *c*, which leads to caspase-9 activation in the presence of apoptosis protease-activating factor 1 (Apaf-1) and ATP. Activated caspase 9 then activates caspase 3, which triggers the structural changes of apoptosis, resulting in DNA fragmentation. Although the mechanisms by which HSPs ameliorate I/R injury to the liver are not fully understood, several hypotheses have been put forward. HSP70 binds to Apaf-1 directly and prevents cytochrome *c*/dATP–mediated caspase-9 activation, thereby suppressing apoptosis

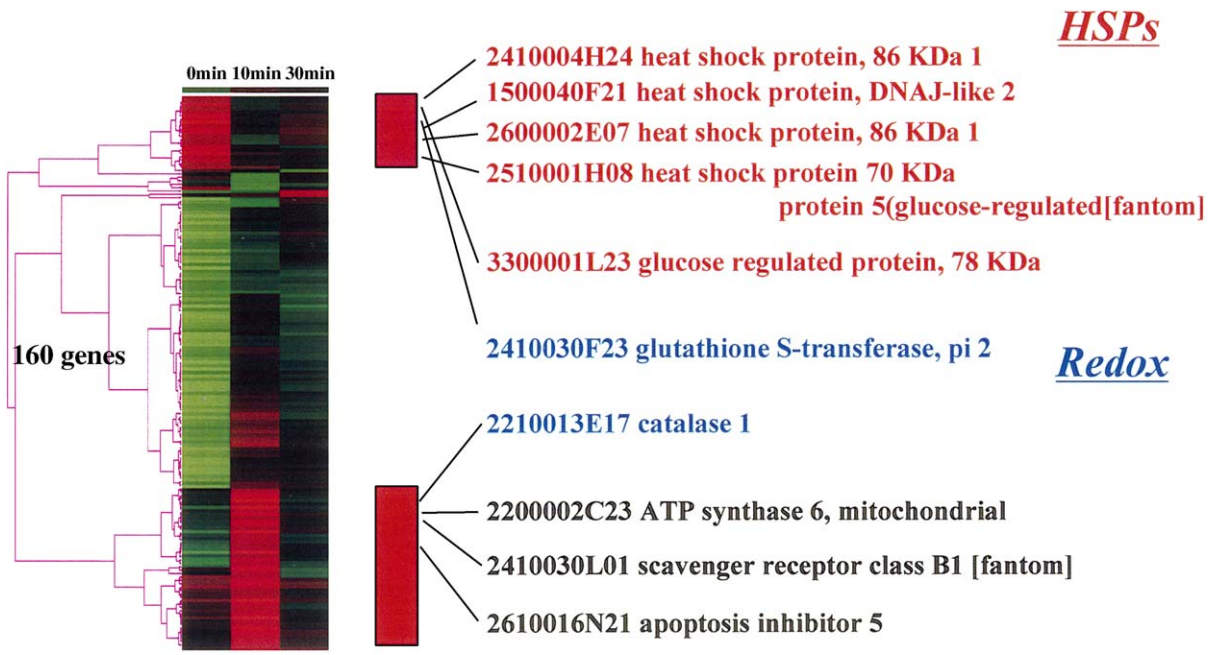

Fig. 5. Cluster analysis of altered gene expression in prostaglandin E_1 (PGE_1)-treated mice. The layout of the figure is similar to that described in Figure 2. HSP-related genes and glutathione *S*-transferase were upregulated in the PGE_1 group 0 minutes postreperfusion. The genes encoding catalase, ATP synthase, scavenger receptor, and apoptosis inhibitor were upregulated in the PGE_1 group 10 minutes postreperfusion.

by directly associating with Apaf-1.[39] Furthermore, the binding of HSP90 to Apaf-1 inhibits cytochrome *c*–mediated oligomerization of Apaf-1 and thereby suppresses the activation of procaspase 9.[40] It is likely that HSPs induced by PGE_1 before treatment protect the liver against I/R injury by inhibiting apoptosis; in other words, PGE_1 probably acts as an inhibitor of apoptosis in the mouse I/R model.

In this experiment, the cDNA microarray revealed changes in other genes in addition to the HSPs, which were the main focus of our study. Within the PGE_1 group, glutathione *S*-transferase was upregulated 0 minutes postreperfusion (Figs. 2 and 5), and catalase, scavenger receptor, ATP synthase (mitochondrial), and apoptosis inhibitor were upregulated 10 minutes postreperfusion (Figs. 4 and 5). The upregulation of clones involved in antioxidant defense (such as glutathione *S*-transferase and catalase) might play an important role in minimizing I/R injury. Numerous studies have suggested that the abundance of ROS generated after reperfusion might contribute to the initiation of postischemic liver injury and to subsequent inflammatory infiltration.[41–43] This theory is supported by studies using freeradical scavengers, which provide partial protection against I/R injury.[44] In addition, glutathione *S*-transferase protects against liver injury resulting from partial hepatectomy or exposure to hepatotoxic compounds.[45]

In the present study, we were unable to accurately determine which clones were downregulated by PGE_1 treatment. Although PGE_1 inhibited the expression of adhesion molecules (such as ICAM-1) and prevented an increase in the intracellular calcium concentration,[19] the results were not conclusive. We were unable to confirm the results of our previous study,[7] because the ICAM-1 clone was not included in the cDNA microarrays in the present experiment. Further attempts should be made in the future to identify the downregulated clones and to determine their functional significance.

Finally, we used the mRNA extracted from all tissues of the liver as the specimen of this study. However, these tissues contain not only hepatocytes but also a mixture of Kuppfer cells, Ito cells, and bile duct cells, among others. Of course, because it is considered that I/R occurs while these are interacting with each other, it is probably preferable to observe the changes in the gene expression of each type of cell separately. In order to do this, however, it is necessary to carry out the laser microdissection and

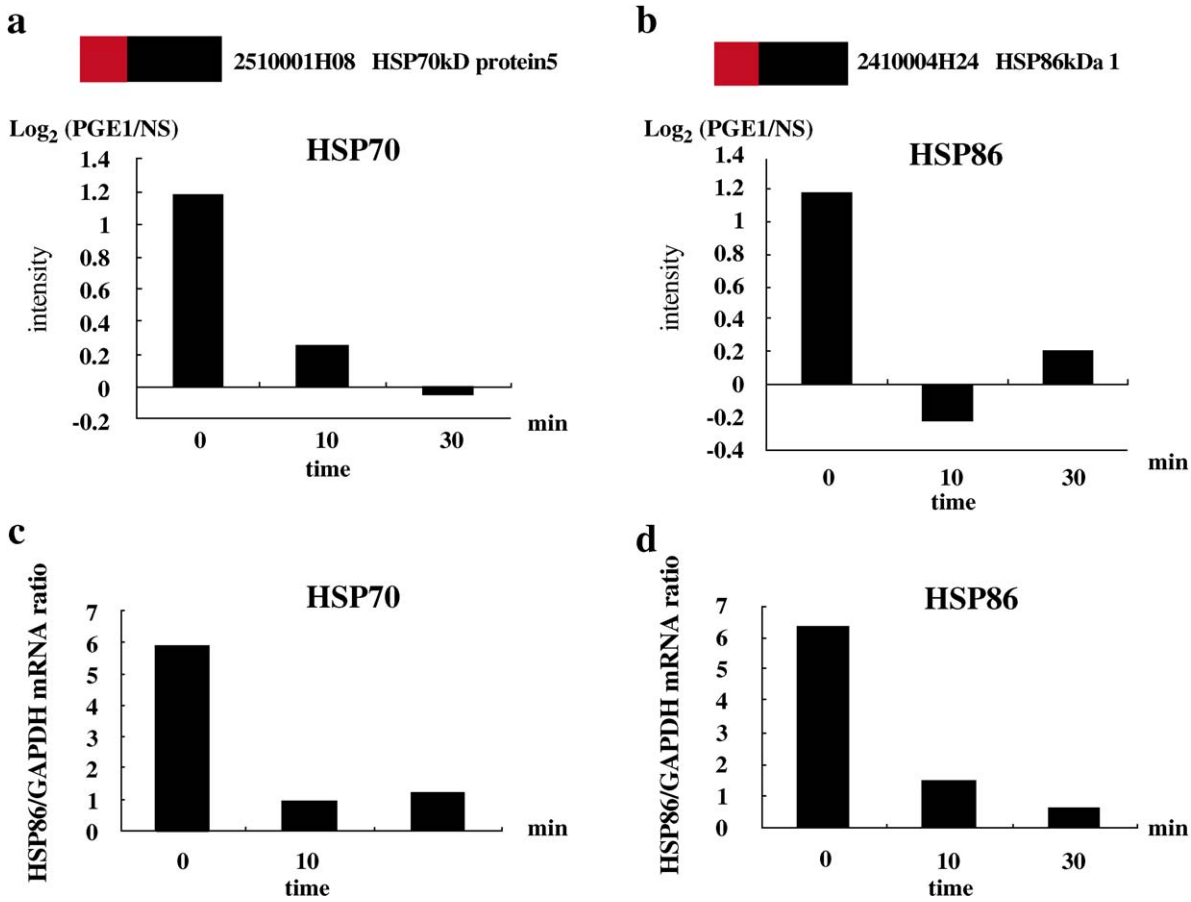

Fig. 6. Real-time reverse transcription–polymerase chain reaction (RT-PCR) with the LightCycler analysis of HSP70 and HSP86. (*a*, *b*) Semiquantitative analysis of RT-PCR for HSP70 and HSP86. HSP70 and HSP86 are upregulated in the prostaglandin E_1 (PGE_1) group at 0 minutes postreperfusion. (*c*, *d*) Quantitative real-time RT-PCR for HSP70 and HSP86. The results of semiquantitative analysis by cDNA microarray were compatible with those of quantitative real-time RT-PCR with LightCycler.

linear amplification required for mRNA extraction, and it is believed that these may cause many alterations in the gene expression of these cells. We therefore consider that it was unavoidable to use all liver tissues, as is done also by many other modern researchers.

CONCLUSION

PGE_1 stimulates the expression of HSPs immediately after I/R, which protects against liver damage. We believe that the therapeutic effect of PGE_1 during I/R involves the overexpression of HSPs, which inhibit apoptosis through the mitochondrial apoptotic pathway. PGE_1 therefore appears to have antiapoptotic and pharmacologic preconditioning effects. Our results indicate that HSPs might play an important role in ameliorating the effects of PGE_1 against I/R-induced liver injury.

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Intraperitoneal Treatment With Dimethylthioampal (DIMATE) Combined With Surgical Debulking Is Effective for Experimental Peritoneal Carcinomatosis in a Rat Model

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The goal was to evaluate the efficiency of intraperitoneal administration of dimethylthioampal (DIMATE), a cellular apoptosis inducer, combined, or not, with cytoreductive surgery on rats with peritoneal adenocarcinomatosis. Peritoneal carcinomatosis was induced in rats by intraperitoneal injection of adenocarcinoma cell line DHD/K12/pro B. Intraperitoneal DIMATE was given at 17.3 mg/kg. Rats were randomized into five groups of eight animals, regarding the day of treatment (2 days or 20 days after peritoneal carcinomatosis induction) and the combination with cytoreductive surgery. All rats were killed at 30 days to evaluate carcinomatosis extent (quantitative score) and ascites volume. The quantitative score of carcinomatosis and the ascites volume were significantly reduced in the groups treated with DIMATE at day 2 ($P = 0.005$ and $P < 0.001$, respectively) and when DIMATE was used with cytoreductive surgery at day 20 ($P = 0.009$ and $P < 0.001$, respectively). Cytoreductive surgery or DIMATE used alone at day 20 had no significant influence. The intraperitoneal DIMATE administration at day 20, when not combined with surgery, had no significant influence on carcinomatosis extent or on ascites volume. Intraperitoneal DIMATE appeared to be an efficient drug in the prevention or treatment of peritoneal carcinomatosis when combined with cytoreductive surgery or when it was given by intraperitoneal route, before the development of macroscopic peritoneal carcinomatosis. It appears to be a promising therapeutic agent to be investigated in a human phase I trial in peritoneal carcinomatosis.
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Key words: Cancer, chemotherapy, surgery, ascites

Colorectal adenocarcinoma is one of the most frequent cancers in occidental countries. Peritoneal carcinomatosis is a common evolution of cancer of the gastrointestinal tract and has been regarded a terminal disease with a short median survival.[1,2] Palliative systemic chemotherapy has shown encouraging tumor response rates but with no improvement in survival.[3,4] However, over the past decade, there has been a renewed interest in peritoneal surface malignancies, and new multimodal therapeutic approaches have been proposed, including peritonectomy procedures,[5] cytoreductive surgery, intraperitoneal chemohyperthermia,[6,7] and immediate postoperative intraperitoneal chemotherapy.[8]

This aggressive but comprehensive locoregional treatment appears to be effective in the treatment of colorectal carcinomatosis.[9–11] To improve survival results, new therapeutic agents delivered by intraperitoneal administration can be used. One of them, dimethylthioampal (DIMATE), an apoptosis inducer, has already been tested and has proved its efficiency in different tumor models.[12–16]

The aim of this study was to evaluate the tolerance and the efficiency of intraperitoneal administration

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of DIMATE combined, or not, with cytoreductive surgery in an animal model of peritoneal carcinomatosis.

MATERIAL AND METHODS

Animal Model

This experimental protocol was carried out in accordance with the guidelines of the declaration of Helsinki for biomedical research. The animal tumor model established by Martin et al.[17] was used. The rat (female BD IX rat, 6 weeks old; Iffa Credo, Lyon, France; weight, 150–200 g) were kept under standard conditions (free access to pelleted chow and water, 24°C room temperature, 12-hour day/night cycle) in the experimental animal facility.

Tumor Cell Implantation

The adenocarcinoma cell line DHD/K12/pro B was used to induce peritoneal carcinomatosis. This cell line originated from a 1,2-dietylhydrazine–induced colon adenocarcinoma in syngenic BD IX rats.[18] Cells were grown in Ham F10 medium (GIBCO BRL, Eragny, France) supplemented with 10% fetal calf serum penicillin A (100 UI/ml), streptomycin (100 µg/ml), and amphotericin B (1.25 µg/ml) at 37°C in a humidified atmosphere with 5% CO_2.

Tumor cells (1 × 10E6 cells) were injected into the peritoneal cavity in a 4-ml cell suspension (Ham F10).

Compounds

DIMATE is an apoptogenic agent derived from a lead compound ATE.[14] It induces cellular apoptosis via a nonreversible enzymatic suicide action on aldehyde dehydrogenase. This action inhibits the transformation of a proapoptotic agent (methional)[15] to a nonapoptotic agent (4-methylthio-2-oxobutanoic acid, the ketoacid of methionine).[16]

DIMATE was used in an ethanol solution (5%) (the synthesis of the DIMATE has been described by authors[14]).

Dose of DIMATE

The DIMATE dose that kills half of the cellular culture was previously determined at 2.7 µmol/L. First, toxicity of DIMATE was studied by the injection of different doses into normal rats to determine the dosage of DIMATE that killed 50% of healthy rats (LD_{50}). The DIMATE dose used was the maximal dose without any mortality.

DIMATE was administered into the peritoneal cavity at a concentration of 17.3 mg/kg (volume of injection, 4 ml).

Treatment and Groups

The rats were randomized into five groups determined by the day of DIMATE injection and the combination with cytoreductive surgery (n = 8 per group): group 1, no treatment after intraperitoneal injection of cancer cells (control group); group 2, surgery (maximal cytoreductive surgery), injection of saline serum at day 20 (surgical control group); group 3, injection of DIMATE (intraperitoneal) at day 2; group 4, injection of DIMATE at day 20; and group 5, surgery (maximal cytoreductive surgery), injection of DIMATE (intraperitoneal) at day 20. Forty rats were randomized into these five groups after the injection of tumor cells.

Surgical Treatment

The rats were anesthetized with an intramuscular injection (left leg) of ketamine (10 mg/kg). Maximal cytoreductive surgery was performed after cutaneous shaving and use of disinfectant (Betadine). By median laparotomy, cytoreductive surgery, including splenectomy and greater omentectomy, was performed. Electrocoagulation was performed on lesions when resection was impossible. Tumor nodules on the small bowel and mesentery were not treated. The laparotomy was closed (two layers) with Prolene 000.

Assessment of Carcinomatosis and Adverse Effects

The rats were kept in a single cage. The occurrence of postoperative adverse effects (loss of appetite, lethargy, and wound infection) was assessed once a day. Rats were killed under general anesthesia 30 days following cancer cell injection and subsequently underwent autopsy to identify peritoneal carcinomatosis, with qualitative and quantitative assessment of metastatic tumor lesions.

Carcinomatosis was assessed using a carcinomatosis score. Abdomen was divided into 18 regions (Fig. 1). The lesion size of the largest implant was scored in each abdominal region. Implants were scored as lesions size 0 through 4 (S-0 to S-4) (Fig. 2). S-0 indicates that no implants were seen throughout the region; S-1, implants that were visible up to 1 mm in greatest diameter; S-2, nodules greater than 1 mm and up to 2 mm; S-3, implants greater than 2 mm; and S-4, confluent lesions. This method quantified

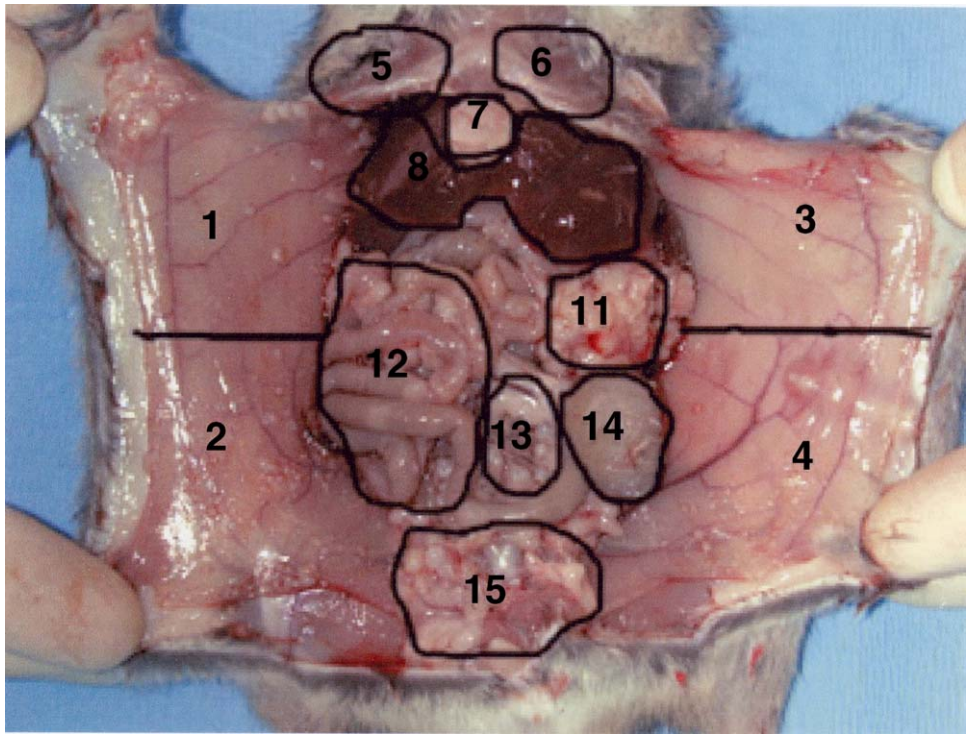

Fig. 1. Division of peritoneal cavity into 18 abdominopelvic regions for the assessment of peritoneal carcinomatosis extent in rats.

the extent of disease within each region and could be summed up as a numerical score (carcinomatosis score) that varied from 0 to 72.

Carcinomatosis was assessed during the autopsy and at the day of surgery for rats that underwent cytoreductive surgery. All rats were weighed before

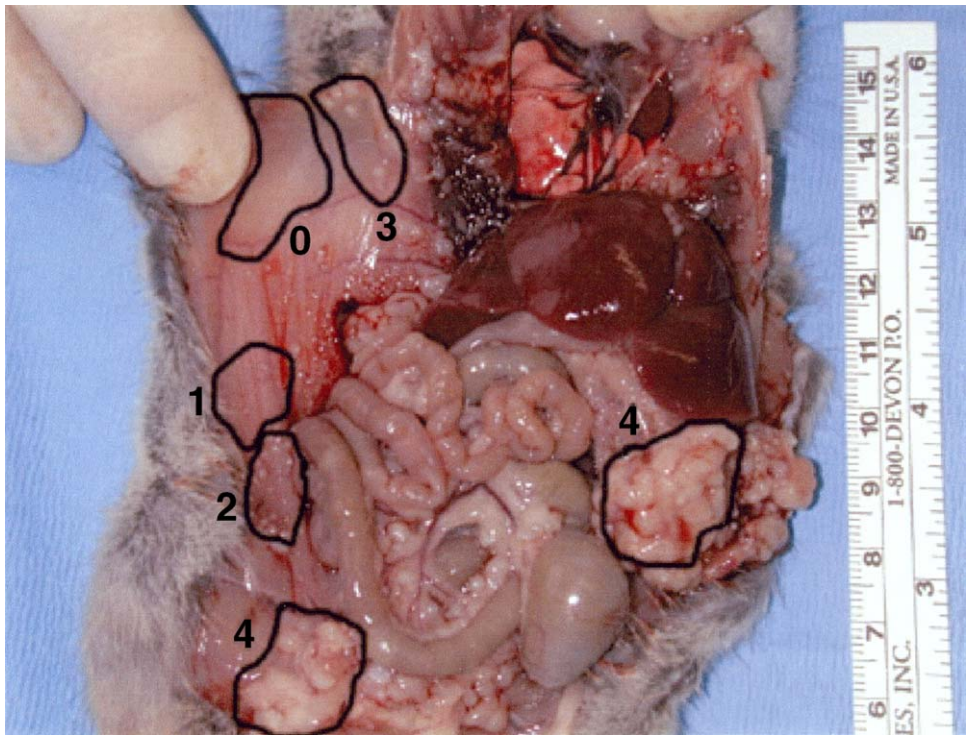

Fig. 2. Example of score establishment regarding the size of tumor nodules in abdominopelvic region for the assessment of carcinomatosis in rats.

being killed and after evacuation of blood and ascitic fluid.

Statistic Analysis

Groups (volume of ascites, carcinomatosis score) were compared using the *t* test (StatView for Windows) as appropriate. A value of $P < 0.05$ was considered statistically significant. The volume of ascites and carcinomatosis score were expressed as mean ± SD.

RESULTS

Global Mortality and Morbidity

No rat died before the time at which they were to be killed. Extreme bradycardia appeared in seven of eight rats in the group treated with cytoreductive surgery combined with DIMATE. Two rats had a small bowel obstruction the day of sacrifice.

Global Results of Carcinomatosis

Abdominal carcinomatosis was detected the day of sacrifice in 99.5% of rats with no significant difference between groups. Histologic examination confirmed for all rats the development of peritoneal carcinomatosis.

Effect on Carcinomatosis Score

The carcinomatosis score and SD are reported in Figure 3. The mean score of carcinomatosis in the control group was 56.4 (SD, 9.1). It was 54.1 (SD, 8.5) in the surgery control group. DIMATE administration on day 2 significantly decreased the carcinomatosis score, which was 28.3 (SD, 22.3) ($P = 0.005$).

Cytoreductive surgery combined with DIMATE at day 20 also significantly decreased the global carcinomatosis score, which was 28.3 (SD, 24.7) ($P = 0.009$). Carcinomatosis score was not significantly affected when DIMATE alone was administrated at day 20 ($P = 0.87$) or when surgery was performed alone ($P = 0.62$).

Effect on Hemorrhagic Ascites

The mean volume of ascites in the control group was 35.0 (SD, 3.2) and 6 (SD, 5.6) in the surgery control group (Fig. 4). DIMATE administration at day 2 significantly decreased ascites volume ($P < 0.001$), which was 1 (SD, 1.8), whereas DIMATE administration at day 20 did not significantly influence ascites volume ($P = 0.26$) which was 27 (SD, 14.1).

Surgery alone or combined with DIMATE significantly decreased ascites volume ($P < 0.001$ and $P < 0.001$, respectively), which were 6 (SD, 5.6) and 3 (SD, 2.6), respectively. Ascites volume was not significantly different between these two groups ($P = 0.25$).

Ascites volume was significantly lower in the group treated with DIMATE administration at day 2 than in the group treated with surgery alone ($P = 0.03$)

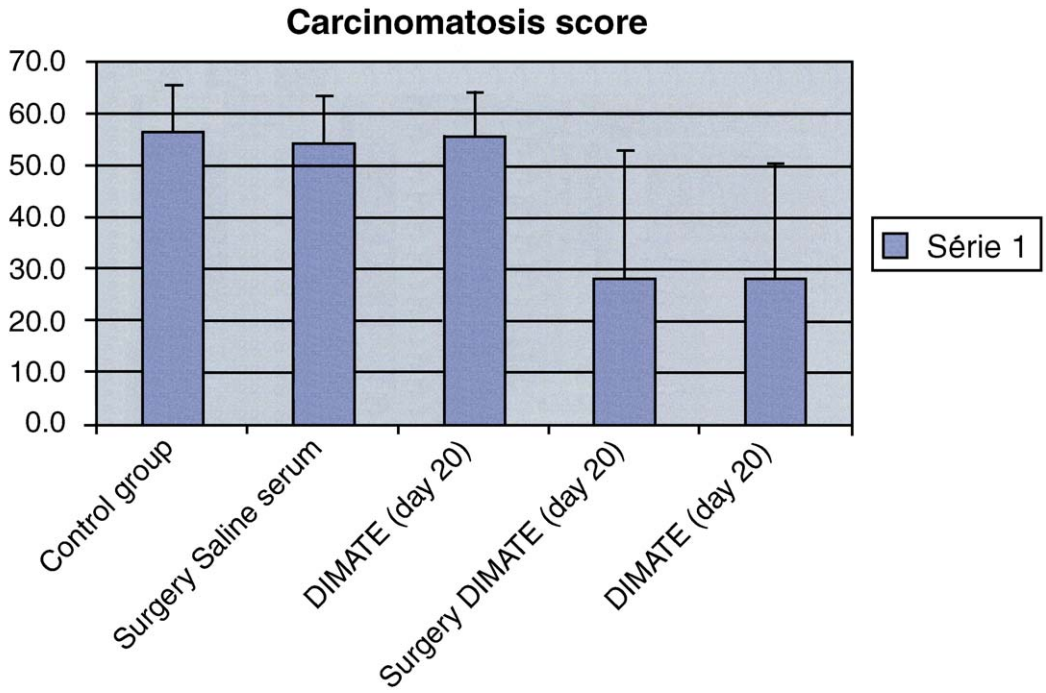

Fig. 3. Carcinomatosis score.

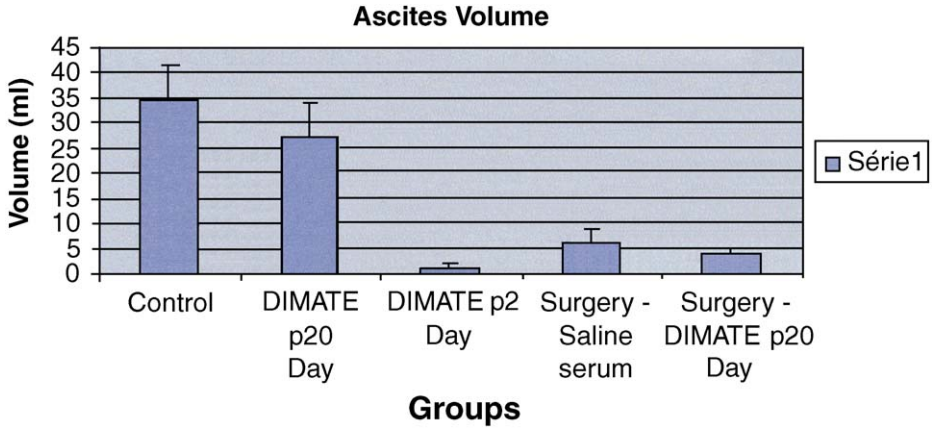

Fig. 4. Ascites volume (after sacrifice).

and with surgery combined with DIMATE at day 20 ($P = 0.04$).

DISCUSSION

Peritoneal carcinomatosis remains an unresolved problem in gastrointestinal cancer. Peritoneal carcinomatosis is detected in approximately 10% of patients at the time of resection of the primary tumor and, after the liver, the peritoneal surfaces are the most common site of recurrence after curative colorectal cancer resection. In colon carcinoma, tumor recurrence rates within the tumor bed or at the mesenteric site are reported to range between 8.5% and 25.6%.

In a multicenter prospective study that included 370 patients with carcinomatosis from nongynecologic malignancies, the median overall survival was 5.2 months for patients with colorectal cancer, and all patients with this condition had a lethal outcome.[2] Hope comes from new locoregional aggressive treatment combining cytoreductive surgery and perioperative intraperitoneal chemotherapy with the report of promising survival results.[9,10,19–21]

New therapeutic agents for intraperitoneal administration need to be tested to improve locoregional control of carcinomatosis. DIMATE, an apoptotic inducer, has been successfully used for the treatment of murine lymphoid cells but has not been previously tested on an animal model.[14–16]

Its administration appeared to be nontoxic for rats even when a high dose is used. The concentration used was 100 times higher than the concentration that killed 50% of cultured cells. No rat died with this dose. The bradycardia observed in the surgery group combined with DIMATE was not explained but was not lethal. This complication was not observed in the other groups. It can be explained in part by a higher systemic level at DIMATE following cytoreductive surgery. The extent of cytoreductive surgery did not seem to modify the pharmacokinetics of intraperitoneal anticancer drugs. The pharmacologic barrier between the abdominopelvic cavity and plasma did not seem to be directly related to an intact peritoneum. But with such systemic toxic effects, evaluation of the effects of cytoreductive surgery on pharmacokinetics of intraperitoneal DIMATE is needed.

In the present experiment, two types of DIMATE administration were used. The administration of a single dose of DIMATE at day 2 significantly decreased carcinomatosis extent and ascites volume, whereas no beneficial effect was observed when DIMATE was given at day 20. The treatment group mimics the clinical situation when free cancer cells can attach to the peritoneal surface because of manipulation by the surgical intervention. In this condition, it was possible to prevent or limit the development of peritoneal carcinomatosis. Similar results were achieved in other experimental studies using intraperitoneal cytotoxic agents.[22]

Groups treated with cytoreductive surgery closely mimic the clinical findings of an established macroscopic advanced carcinomatosis. In this condition, extensive cytoreductive surgery (even if debulking could not be complete) combined with intraperitoneal DIMATE injection at day 20 significantly reduced carcinomatosis extent and ascites volume, whereas DIMATE or cytoreductive surgery alone did not have the same effective effects (even if cytoreductive surgery alone significantly decreased ascites volume). Theoretically, cytoreductive surgery is performed to treat macroscopic disease and intraperitoneal DIMATE is performed to treat microscopic residual disease, to try to eradicate the disease completely during one procedure. When resection does

not allow sufficient reduction in tumor volume, intraperitoneal chemotherapy or DIMATE does not seem to be efficient.

The therapeutic approach of peritoneal carcinomatosis might have failed because DIMATE did not reach central parts of established tumor nodules that were not removed. Some authors using the same design of experiment described the same limitation.[22] As in the present study, the study was a multimodal treatment concept combining cytoreductive surgery with intraperitoneal administration of chemotherapy of anticancer agents. This combination was the most efficient, but a total cure was not achieved.

In human carcinomatosis, such treatments are effective only if a complete or subcomplete reduction of carcinomatosis is possible. When this complete reduction is possible, local chemohyperthermia can be used.[6,11]

Even though the effect of DIMATE combined with cytoreductive surgery is promising, data cannot be simply transferred to human studies. The complete toxicity of potential adverse effects on animals is being studied. This has to be taken into consideration in planning novel studies to investigate the beneficial effects of DIMATE in combination with different antineoplasic drugs and with hyperthermia.

CONCLUSION

Under experimental conditions, DIMATE appeared to be an efficient drug in the treatment or prevention of peritoneal carcinomatosis from colorectal origin. It significantly reduced the extent of carcinomatosis when it was administered before the development of carcinomatosis or when it was combined with cytoreductive surgery for established carcinomatosis. Pharmacokinetics studies are needed to evaluate potential influence of surgery on systemic levels after intraperitoneal administration.

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Hand-Sewn Coloanal Anastomosis for Distal Rectal Cancer: Long-Term Clinical Outcomes

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As the oncologic safety of coloanal anastomosis (CAA) has been proved by many other authors, the incidence of CAA following ultralow anterior resection has increased. The purpose of this study is to evaluate the functional outcome and complications of patients who underwent ultralow anterior resection and CAA for distal rectal cancer. Fifty-seven patients underwent CAA following ultralow anterior resection between July 1997 and November 2003. Forty-four patients, who were followed up more than 6 months after diverting ileostomy closure, were evaluated for recurrence, complications, and functional outcomes. The mean follow-up period was 36.3 ± 22.8 months (range, 8–83 months). The complications were multiple fistula (n = 3), fistula with anal stenosis (n = 1), local recurrence with anal stenosis (n = 1), and anal stenosis (n = 7). Anal incontinence (Kirwan grade III) was noted in 14 patients, and bowel movements were observed more than six times per day in 16 patients. Overall recurrence occurred in six patients (13.6%). The 5-year survival rate was 85.3%, and the disease-free 5-year survival rate was 73.3%. Although CAA in patients with rectal cancer provides excellent long-term survival, a low risk of recurrence, and tolerable function, complications and poor functional outcomes of CAA do occur. Therefore, the choice of this method should be considered carefully. (J GASTROINTEST SURG 2005;9:775–780)

KEY WORDS: Rectal cancer, hand-sewn coloanal anastomosis, ultralow anterior resection

The first sphincter-saving excision of the rectum and anastomosis of the colon to the external sphincter was performed by Kraske[1] in 1875. However, this procedure was not popular because of high complication rates and poor functional results. After this period, the method of curative operation for rectal cancer has been developed according to expanded knowledge of pelvic anatomy. In 1982, Parks and Percy[2] reported the technique of anastomosis of the colon to the anal canal in patients with distal rectal cancer. They reported acceptable complications and a low rate of pelvic abscess, whereas long-term disease-free survival was comparable to that in abdominoperineal resection. As the oncologic safety of coloanal anastomosis (CAA) has been proven by many other authors,[3–6] the use of CAA following ultralow anterior resection for low-lying rectal cancer has increased, enhancing the patients' quality of life. Thus, we evaluated the functional outcome, complications, and cancer recurrence rate of patients who underwent ultralow anterior resection and CAA for distal rectal cancer.

MATERIAL AND METHODS

Between July 1997 and November 2003, the records were reviewed of 57 patients who underwent CAA following ultralow anterior resection for distal rectal cancer. All operations were performed in the same university hospital by one senior surgeon. Eligible patients had histologically confirmed primary adenocarcinoma of the rectum. Patients with possible invasion into adjacent organs, such as the vagina, prostate, or seminal vesicles, detected by transrectal

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ultrasonography and external anal sphincter or levator ani muscles invasion and confirmed by pelvic magnetic resonance imaging were excluded. Among these 57 patients, 44 patients who were followed more than 6 months after closure of the diverting ileostomy were evaluated for recurrence, complications, and functional outcomes. The mean follow-up period was 36.3 months (range, 8–83 months), and the follow-up was performed by physical examination and questions in the outpatient department. For this study, only the patients who underwent CAA following ultralow anterior resection for distal rectal cancer were enrolled. All cases underwent hand-sewn anastomosis for reconstruction performed at the level of dentate line, and all had the location of anastomosis confirmed exactly.

A diverting ileostomy was performed in all cases, and reconstruction methods were straight CAA and J-pouch CAA. The operative technique was as follows. The patient was placed in the Trendelenburg lithotomy position with the legs supported in Lloyd-Davies stirrups. A midline abdominal skin incision was made, a bowel bag was used to wrap the small bowel, and a Thompson self-retractor was placed. The inferior mesenteric vein was divided just caudad to the pancreas, while the inferior mesenteric artery was divided just above the superior hypogastric nerves overlying the aorta. The rectum was sharply dissected to the anal hiatus of the pelvic diaphragm. The plane of pelvic dissection was along the parietal pelvic fascia, leaving the hypogastric nerves over the aorta. Dissection along the adventitia of the internal iliac vessels was not performed, the lateral points of fixation were divided meticulously by electrocauterization or by ligation with surgical clips, and the sacral parasympathetic pelvic plexus was preserved. A proper rectal fascia-enveloping mesorectum remained intact during pelvic dissection. In all selected cases, a distal, lateral margin could be obtained and separated from the pelvic diaphragm after completion of the pelvic dissection. Transection of the specimen at the distal margin was performed from the abdomen or using an abdominotransanal approach.

In the transanal approach, using the technique of Parks, the mucosa was stripped from the dentate line to just above the levators. The muscular rectal wall was divided by cautery at the level of the anorectal ring, and the specimen was removed. The splenic flexure of the colon was mobilized to gain a length sufficient to reach the anal canal. The colon was delivered through the anus, where CAA was performed using Vicryl 3-0 interrupted hand-sewn sutures. A Lone-Star retractor facilitated exposure. In J-pouch CAA, the length of the J-pouch was 8 cm.

The size of the tumor and the length of distal and proximal resection margin were measured immediately after removing the specimen. Stool continence was assessed using the Kirwan classification[7] (grade 1 = perfect; 2 = incontinence to gas; 3 = occasional minor leak; 4 = frequent major soiling; 5 = colostomy). The distance from the anastomosis to the anal verge was measured by rigid sigmoid scope 6 months after CAA.

The distance was also measured 6 months after closure of the diverting ileostomy using a rigid sigmoidoscope. Survival and disease-free survival were estimated by the Kaplan-Meier method.

RESULTS

Patient Characteristics

The mean age of patients was 55.6 years (range, 25–74 years). Male patients outnumbered female patients (31 [70.5%] and 13 [29.5%], respectively). Five patients (8.8%) were treated by preoperative chemoradiation treatment. The mean follow-up period was 36.3 ± 22.8 months (range, 8–83 months). The mean distal resection margin was 1.3 ± 0.7 cm (range, 0.2–3 cm), and the mean distance of anastomosis following CAA after 6 months was 3.2 ± 0.6 cm (range, 2–4 cm). Straight CAA was performed in 19 patients (43.2%), and J-pouch CAA was performed in 25 patients (56.8%) (Table 1). Using the TNM staging system, 9 patients (20.5%) were stage I (T2 N0), 15 patients (43.1%) were stage II, 19 patients (43.2%) were stage III, and 1 patient (2.3%) was stage IV.

Functional Outcome After Operation

Forty-four patients were evaluated 6 months later after closure of the diverting ileostomy. Fecal incontinence (Kirwan classification grade III) was observed in 14 patients (31.8%). At 12 months after repair of the diverting ileostomy, fecal incontinence (Kirwan classification grade III) was observed in 6 patients (13.6%). Sixteen patients (36.4%) complained of bowel movement more frequent than six times per day 6 months later after closure of the diverting ileostomy, and 9 patients (20.5%) complained of bowel movement more frequent than six times per day 12 months after closure of the diverting ileostomy.

Complications and Treatment

The incidence of complications after operation was 27.3%. Rectovaginal fistula was observed in one patient (2.3%), and perianal fistula was observed in two patients (4.5%). Rectovaginal fistula and anal stenosis were observed simultaneously in one patient (2.3%), and local recurrence and anal stenosis were observed simultaneously in one patient (2.3%). Simple anal stenosis was noted in seven patients (15.9%) (Table 2).

Table 1. Patient characteristics

Age (mean ± SD yr)	55.6 ± 9.0 (range, 25 to 74)
Male gender (n)	31 (70.5%)
Female gender (n)	13 (29.5%)
Preoperative chemoradiation (n)	5 (8.8%)
Follow-up period (mean ± SD mo)	36.3 ± 22.8 (range, 8 to 83)
Distal resection margin (mean ± SD cm)	1.3 ± 0.7 (range, 0.2 to 3)
Tumor size (mean ± SD cm)	4.1 ± 1.9 (range, 2 to 8)
Distance, anastomosis to dentate line (mean ± SD cm)	3.2 ± 0.6 (range, 2 to 4)
No. (%) of patients receiving straight CAA/colonic J pouch CAA	19 (43.2%)/25 (56.8%)

CAA = coloanal anastomosis.

Diverting ileostomy was performed for treatment of rectovaginal fistula (n = 2) and for treatment of multiple perianal fistula that did not respond to conventional, nonoperative treatment. Abdominoperineal resection was performed for the patient who had local recurrence and anal stenosis simultaneously. Anal stenosis occurred in seven patients. Diverting ileostomy was performed for one patient who had severe anal stenosis, and anoplasty was performed for another patient who had severe anal stenosis and wanted the anus to be spared. Abdominoperineal resection was performed for a patient who simultaneously had severe anal pain and anal stenosis (Table 3).

Recurrence and Survival

Recurrence of cancer occurred in 6 (13.6%) of the 44 patients during the follow-up period. Anastomotic recurrence was noted in three of these patients (6.8%), and systemic recurrence was noted in two patients (4.5%). Anastomotic recurrence and systemic recurrence occurred in one patient. There was one case of anastomotic recurrence (one of 9), in the stage I group (T2 N0), and one case of systemic recurrence (1 of 15), in the stage II group. Two cases of anastomotic recurrence (2 of 19) and one case of combined local and systemic recurrence (1 of 19) occurred in the stage III group. One case of systemic recurrence (one of one) occurred in the stage IV group (Table 4). Abdominoperineal resection was performed in the three patients with anastomotic recurrence. Disease-related death was observed in three cases (6.8%). The 5-year survival rate was 85.3%, and the disease-free, 5-year survival rate was 73.3% among 44 patients (Figs. 1, 2).

DISCUSSION

Abdominoperineal resection of the rectum and anal canal has been performed frequently as a treatment for distal rectal cancer. Nevertheless, following the social pattern of patients with emphasis on the quality of life after surgery, the trend for the anal sphincter–saving operation has increased recently. After many authors[3–6] have reported the oncologic safety of CAA following an ultralow anterior resection for distal rectal cancer, the rate of performing this procedure has increased. However, the complications after CAA have increased as well.

Many patients who have undergone these anterior resections have developed the "anterior resection syndrome," which includes irregular bowel movements, urgency of defecation, fecal leakage, and frequent urination. The incidence of the syndrome has been reported to be about 30% among patients after low anterior resection.[8,9] The syndrome occurs because

Table 2. Postoperative complications of coloanal anal anastomosis among 44 patients

Complication	Straight CAA (n)	J-pouch CAA (n)	No. of patients (% of total patients operated on)
Rectovaginal fistula	1	0	1 (2.3)
Perianal fistula	0	2	2 (4.5)
Rectovaginal fistula + anal stenosis	1	0	1 (2.3)
Local recurrence + anal stenosis	1	0	1 (2.3)
Anal stenosis	2	5	7 (15.9)
Total	5	7	12 (27.3)

CAA = coloanal anastomosis.

Table 3. Treatment of postoperative complications

Complication	Treatment
Rectovaginal fistula (n = 1)	T-colostomy
Perianal fistula (n = 2)	T-colostomy (n = 2)
Rectovaginal fistula + anal stenosis (n = 1)	T-colostomy
Local recurrence + anal stenosis (n = 1)	APR
Anal stenosis (n = 7)	Anoplasty (n = 1), T-colostomy (n = 1), APR (n = 1) Conservative treatment (n = 4)

APR = abdominoperineal resection.

of a marked reduction in the reservoir capacity of the rectum,[10] and it may be aggravated severely in patients who have received a CAA after ultralow anterior resection. Thus, this is a significant issue considering the degradation of the patient's quality of life.

In this study, fecal incontinence was noted in 14 patients (31.8%) 6 months after closure of the diverting ileostomy and in 6 patients (13.6%) 12 months after closure of the diverting ileostomy. Conservative treatment was sometimes adequate for these patients. Sixteen patients (36.4%) had bowel movement more frequent than six times per day 6 months after closure of the diverting ileostomy, and nine patients (20.5%) had a similar pattern 12 months after closure of the diverting ileostomy. It is believed that these clinical problems disappear with the passage of time, but Miller and colleages[11] reported that 19 of the 30 patients had persistent problems 1 year after the operation. Paty and collegues[3] estimated the patients' functional results in 4.3 years (range; 1.3–12.3 years) after operation and reported complete fecal continence in 51%, incontinence to gas in 21%, minor leakage in 23%, and uncontrolled leakage in 5%. Overall, function was also reported as good or excellent in 56%, fair in 32%, and poor in 12%. In those patients with poor function, resting anal sphincteric pressure, which is primarily a reflection of internal anal sphincter function, was significantly lower.[11] Although Miller et al.[11] reported that it is uncertain whether this functional loss of anal sphincter was entirely the result of the operation or possibly occult damage to the anal sphincter caused, for example, by childbirth or past minor anal surgery, they suggested that careful preoperative evaluation with manometry and endoanal ultrasonography may detect such damage and allow selection of patients for coloanal reconstruction. Therefore, if there is preoperative poor anal sphincter function or occult anal sphincter injury that was detected on manometry and endoanal ultrasonography, CAA following ultralow anterior resection would not likely be proper, because anal sphincter function may fail to improve after the operation.

In addition, there were some complications after CAA. Cavaliere et al.[12] reported that anastomotic leakage occurred in 18% of patients, urinary retention in 15%, and biliary tract infection in 4% as early complications, whereas anastomotic stricture occurred in 21% and sexual dysfunction occurred in 14% as late complications. Luna-Pérez et al.[13] reported that rectovaginal fistula occurred in 2 patients (6.3 %) and anastomotic stricture in 2 patients (6.3%)

Table 4. Recurrence of related cancer after surgery

TNM Stage*	Type of recurrence (No. of patients)		
	Local	Systemic	Local + Systemic
Stage I (n = 9)	1	0	0
Stage II (n = 15)	0	1	0
Stage III (n = 19)	2	0	1
Stage IV (n = 1)	0	1	0

*Overall recurrence = 6 of 44 patients (13.6% of total).

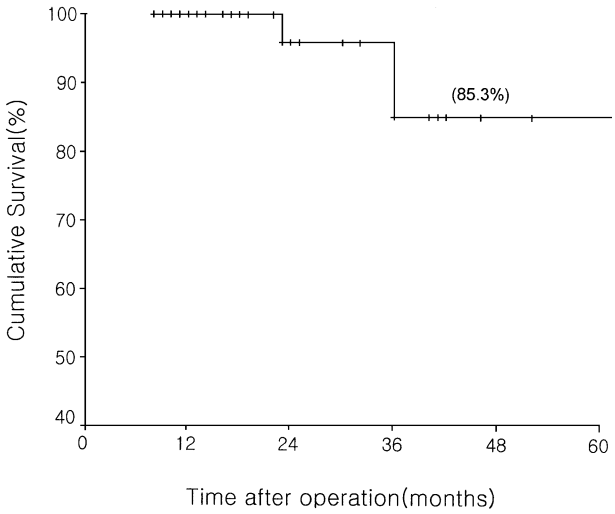

Fig. 1. Cumulative 5-year survival curve among 44 patients.

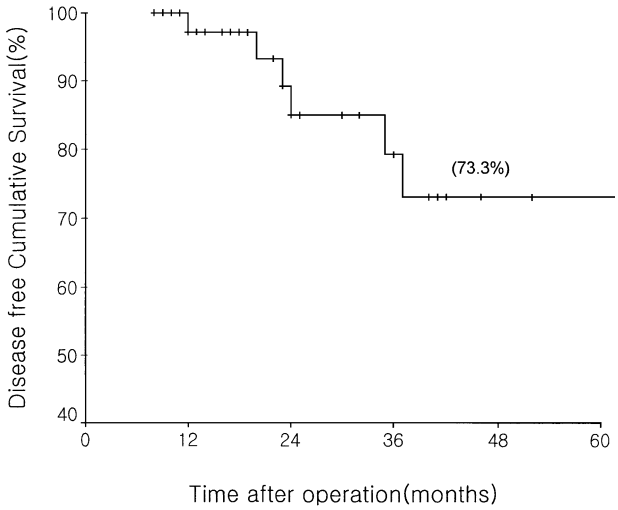

Fig. 2. Cumulative disease-free 5-year survival curve among 44 patients.

among 32 patients who underwent CAA after preoperative chemoradiation for rectal cancer. Bernard et al.[14] reported that anastomotic stricture occurred in 16 patients (42.1%) among 38 patients who underwent CAA, and 8 among 16 patients needed more than one dilation. In this study, complications occurred in 12 patients (27.3%). Therefore, complications and poor functional outcomes after the CAA, the method of preserving anal sphincter for distal rectal cancer, should be considered carefully. An experienced surgeon will be necessary to reduce these complications. The choice of CAA following ultralow anterior resection for rectal cancer should be decided carefully after precise clinical evaluation of the patient's tumor status. Enker et al.[5] and Paty et al.[3,4] suggested that CAA be performed only when the tumor can be resected without injury to the anal sphincter and levator ani muscles and not when anastomosis in the pelvic cavity was impossible because of a small pelvic size. These complications, such as anal stenosis, rectovaginal fistula, and multiple perianal fistula, may occur, because a normal anatomical structure, for example, an anal gland, was injured by an anastomosis at the dentate line. The etiology of this type of complication is uncertain at this time. Thus, further study will be necessary.

In this study, there was no significant difference in the recurrence rate comparing to other investigator's results. Cavaliere et al.[15] reported that local recurrence occurred in 5% of patients and overall recurrence in 27% of patients. Parc et al.[16] reported that local recurrence occurred in 6% of patients, with overall recurrence in 17% of patients. Huguet et al.[17] and Hautefeuille et al.[18] reported local recurrence occurred in 5% and 20% of patients, and overall recurrence occurred in 15% and 23% of patients, respectively. Also, they reported that disease-free survival was 79% and 64%, respectively. In our study, the local recurrence rate was 6.8%, the overall recurrence rate was 13.6%, the 5-year survival rate was 85.3%, and the 5-year disease-free survival rate was 73.3%. In the major series on oncologic outcomes of abdominoperineal resection for distal rectal cancer, Nakagoe et al.[19] reported that local recurrence rate was 7%, the overall recurrence rate was 21%, the 5-year survival rate was 71.5%, and the disease-free 5-year survival rate was 67.6%. Bozzetti et al.[20] reported that there was no significant difference in oncologic outcomes between sphincter-saving operations and abdominoperineal resection. Consequently, we believe that the recurrence rate and mortality rate of patients undergoing CAA following ultralow anterior resection for distal rectal cancer are not greater than those of patients undergoing abdominoperineal resection. This may be, in part, because total mesorectal excision was performed with CAA after ultralow anterior resection and after abdominoperineal resection.

CONCLUSIONS

Complications and poor functional outcomes can occur after CAA that some patients cannot endure. The possibility of these complications should be considered carefully before the surgeon decides on this procedure to treat distal rectal cancer. Patient status and location of tumor and the relation between the tumor and the levator ani muscle should be evaluated before the operation.

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Surgical Outcome of Para-aortic Lymph Node Dissection Preserving Neural Tissue Based on Anatomical Evaluations

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The anatomical distribution of the para-aortic lymph nodes was studied to establish an effective operative procedure that preserves neural tissue for patients with advanced gastric cancer. Para-aortic lesions were anatomically examined in 31 cadavers, and histologic preparations of 14 cadavers were used to evaluate the relationship between para-aortic lymph nodes and surrounding neural tissue. Surgical results were analyzed in patients with D3 gastrectomy based on anatomical findings (n = 33). Anatomically, the splanchnic nerves merged into the celiac ganglion, which consisted of either one ganglion (type I) or several ganglia (type II). The average number of lymph nodes were 17.4 in the area superior to the superior mesenteric artery (SMA) and 13.3 in the area inferior to the SMA. According to the number of metastatic lymph nodes ($\leqslant 3$, $\geqslant 4$), the median survival time was 14.7 and 9.7 months, respectively ($P < 0.02$). Patients either with or without metastatic lymph nodes behind the neural tissue had a median survival time of 14.7 and 9.7 months, respectively ($P < 0.02$). We conclude that para-aortic lymph node dissection preserving neural tissue is useful in patients with three or fewer para-aortic metastatic lymph nodes that are in front of the neural tissue. (J GASTROINTEST SURG 2005;9:781–788)

KEY WORDS: Para-aortic lymph node dissection, neural tissues, advanced gastric cancer

In Japan, it is thought that lymph nodes around the abdominal aorta (para-aortic lymph nodes) are the final regional lymph nodes to receive lymphatic flow from the stomach.[1] Para-aortic lymph node dissection has been adopted in many institutions for advanced gastric cancer. However, the operative technique and procedure have not been well established, resulting in discrepancies in surgical practice between institutions.[1–8] Excessive lymph node dissection, which includes dissection of the neural plexus, results in serious morbidity such as diarrhea,[8–12] but less extensive surgery would render the procedure ineffective as a curative technique. Therefore, we evaluated the anatomy of the periaortic nerve tissues, lymphatics, lymph nodes, and microvessels to establish an effective operative technique that would maintain the quality of life of patients (QOL) and to provide a surgical resolution for patients with advanced gastric cancer. Furthermore, we analyzed the surgical outcome of para-aortic lymph node dissection (D3 gastrectomy) in patients with advanced gastric cancer, based on the anatomical findings.

MATERIAL AND METHODS

Anatomical Evaluation

The anatomical distribution of the splanchnic nerve and celiac ganglia around the abdominal aorta was macroscopically examined in 31 cadavers. In the current study, the neural organs around the abdominal aorta were defined as follows: celiac ganglia, the nodular components connecting greater and lesser splanchnic nerves; neural bundle, the funicular units that diverge from each ganglion except the splanchnic

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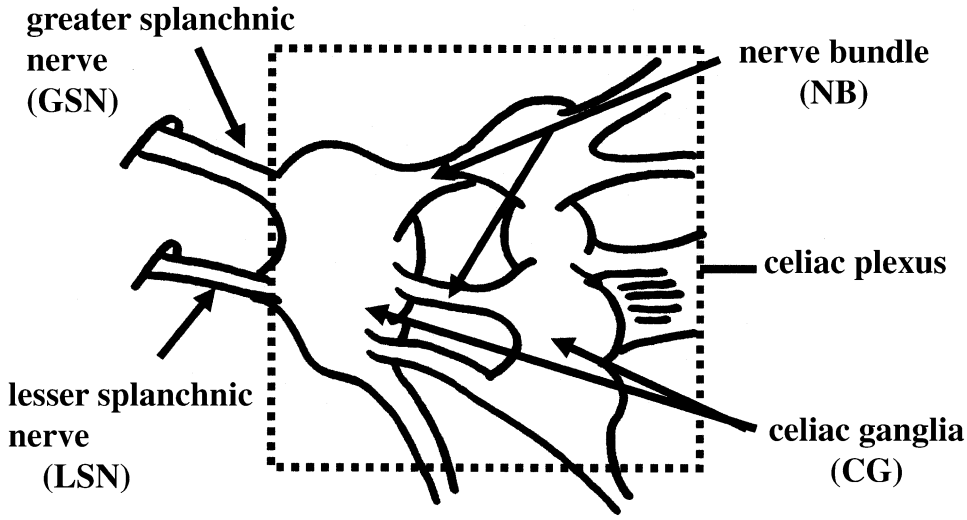

Fig. 1. The definition of each part of the neural tissue. Celiac ganglia is nodular tissue linked to the splanchnic nerve, nerve bundle is a thick fiber running from the proximal ganglion to distal neural tissue, and celiac plexus is the whole neural tissue, which includes celiac and aortorenal ganglia, neural bundles, and fibers from ganglia.

nerves; and celiac plexus, the plural components including the celiac ganglia, the splanchnic nerves, and the neural bundles (Fig. 1).

Furthermore, we microscopically evaluated the surrounding anatomy of the abdominal aorta, including the body of the vertebra, of 14 cadavers that had no neoplastic lesions. The microscopic evaluation was extended 2 cm on the cranial side of the celiac root, caudally to the inferior mesenteric artery root, and laterally to the bilateral renal hila. At 5-mm horizontal intervals, tissue sections were taken from this area, dipped in formalin, and paraffin embedded (Fig. 2). The nerve tissues, microvessels, and lymph nodes were histologically preserved by this method.

The anatomical area was classified into two regions: the superior site, from the height of the celiac artery root to the inferior margin of the left renal vein; and the inferior site, from the inferior margin of the left renal vein to the inferior mesenteric artery root (Fig. 3). From the 5-mm horizontal sections, two sections at 2.5-mm intervals were prepared and stained with hematoxylin-eosin to examine the following factors: the number of para-aortic lymph nodes and anatomical distribution of para-aortic lymph nodes, celiac plexus, and splanchnic nerves. This study was approved by our institutional review board.

Patients

After sufficient macroscopic and microscopic evaluations of anatomy around the abdominal aorta, an operative procedure for advanced gastric cancer was developed. A series of 150 patients with advanced gastric cancer were enrolled in this study between April 1992 and March 2000. D3 gastrectomy was used for patients who gave informed consent and had no critical comorbid disease (no abnormal findings on electrocardiograms, 24-hour creatinine clearance $\geqslant$70 mL/min, forced expiratory volume 1.0 $\geqslant$70%, vital capacity $\geqslant$80%, and indocyanine green (ICG) 15 $\leqslant$10%). Patients underwent D3 gastrectomy with preservation of the splanchnic nerves and the celiac ganglia. Of these patients, the surgical outcomes of 33 patients with metastasis of para-aortic lymph nodes were evaluated.

Statistical Analysis

Analyses were undertaken with statistical software (SPSS, version 10.0; SPSS, Inc, Chicago, IL). Survival curves were constructed using the Kaplan-Meier method and then compared with the log-rank test. Continuous variables were assessed by Student's t tests and expressed as the median $\pm$ SD. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Anatomical Evaluation

Formation of the greater and lesser splanchnic nerves in the abdominal cavity was evaluated. The greater splanchnic nerve runs between the diaphragm crural intermediate leg and the medial crus and enters into the abdominal cavity. It runs toward the cranial

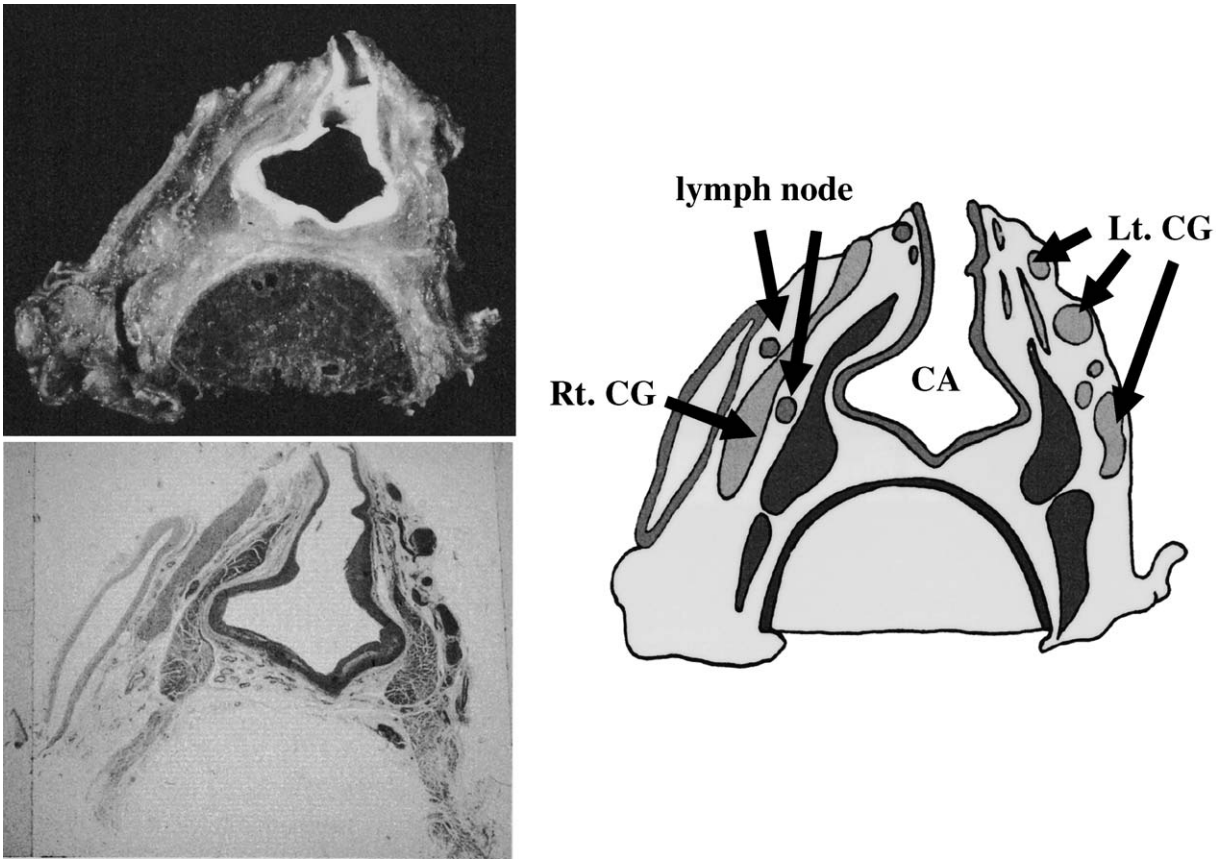

Fig. 2. Level of the celiac artery. (**A**) A 5-mm-thick transverse specimen including the root of the celiac artery. (**B**) Photomicrograph of A (hematoxylin-eosin stain, original magnification ×1). (**C**) Schematic of B. Note the lymph node behind the celiac ganglia. Lt. CG = left celiac ganglion; Rt. CG = right celiac ganglion; CA = celiac artery.

side about 1 cm in the median direction and ends in the celiac ganglion. The lesser splanchnic nerve either runs alongside the greater nerve or runs into the abdominal cavity through the diaphragm at the caudal side of the greater splanchnic nerve. In the abdominal cavity, the lesser nerve runs along the median side for about 1.5 cm and ends in the celiac ganglion on the caudal side of the greater splanchnic nerve (Fig. 4). There was no difference between the formation of the right splanchnic nerve and the left splanchnic nerve in the abdominal cavity.

Anatomical Distribution of the Celiac Ganglion

The anatomical distribution of the celiac ganglia was classified into two types. Type I was composed of a single ganglion (Fig. 5), whereas type II was composed of several ganglia connected to each other by the neural bundles (Fig. 6). The incidence of type I and II celiac ganglia was 61.3% and 38.7%, respectively, on both the right and the left side. The incidence of type I in both the right and the left side was the most frequently observed with 41.8%. The other incidence rates are shown in Table 1. Lymph nodes located between the ganglion and the neural bundles occurred in 16.1% of type II ganglia. Conversely, there were no lymph nodes between the ganglion and the neural bundles in type I ganglia.

Histologic Evaluation

The number of para-aortic lymph nodes in the superior site and the inferior site was 17.4 ± 4.5 and 13.3 ± 6, respectively. The total number of lymph nodes was 27.6 ± 7.0 (Table 2).

Anatomical Distribution of the Para-aortic Lymph Nodes, the Celiac Plexus, and the Splanchnic Nerves

In the superior site, lymph nodes in the dorsum of the layer composed of the celiac plexus and the splanchnic nerves were observed in all cases. The mean number of lymph nodes in the dorsum in the cranial

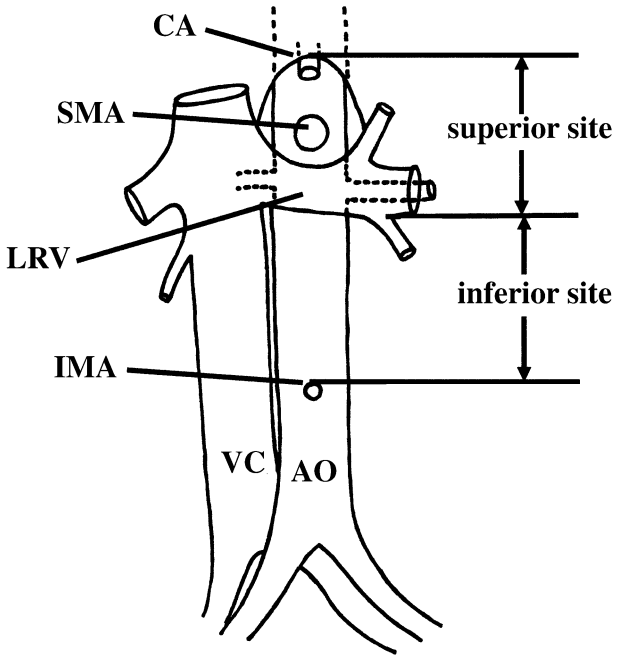

Fig. 3. Location of the para-aortic lymph node. Superior site: from the upper margin of the celiac artery (CA) to the lower margin of the left renal vein (LRV). Inferior site: from the lower margin of the LRV to the upper margin of the inferior mesenteric artery (IMA). SMA = superior mesentric artery; AO = abdominal aorta; VC = inferior vena cava.

site was 3.1 ± 2.3 on the right side and 4.1 ± 1.3 on the left side (Table 3).

Establishment of an Effective Operative Procedure Based on the Anatomical Evaluation

An alternative operative procedure was developed according to the results of the anatomical evaluation. We routinely dissected the para-aortic lymph nodes around the celiac plexus circumference and between the celiac artery axis and the inferior mesenteric artery.

Lymph Node Dissection Around the Right Celiac Ganglion. Applying Kocher's maneuver allowed effective taping of the right renal artery behind the left renal vein, revealing the right diaphragm crus at the inferior vena cava left border, which in turn allowed for the right inferior phrenic artery to also be taped. The celiac artery root and the location of the splanchnic nerves in the celiac ganglion (about 3.5 cm lateral to the celiac axis) were both identified by touch. The splanchnic nerves were taped while the inferior vena cava was pulled across to the right side. Dissection of the lymph nodes on the ventral side of the celiac ganglion could then be performed. Furthermore, we classified the anatomical distribution of type I or type II ganglia by taping together the nerve bundles of the ganglia.

The operative procedure used was determined by the anatomical distribution of the ganglia. For type I ganglia, the splanchnic nerves were taped and lifted to reveal the dorsal site of the ganglion. For type II ganglia, both the splanchnic nerves and the neural

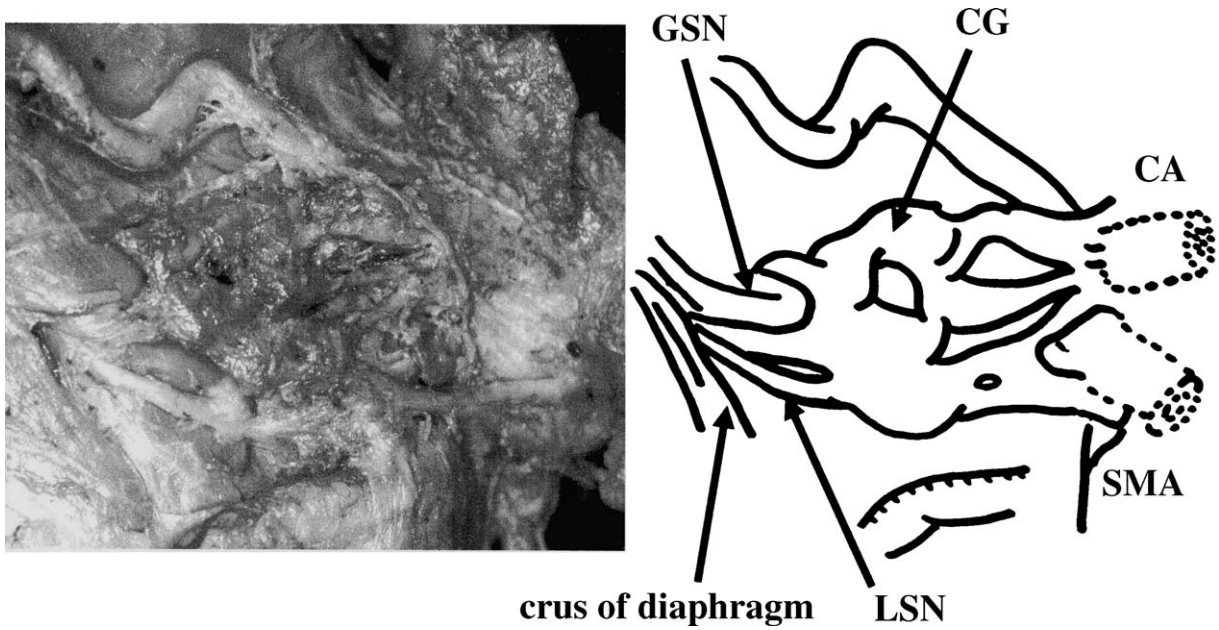

Fig. 4. Traveling modality of the greater and lesser splanchnic nerve. The greater and lesser splanchnic nerves traverse through the diaphragm and pass horizontally into the celiac ganglion, respectively. GSN = greater splanchnic nerve; CG = celiac ganglion; CA = celiac artery; SMA = superior mesenteric artery; LSN = lesser splanchnic nerve.

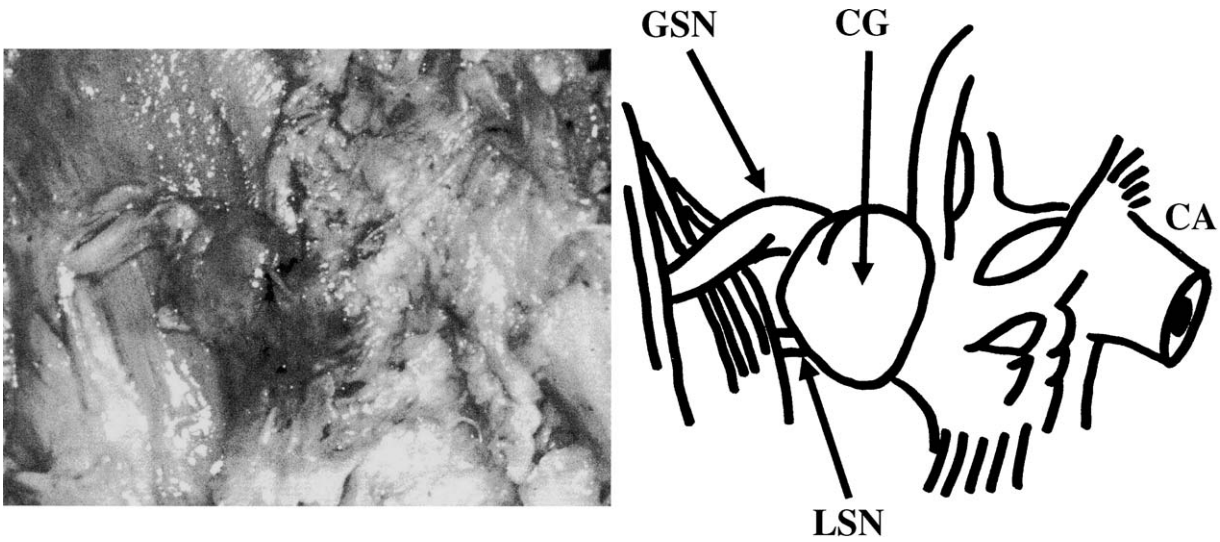

Fig. 5. Macroscopic form of celiac ganglia, type I. Type I is composed of a single ganglion. CG = celiac ganglia; CA = celiac artery; GSN = greater splanchnic nerve; LSN = lesser splanchnic nerve.

bundles between the ganglion were taped, and the lymph nodes were carefully dissected by lifting the neural tissue. Para-aortic lymph node dissection is more difficult in patients with type II ganglia. The abundant neural tissue often distorted the view of the dorsal side of the neural tissue, and extensive tape was needed to lift the tissue. Furthermore, extreme care was needed to avoid injuring the microvessels arising from the abdominal aorta in type II ganglia. In both types, it is important to divide and ligate the tissue gently to avoid lymphorrhea.

Lymph Node Dissection Around the Left Celiac Ganglion. After we lifted up the left kidney, the left greater and lesser splanchnic nerves that run straight along the ventral side of the vertebra, caudal to the arcuate ligament, could be identified and taped. The pancreatic tail and spleen were then lifted to reveal the left celiac plexus and the left adrenal gland.

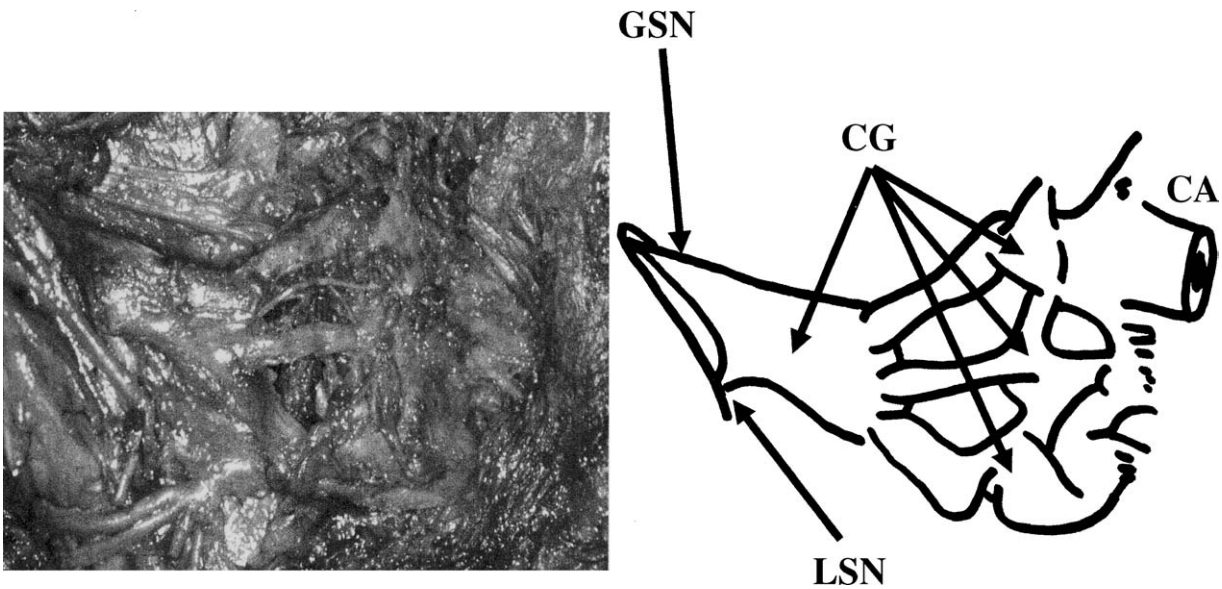

Fig. 6. Macroscopic form of celiac ganglia, type II. Type II is composed of several ganglia. GSN = greater splanchnic nerve; CG = celiac ganglion; CA = celiac artery; LSN = lesser splanchnic nerve.

Table 1. Patterns of celiac ganglia in 31 cadavers

	Type I (n)	Type II (n)
Right	61.3% (19)	38.7% (12)
Left	61.3% (19)	38.7% (12)

Right, Left	Percent (No.)
Type I, type I	41.8 (13)
Type I, type II	19.4 (6)
Type II, type I	19.4 (6)
Type II, type II	19.4 (6)

The lateroaortic lymph node dissection is similar to that of the right side. First, classification of the ganglia determines the operative procedure; then dissection preserving the neural tissue is performed. We routinely resect a portion of the left adrenal gland to allow for easier dissection of the lymph nodes. Following this, we can find the taped splanchnic nerves, and then the lymph nodes behind the left renal vein and artery were dissected.

Surgical Outcomes

Patients with three or fewer para-aortic metastatic lymph nodes had a median survival time of 14.7 months and a 5-year survival rate of 25.1%. Patients with four or more metastatic lymph nodes had a median survival time of 9.7 months and no 5-year survival rate. There was a significant difference in survival rates between both groups ($P < 0.02$) (Fig. 7). A significant difference was also seen in survival rates between patients with or without metastatic lymph nodes behind the neural tissue. The median survival time was 9.7 months for patients with metastasis behind the neural tissue and 14.7 months for patients without metastasis behind the neural tissue ($P < 0.02$) (Fig. 8).

DISCUSSION

Many institutions in Japan have reported on the surgical outcome of para-aortic lymph node dissection (D3 gastrectomy).[1–6,9] Some clinicians reported that D3 gastrectomy improved surgical outcomes for patients with para-aortic lymph node metastasis (5-year survival rate; 12.1%−23.1%).[1–4,9] By contrast, other reports showed no significant difference in overall survival rates between D2 and D3 gastrectomy.[5,6] Furthermore, one report demonstrated adverse effects following D3 gastrectomy on postoperative morbidity.[5,6] The differences in operative procedures such as combined resection of the neural plexus and adrenal gland, and the difference in the extension of the dissected field, would contribute to the discrepancies in surgical results between institutions.

Table 2. Number of para-aortic lymph nodes in 31 cadavers

Site	No. of nodes (mean ± SD)
Superior site	17.4 ± 4.5
The deep layer to nerve tissue	
Right	3.1 ± 2.3
Left	4.1 ± 1.3
Inferior site	13.3 ± 6.0
Total	27.6 ± 7.0

Table 3. Incidence and number of lymph nodes behind the celiac plexus in the superior site in 31 cadavers.

	Percent of sites with nodes	No. of nodes (mean ± SD)
Right	100 (14/14)	3.1 ± 2.3
Left	100 (14/14)	4.1 ± 1.3

The increase in the amount of operative bleeding, lengthy operation times, peritoneal infections, intractable diarrhea, and erectile dysfunction were regarded as the main adverse effects of D3 gastrectomy.[8–11] The current anatomical study aimed to decrease the incidence of postoperative morbidity caused by super-extended lymph node dissection. We hypothesized that by determining the anatomical relationship between para-aortic lymph nodes and the celiac ganglion, a useful and safe operative technique in D3 gastrectomy could be established. In this study, in our institution the incidence of uncontrollable diarrhea was 1.8% and erectile dysfunction did not occur when the neural tissue preservation technique was performed.[8]

There have been a number of reports concerning the anatomical distribution of the celiac ganglion, focusing on either the number of the ganglion[13] or the shape of the plexus.[14] In the present study, the celiac ganglia were classified as either type I or type II. The type of celiac ganglion determined which operative method would be performed. In patients with type I celiac ganglia, para-aortic lymph node dissection was performed by lifting the splanchnic nerves and neural bundle to reveal a clear view of the dorsal side of the plexus. In type II patients, the splanchnic nerves, neural bundles, and the nerve bundles between each ganglion were taped together by lifting the nerve tissue in all directions. This revealed the dorsal aspect of the para-aortic lymph node, making it accessible for dissection. Determining the anatomical

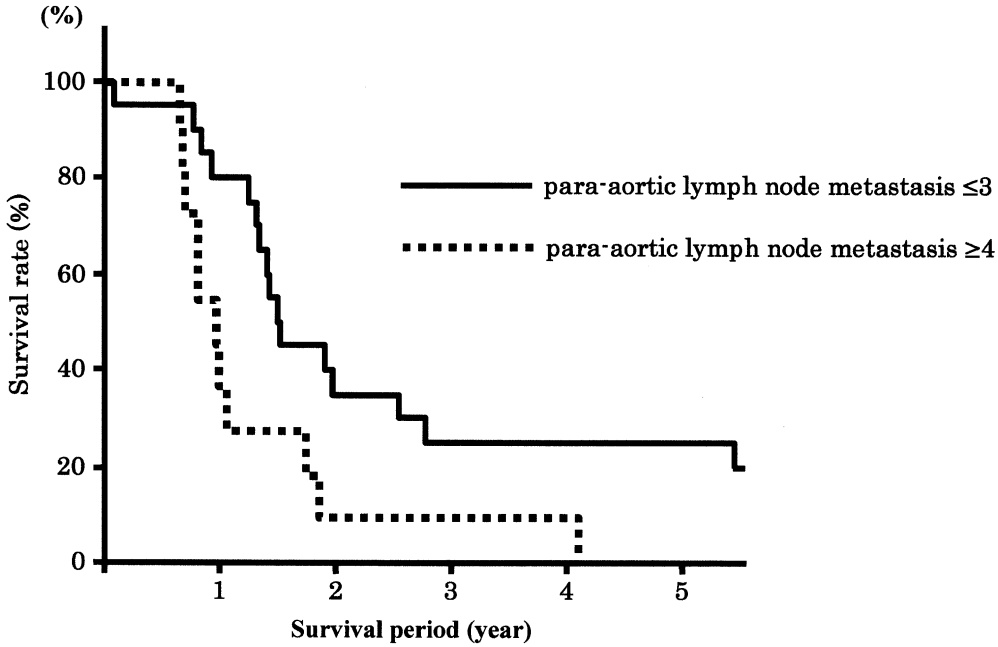

Fig. 7. Survival period of patients who had fewer than three para-aortic lymph nodes containing metastases and those who had more than four para-aortic lymph nodes containing metastases.

distribution of celiac ganglia allows for efficient lymph node dissection while preserving the neural tissue.

Histologic examinations were performed to determine the number of lymph nodes and the anatomical relationship between the nerve tissue and lymph nodes. Because the anatomical examination destroys the normal three-dimensional distribution of the tissue, we could not evaluate the precise microscopic histology.

Therefore, we made a transverse section without any alteration to the configuration of the para-aortic

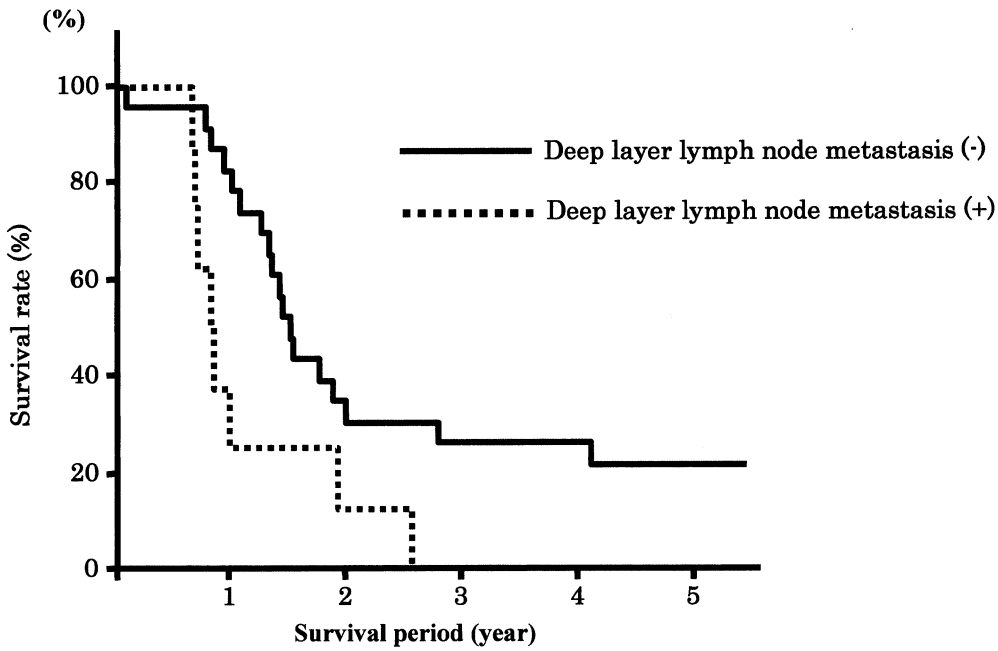

Fig. 8. Survival period of patients who had para-aortic lymph node metastases with or without deep-layer lymph node metastases.

tissue to examine the anatomical relationship of the para-aortic lymph nodes and neural tissue. Because para-aortic lymph nodes are said to be the last regional lymph nodes in the abdomen, we targeted these lymph nodes in D3 gastrectomy.

Analysis of the surgical outcomes of patients in this study revealed that patients with four or more para-aortic lymph node metastasis had a reduced survival rate compared with patients with three or fewer metastatic nodes. In parallel, the survival rate was lower in patients with metastatic lymph nodes behind the neural tissue such as the celiac ganglion or the splanchnic nerves. This shows that patients with multiple metastatic lymph nodes behind the neural tissue have the least favorable surgical outcome.

CONCLUSIONS

Para-aortic lymph node dissection provides surgical benefits for patients with three or fewer metastatic lymph nodes. However, it is impossible to precisely diagnose preoperatively the number of metastatic lymph nodes. Here, we used the intraoperative pathologic diagnosis to determine the most appropriate para-aortic lymph node dissection operative procedure for each patient. Development of new imaging modalities that can preoperatively diagnose lymph node metastasis is expected in the future.

We thank Professor Hajime Sawada and Professor Hitoshi Kitamura for their kind advice regarding our anatomical study.

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Tissue-Engineered Patch for the Reconstruction of Inferior Vena Cava During Living-Donor Liver Transplantation

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In living-donor liver transplantation, only a portion of the donor's liver is grafted into the recipient; therefore, if the hepatic vein and inferior vena cava (IVC) in the recipient fail to be transformed or dilated properly, it could cause inadequate blood flow from the liver graft to the IVC. We have developed an easy-to-use tissue engineered patch that can be used for the reconstruction of the hepatic vein and IVC. Five hybrid pigs (weighing 15–30 kg) served as the recipients of the patch. A bioabsorbable polymer sheet was used to produce the patch, with no cells seeded. The pigs were laparotomized, followed by the removal of a 3 × 2-cm portion of the infrahepatic IVC, which was then patched with the polymer sheet. Three months after the operation, the graft site was removed and subjected to gross and histologic examinations. All five pigs survived until they were killed 3 months after the operation. On gross examination, the polymer sheet grafted onto the IVC was completely absorbed, and the graft site was morphologically similar to the native IVC. In all five pigs, the patched IVC was free of stenosis or deformation. Immunohistochemical examination revealed that the patch site was lined with endothelial cells and that smooth muscle was present under the epithelium. Like the native IVC, the patch site tested positive for factor VIII. These findings suggest that this polymer sheet may be useful for the reconstruction of the IVC and hepatic vein during living-donor liver transplantation in humans. (J GASTROINTEST SURG 2005;9:789–793)

KEY WORDS: Living donor liver transplantation, tissue engineering, IVC patch, bioabsorbable polymer

Living-donor liver transplantation involves replacing the recipient's liver with a portion, not the whole, of the donor's liver; therefore, if the inferior vena cava (IVC) and hepatic vein in the recipient failed to be transformed or dilated properly, it could cause stenosis at the site of hepatic vein anastomosis and block the blood flow from the liver graft to IVC.[1] Currently, nonbioabsorbable polytetrafluoroethylene (PTFE),[2] homografts from cadavers[3] or the portal vein, external iliac vein, and other autologous tissues harvested from the recipient[4] are used to properly transform or dilate the hepatic vein and IVC. However, expanded PTFE (ePTFE) has the disadvantage that the artificial blood vessel is difficult to suture because of its hardness. Homografts are in very short supply; and in the case of harvesting a vein, the surgical procedure is very complicated, and it may be impossible to obtain a blood vessel of sufficient diameter. In cases where the surgical field is contaminated to some extent, such as living-donor liver transplantation or gastrointestinal surgery, artificial blood vessels made of nonbioabsorbable materials are at risk of being obstructed or ruptured.[5,6] An easy-to-use, infection-resistant patch is therefore required for the reconstruction of the hepatic vein and IVC.

With recent technological advances, tissue engineering has been studied in various medical fields; tissues and organs produced by this technology are gradually becoming available in clinical settings.[7,8] For revascularization in the thoracic cavity, the pulmonary artery was successfully replaced by a cell-seeded bioabsorbable polymer.[9] On the other hand,

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few studies have evaluated bioabsorbable materials for revascularization in the peritoneal cavity, although a considerable amount of research has been conducted on nonbioabsorbable grafts.[10,11]

The present study was designed to assess the applicability of a cell-free bioabsorbable polymer sheet for reconstruction of the hepatic vein or IVC during living-donor liver transplantation or gastrointestinal surgery. Another objective was to determine whether the graft site was endothelialized after the polymer was absorbed into the body.

MATERIALS AND METHODS

Bioabsorbable Polymer

The patch grafted onto the IVC was a sponge-like polymer sheet composed of polycaprolactone and polylactide that was reinforced with polyglycolic acid fibers. The sheet was cut into pieces measuring approximately 3 × 2 cm. It was approximately 1 mm in thickness. With an air porosity of 95% or more, the patch was designed to be absorbed into the body within 6 to 8 weeks (Fig. 1).

Animal Operation

Five hybrid pigs weighing 15–30 kg served as the recipients of the patch produced by tissue engineering. Under general anesthesia, induced with 20 mg/kg of intramuscular ketamine and maintained with a continuous infusion of 0.2 mg/kg per minute of propofol, the upper abdomen was opened by a midline incision, and the infrahepatic IVC was identified. Using forceps, a side clamp was placed on the ventral side of the infrahepatic IVC, followed by the removal of a 3 × 2-cm, elliptical portion of the IVC. The polymer sheet was cut into pieces of the same size as the removed portion, and the IVC was patched with it using continuous 5-0 Proline sutures (Fig. 2). Three months after operation, the five pigs grafted with the patch were laparotomized again under general anesthesia. The tissue around the patch was observed for evidence of inflammation, followed by the removal of the patch site; then, the animals were sacrificed. The patch site was subjected to gross and histologic examinations. All animal experiments were conducted in compliance with the NIH *Guide for the Care and Use of Laboratory Animals*.

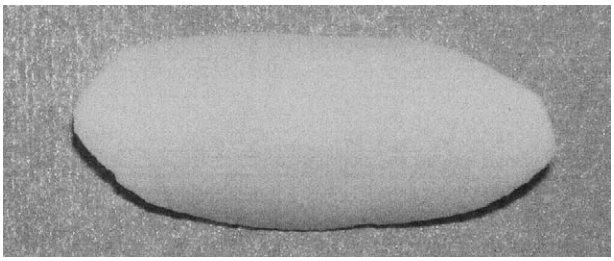

Fig. 1. Inferior vena cava (IVC) patch (bioabsorbable polymer). The patch used was a sponge-like polymer sheet composed of polycaprolactone and polylactide which was reinforced with polyglycolic acid fibers. The sheet was cut into pieces measuring approximately 3 × 2 cm. It was approximately 1 mm in thickness.

Morphologic Quantification

Three months after operation, the graft site was removed and examined histologically. The removed tissue was fixed in formalin, stained with hematoxylin and eosin (H&E) and factor VIII (Sigma, Japan), and observed under a light microscope, comparing it with the native IVC.

RESULTS

The five pigs grafted with the patch survived until they were killed for the examination of the patch site 3 months later. All of them gained weight over the 3 months. Laparotomy findings at 3 months after operation were similar in all the animals; the patch site was slightly adhered to the surrounding tissue and was readily accessible and easily identified (Fig. 3). Gross examination revealed that the polymer grafted as the patch was completely absorbed and that the graft site was morphologically similar to the native IVC. The patched IVC was neither stenosed nor deformed. Examination of the specimen showed that the patch site was slightly thicker than the native IVC (Fig. 4). H&E staining revealed that the lumen of the patched IVC was lined with vascular endothelial cells and that connective tissue grew under the endothelium. Although it was difficult to differentiate the media and adventitia, the smooth muscle was found within the connective tissue. The proportion of smooth muscle at the patch site was lower than that in the native IVC (Fig. 5). When immunostained with factor VIII, which provides evidence of the presence of vascular endothelial cells, the patch site and the native IVC tested positive for it (Fig. 6).

DISCUSSION

The results of this study suggest that a cell-free bioabsorbable polymer sheet can be used as the patch to maintain the diameter of the IVC, although our evaluation was limited to an early stage after grafting.

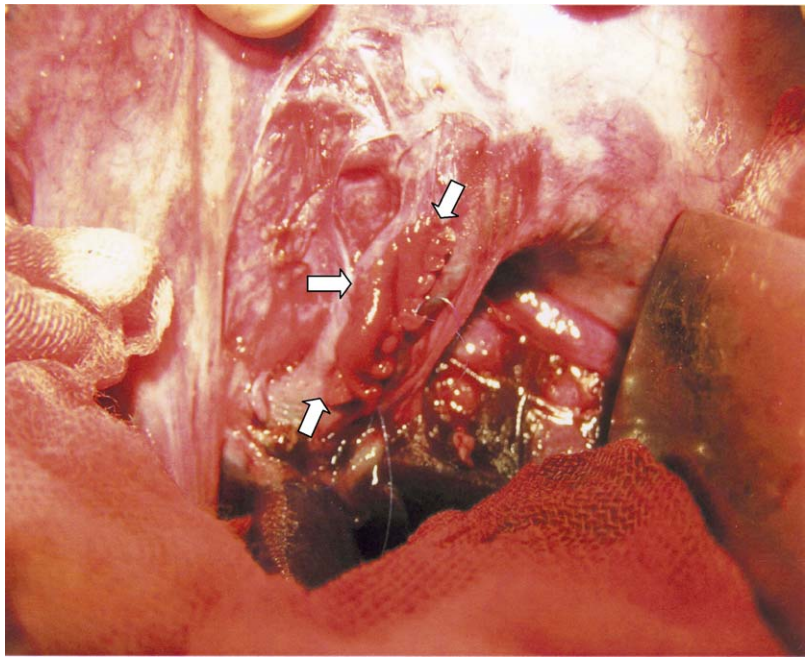

Fig. 2. After the defect in the inferior vena cava (IVC) was created, the IVC was patched with the polymer sheet using continuous 5-0 Proline sutures (*arrow*).

Our cell-free, bioabsorbable polymer sheet functioned well as an IVC patch, resulting in the generation of vascular endothelial cells. We used a cell-free patch, because cell seeding can increase the risk of infection and requires time for preparation. Another reason was that the use of the patch may be urgently needed based on an intraoperative decision in order to prevent the blood flow from a liver graft to the IVC from being blocked, although it is ideal to decide before operation whether to use the patch.

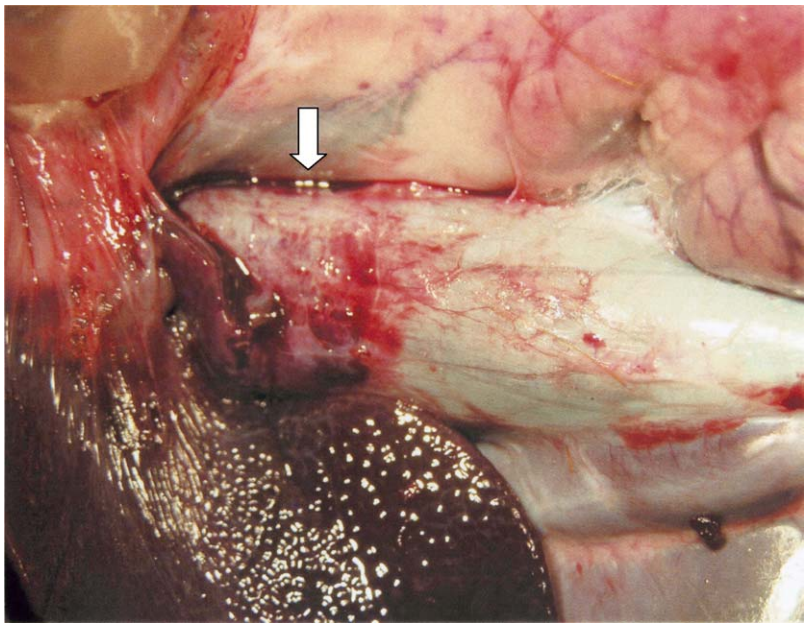

Fig. 3. Gross findings 3 months after patch grafting. On gross examination, the polymer grafted as the patch was completely absorbed, and the graft site was morphologically similar to the native inferior vena cava (*arrow*).

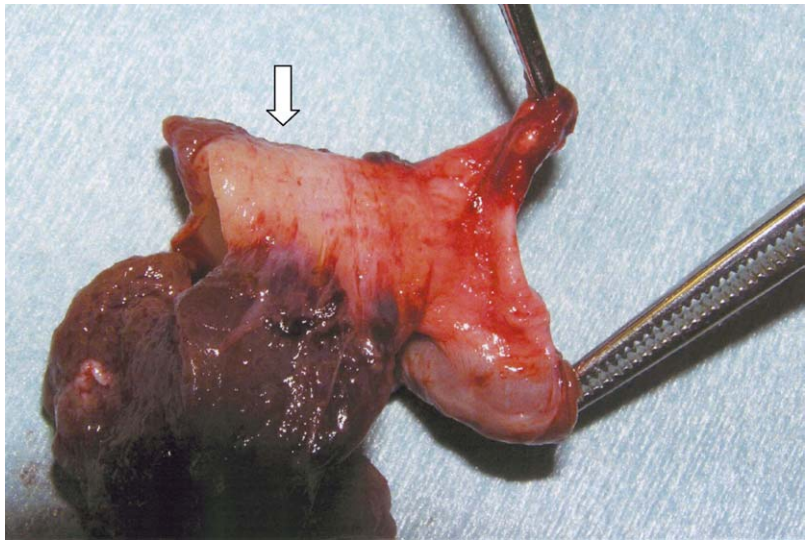

Fig. 4. Specimen of the patch site removed 3 months after grafting. The patched inferior vena cava (IVC) was neither stenosed nor deformed. Examination of the specimen showed that the patch site was slightly thicker than the native IVC (*arrow*).

We used the polymer sheet with no cells seeded in consideration of its easy manipulation, although some authors report that vascular endothelialization occurs earlier in the presence of cells.[12]

One of the advantages of the polymer sheet used in this study is that it is very easy to use during the suturing process; more specifically, it is softer than nonbioabsorbable PTFE, allowing the suture needle to pass it through smoothly. Also, it is more break resistant during suturing. In addition, PTFE is likely to cause infection or obstruction due to its nonbioabsorbability,[6] whereas our polymer seems to have a lower risk, because it is absorbed into the body and replaced by native cells. Recently, the small intestinal submucosa (SIS) of pigs has been used for the reconstruction of the artery,[13] urinary tract,[14] and other tissues. Compared with our polymer, SIS, which is derived from the tissue of a nonhuman animal, carries a risk of causing infection with unknown viruses[15] and has been reported to result in tissue shrinkage when used for the reconstruction of the urinary tract and other sites.[16] Our polymer, on the other hand, seems to be safer than SIS, because the safety of the material has already been established based on the clinical experience with a suture thread made from it.[17] Our

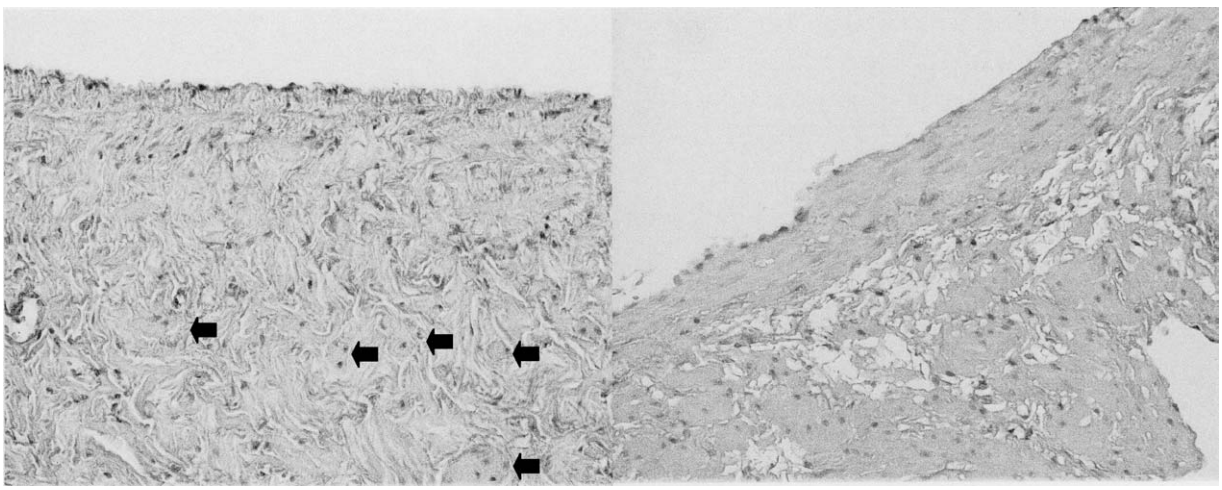

Fig. 5. Hematoxylin and eosin staining of the patch site 3 months after grafting (*left*, patch site; *right*, native inferior vena cava [IVC]). **Left**, lumen of the patched IVC was lined with vascular endothelial cells, and connective tissue grew under the endothelium. Smooth muscle (*arrows*) was found within the connective tissue. **Right**, amount of smooth muscle at the patch site was less than that in the native IVC.

Fig. 6. Immunohistologic test 3 months after patching (factor VIII staining). The site, which seemed to be vascular endothelial cells in the patch site, was factor VIII positive.

polymer appears to be superior to SIS in that it does not shrink and narrow the vascular diameter.

The bioabsorbable polymer is absorbed by the body in 8 weeks. We removed and assessed the patched area as early as 3 months post-transplantation. It was already epithelialized at 3 months, showing tissue continuity with the native IVC. The absence of stenosis supports the use of this polymer sheet as an IVC patch. The 3-month observation, short as it was, led us to consider that the polymer patch would be applicable to veins that operate at lower pressure than arteries. The regenerated smooth muscles were thin but sufficient to bear the IVC pressure and protected the patched area from damage or dilatation for 3 months after transplantation. These findings indicate that our tissue-engineered patch is useful for transforming or dilating the IVC or hepatic vein at least in the short term. We did not evaluate the risk of thrombus formation and stenosis in the patched IVC over the long-term outcome.

Immunohistologic staining with factor VIII, which selectively stains vascular endothelial cells, revealed tissue continuity from the native to the patched IVC. The polymer, which had no cells seeded, was absorbed by the body and covered with regenerating endothelial cells 3 months posttransplantation. We are not certain of the origin of these endothelial cells. Whether vascular endothelial cells of the native IVC in the vicinity of the patch divided and grew onto the patch or cells flowing through the IVC attached to the polymer and grew there, or both, remains to be elucidated.

Our study demonstrated that vascular endothelial cells regenerated and grew in the cell-free bioabsorbable polymer patch applied to the IVC. We suggest, therefore, that such a bioabsorbable patch may be useful in the reconstruction of the IVC in humans.

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Multicenter Prospective Randomized Trial Comparing Standard Esophagectomy With Chemoradiotherapy for Treatment of Squamous Esophageal Cancer: Early Results From the Chinese University Research Group for Esophageal Cancer (CURE)

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We conducted a prospective randomized trial to compare the efficacy and survival outcome by chemoradiation with that by esophagectomy as a curative treatment. From July 2000 to December 2004, 80 patients with potentially resectable squamous cell carcinoma of the mid or lower thoracic esophagus were randomized to esophagectomy or chemoradiotherapy. A two- or three-stage esophagectomy with two-field dissection was performed. Patients treated with chemoradiotherapy received continuous 5-fluorouracil infusion (200 mg/m^2/day) from day 1 to 42 and cisplatin (60 mg/m^2) on days 1 and 22. The tumor and regional lymphatics were concomitantly irradiated to a total of 50–60 Gy. Tumor response was assessed by endoscopy, endoscopic ultrasonography, and computed tomography scan. Salvage esophagectomy was performed for incomplete response or recurrence. Forty-four patients received standard esophagectomy, whereas 36 were treated with chemoradiotherapy. Median follow-up was 16.9 months. The operative mortality was 6.8%. The incidence of postoperative complications was 38.6%. No difference in the early cumulative survival was found between the two groups (RR = 0.89; 95% confidence interval, 0.37–2.17; log-rank test $P = 0.45$). There was no difference in the disease-free survival. Patients treated with surgery had a slightly higher proportion of recurrence in the mediastinum, whereas those treated with chemoradiation sustained a higher proportion of recurrence in the cervical or abdominal regions. Standard esophagectomy or chemoradiotherapy offered similar early clinical outcome and survival for patients with squamous cell carcinoma of the esophagus. The challenge lies in the detection of residue disease after chemoradiotherapy. (J GASTROINTEST SURG 2005;9:794–802)

KEY WORDS: Carcinoma of esophagus, squamous cell carcinoma, esophagectomy, chemoradiotherapy, chemoradiation

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Cancer of the esophagus is notorious for its grave prognosis.[1–3] Esophagectomy with curative intent remains the most effective treatment for this disease. Recent reports on esophagectomy showed a great improvement in the perioperative outcomes and survival achieved.[4,5] The perioperative mortality is around 5% at renowned centers. However, the 5-year survival in those squamous cell carcinomas treated by surgery alone is just 10–20%.[5,6] Numerous clinical studies in the past decades have used adjuvant or neoadjuvant chemotherapy and radiotherapy as a tool to improve the clinical outcome of surgery.[7] However, results from prospective randomized trials on neoadjuvant radiotherapy or chemotherapy alone were not satisfactory. There was no survival benefit conveyed with these approaches.[7–12]

The combination of chemotherapy and radiotherapy has greater clinical efficacy in achieving complete pathologic regression of esophageal tumor. Numerous randomized studies have been conducted on investigating the effect of neoadjuvant chemoradiotherapy on carcinoma of the esophagus.[13–16] Most of them showed an up to 30% complete tumor shrinkage with combined chemoradiotherapy. In a systematic review comparing definitive chemoradiation versus radiotherapy alone for treatment of esophageal cancer, the authors reported that combined chemoradiation is superior to radiotherapy alone in terms of 2-year survival and reduction in local recurrence.[17] Preliminary results from our own pilot study suggested the clinical efficacy of inducing tumor regression was enhanced when combining chemotherapy and radiotherapy. Forty percent of our patients had complete pathologic regression proven on the resected specimens when they received a preoperative 50-Gy dose of adjuvant radiotherapy, and 83% of our nonoperative patients had complete tumor regression endoscopically when they received a concurrent 60-Gy dose of radiotherapy with chemotherapy. Curative treatment of squamous esophageal carcinoma by aggressive chemoradiotherapy is potentially feasible. Therefore, we conducted a multicenter randomized trial to evaluate the efficacy and patient survival by comparing chemoradiotherapy with salvage surgery versus standard esophagectomy as treatment for squamous esophageal cancer.

METHODS

A multicentered, prospective, randomized controlled trial was conducted that includes five regional hospitals in Hong Kong: the Prince of Wales Hospital, the Alice Ho Nethersole Tai Po Hospital, the Northern District Hospital, the Pamela Youde Nethersole Eastern Hospital, and the United Christian Hospital. A total population of 2 million was served by these five hospitals. This randomized study was approved by the ethics committee of the Chinese University of Hong Kong. Informed consent was obtained from all patients.

Eligibility Criteria and Pretreatment Investigations

Eligible patients had mid or lower thoracic esophageal cancers that were confirmed on histology to be a squamous cell carcinoma deemed to be resectable. These patients received further staging workup, including esophagoscopy, bronchoscopy for midthoracic tumor, endoscopic ultrasonography (EUS), computer tomography (CT) of the thorax and abdomen with contrast, and ultrasonography of the cervical region with fine needle aspiration cytology for any suspicious nodes. We excluded those patients who had distant metastasis to solid visceral organs or local invasion into trachea, descending aorta, or recurrent laryngeal nerve. Those patients who were older than 75 years or who had a serious premorbid condition or a poor physical status that compromised a thoracotomy were also excluded. Moreover, patients with compromised cardiac function or creatinine clearance less than 50 ml/min were not eligible.

Interventions

Standard Esophagectomy. The surgery was performed by specialists in upper gastrointestinal surgery at each respective hospital. The surgical approach to mid or lower thoracic esophagus was standardized to two-stage esophagectomy to achieve a minimum of 5-cm proximal margin. For tumors located over the proximal mid thoracic esophagus where a 5-cm proximal margin could not be achieved, a three-stage esophagectomy was performed. We performed a two-field lymphadenectomy in both situations of either cervical or thoracic anastomosis. All of the esophagectomies were performed through an open approach. A curative surgical resection was defined as macroscopic clearance of the esophageal tumor with no residue disease left. The continuity of the gastrointestinal tract was restored using a transposed stomach unless the patient had had a previous gastrectomy, in which case colonic interposition was performed instead. Patients in the standard esophagectomy group receive postoperative adjuvant chemotherapy or radiotherapy if the resection was considered to be R1; that is, if microscopic disease is left behind.

Chemoradiotherapy. Patients randomized to the chemoradiotherapy (chemoRT) group received two

3-weekly cycles of cisplatin and 5-fluorouracil chemotherapy. Cisplatin 60 mg/m^2 with hydration therapy was given on day 1 and day 22, whereas 5-fluorouracil was administrated as a continuous infusion at 200 mg/m^2/day through a Hickman catheter and a portable infusion pump from day 1 to day 42.

Radiotherapy was delivered in a three-dimensional conformal mode with a total of 50–60 Gy given in 25–30 fractions over 5–6 weeks. The dosage for individual patients was governed by the dose constraints of normal organs. Target volume length included 5 cm on each side of image visible tumor and malignant nodes. The radiotherapy was delivered in three consecutive phases. Phase I started with anterior-posterior opposing portals to 30 Gy, while phase II was given with three fields to another 20 Gy. Phase III used reduced portal length to give up to 10 Gy, subject to limiting radiation dose to the heart, lung, and spinal cord.

Follow-up

All patients were followed in a joint esophageal cancer clinic at 6- to 8-week intervals in the first year and at 3-month intervals thereafter. Local or systemic recurrences were documented. For the chemoRT group, tumor surveillance was conducted with a repeat CT scan of the thorax and endoscopy at 6 weeks after completion of the treatment and then 3 months afterward. Resectable local recurrences or residue tumors were treated with salvage esophagectomy.

Outcome Definitions

The primary outcome measure was overall survival at 2 years. Secondary outcomes included disease-free survival and the hospital stay. The morbidities in both treatment groups were also analyzed. The recurrence of the disease was defined as either endoscopic recurrence confirmed with biopsy or radiologic evidence of extra-anatomical nodal or distant metastasis. The operative mortality was defined as an in-hospital death within 30 days.

Sample Size Estimation and Statistical Analysis

Sample size calculation was based on a median survival in patients treated with esophagectomy of 15 months. We predicted that primary chemoradiotherapy could achieve a median survival of 30 months based on our pilot study. We used the log-rank test to compare the survival difference between the two groups. We defined the α as 0.05, and β as 0.2. A sample size of 40 patients was determined to be required for each treatment arm.

The baseline data of patient's characteristics and the primary and secondary outcome measures were compared using the Student *t* test for parametric data and the Mann-Whitney *U* test for nonparametric data. For those data in proportions, we used the χ^2 test or the Fisher exact test, if one of the expected values was less than 5. We calculated the relative risks for recurrence of the cancer, morbidities, and mortalities related to each of the therapies with the provision of a 95% confidence interval. We used the Kaplan-Meier curve to represent the probability of survival within 2 years after initial diagnosis, and compared the two groups using the log-rank test. A value of $P < 0.05$ was considered to be statistically significant. The statistical analysis was performed with the SPSS software (version 11.5, SPSS Inc., Chicago, IL). The analysis was performed according to an intention-to-treat principle.

RESULTS

Demographics

From July 2000 to December 2004, 81 patients were recruited. Forty-five patients were randomized to the standard esophagectomy group (surgery group) and 36 to the chemoRT group. There was no patient who defaulted follow-up. There was no significant difference between the two groups in terms of baseline demographics or the grade and the duration of the dysphagia before treatment (Table 1). All of the esophageal tumors were confirmed to be squamous cell carcinoma. The location of the tumor, the mean tumor length, and the pretreatment tumor stage were similar for the two groups (Table 2). The median follow-up of the patients was 16.9 months. One patient was excluded from the study after inclusion into the surgery group. He was initially suspected to have resectable disease, but subsequently the operation was not performed because of potential advanced local disease.

Standard Esophagectomy Group

Forty-four patients were treated with primary surgery. The majority of the patients in the primary surgery group received a two-stage esophagectomy (75.0%). Seven patients were treated with three-stage esophagectomy, while one patient was treated with pharyngolaryngoesophagectomy. Three patients were determined nonresectable during thoracotomy or laparotomy (Table 3). Two of them were subsequently treated with chemoradiation. Six tumors (13.6%) were found to be adherent to the adjacent organs during intraoperative dissection, and the organs involved included the pleura and pericardium (one), trachea (two), aorta (two), and spleen (one). The majority of the tumors were T3 disease (70.5%), with

Table 1. Baseline demographics of the study population

	Surgery (N = 44)	Chemoradiation (N = 36)	*P* Value
Gender			
Men	39 (89)	27 (75)	
Female	5 (11)	9 (25)	0.10
Age, yr			
Mean ± SD	62 ± 9.7	62 ± 8.6	
Median (range)	62 (47–76)	62 (42–74)	0.88
Presenting symptoms			
Dysphagia on presentation	37 (82%)	33 (92%)	0.33
Grade 2	31 (84%)	31 (94%)	
Grade 3	6 (16%)	2 (6.1%)	0.27
Duration of dysphagia, mo			
Median, range	1.5 (0.3–6)	1 (0.3–8)	0.44
Weight loss	23 (50%)	17 (47%)	0.73
Anorexia	2 (4.4%)	2 (5.6%)	1.00

Values given in No. of patients (%) unless otherwise specified.

half of them having lymph node involvement (43.2%) (Table 3). Five patients had spread to the lymph nodes of the celiac axis; we categorized them as having M1a disease. The overall operative mortality was 6.8%, with a postoperative morbidity of 38.6%. Chest infection and respiratory failure comprised one third of the morbidities. Of these patients, 13.6% were treated with postoperative adjuvant radiotherapy or chemoradiation as the resections were either declined or considered as R1 basing on pathology.

Chemoradiotherapy

Thirty-six patients were randomized to receive primary concurrent chemoradiation. Thirty of these patients (83.3%) completed the full course of chemoradiation. Six patients did not complete the whole course of chemoradiation. One of them developed arrhythmia, whereas another had an episode of severe sepsis. Four had neutropenic fever. Immediately after the chemoradiation, patients did not have a

Table 2. Baseline characteristics of the esophageal tumor between the two groups

	Surgery (N = 44)	Chemoradiation (N = 36)	*P* Value
Tumor site			
Middle third	26 (58%)	21 (58%)	
Lower third	19 (42%)	15 (42%)	0.96
Tumor length, cm			
Mean ± SD	5.3 ± 2.0	5.3 ± 1.9	
Median (range)	5 (2–11)	5 (2–9)	0.99
Pretreatment tumor stage by CT thorax (TNM stage 1987)			
T2	10 (22.7%)	13 (36%)	
T3	34 (77.3%)	23 (64%)	0.17
N1	23 (51.1%)	14 (39%)	0.27
Pretreatment tumor volume by CT thorax, cm^3			
Mean ± SD	27.5 ± 14.8	23 ± 18	0.34
Median (range)	26.5 (2–51)	19 (3–54)	0.22
Pretreatment tumor stage by EUS			
T1	1 (2.5%)	2 (5.6%)	
T2	12 (27%)	11 (31%)	
T3	29 (66%)	21 (58%)	
T4	2 (4.3%)	2 (5.6%)	0.81
N1	25 (57%)	17 (47%)	1.0

CT = computer tomography; RT = radiotherapy; EUS = endoscopic ultrasonography.
Values given in No. of patients (%) unless otherwise specified.

Table 3. Outcomes of the standard esophagectomy group

Outcomes	Esophagectomy (N = 44)
Type of operation	
Two-stage esophagectomy	33 (75%)
Three-stage esophagectomy	7 (16%)
Pharyngolaryngoesophagectomy	1 (2.3%)
Staging thoractomy or laparotomy	3 (6.8%)
Pathologic staging (TNM staging)	
T1	3 (6.8%)
T2	7 (16%)
T3	31 (71%)
T4	3 (6.8%)
N1	19 (43%)
M1a	5 (11%)
Operative outcomes	
Mean blood loss, ml	726 ± 704
Mean operative time, min	363.8 ± 79.9
Operative mortality (30 days)	3 (6.8%)
Cause of operative mortality	
Pneumonia	2 (67%)
Sepsis	1 (33%)
Postoperative morbidities	17 (39%)
Anastomotic leakage	1
Respiratory failure	7
Chest infection	7
Wound infection	3
Cord palsy	3
Stomach perforation	1
Pancreatic fistula	1
Intraoperative bronchial laceration	1
Mean extubation time after surgery, hr	21 ± 30
Median ICU stay, days	4 (1–60)
Adjuvant therapy after surgery	6 (14%)
Radiotherapy	4 (9.1%)
Chemoradiation	2 (4.5%)

ICU = intensive care unit.
Values given in No. of patients (%) unless otherwise specified.

significant reduction in the dysphagia. There was only an improvement in the symptoms of dysphagia at 4.5 months after the therapy. No chemoradiation-related death occurred, and the major morbidities from the chemoradiation were gastrointestinal upset, neutropenia, and fever (Table 4). Five patients who had recurrent or persistent disease in the chemoRT group were treated with salvage esophagectomy, and one patient had an exploratory thoracotomy only. One of the six patients treated by the salvage esophagectomy died 2 weeks after initial operation due to catastrophic bleeding from the residue tumor left in the mediastinum (16.7%).

Comparison of Standard Esophagectomy to Chemoradiation

The overall survival at 2 years was 54.5% for the standard esophagectomy group and 58.3% for the chemoRT group (RR = 0.89; 95% confidence interval [CI], 0.37–2.17; log-rank test $P = 0.45$). No difference was present in the 2-year survival achieved by standard esophagectomy or chemoradiation (Fig. 1). Eighteen patients in the esophagectomy group (40%) and 16 in the chemoRT group (44.4%) were found to have recurrence upon follow-up (RR = 1.2; 95% CI, 0.49–2.92) (Fig. 2). The group of patients treated by chemoradiation had a longer hospital stay compared with the esophagectomy group (Mann-Whitney U, $P = 0.022$) (Table 5). Patients treated by esophagectomy developed recurrence mainly in the mediastinum, whereas those treated by chemoradiation developed recurrence in the cervical or abdominal regions, although this does not show statistical significant difference.

DISCUSSION

Esophagectomy remained the gold standard of curative treatment for carcinoma of esophagus. Recently, chemoradiation was used as a neoadjuvant treatment to achieve better locoregional control.[13–22] The rate of complete pathologic response assessed after surgical resection can be up to 30%.[13,14] In this study, we found that both standard esophagectomy and chemoradiation achieved a similar survival at 2 years (RR = 0.89; 95% CI, 0.37–2.17; log-rank test $P = 0.45$). The overall survival achieved by standard esophagectomy was 54.5%, whereas that of definitive chemoradiation was 58.3%. Cooper et al.[23] reported their experience in concurrent chemoradiation compared with radiotherapy alone in treating advanced carcinoma of the esophagus. They included patients with carcinoma of the esophagus with stage T1-3 N0-1, which had a similar tumor staging as our patients. The 2-year survival in the chemoRT group was 38%, compared with 10% in the radiotherapy-alone group. With the advancement in technology, definitive chemoradiation could achieve a comparable 2-year survival of 30–50% of that of esophagectomy, which is confirmed by the early results of our study.[24]

Four patients in the surgery group received adjuvant radiotherapy because of the involvement of either proximal or the adventitial margin. Two patients randomized to the esophagectomy group subsequently treated with chemoradiation after exploratory thoracotomy were deemed to have nonresectable disease. We analyzed these patients on the intention-to-treat principle. This effect of additional chemoradiation therapy in the surgical group is, however, balanced by the necessity of salvage surgery to treat detectable residue disease in the chemoRT group. Moreover, six patients in the chemoRT group did not complete the whole course of therapy.

Table 4. Outcomes of the chemoradiation (chemoRT) group

Outcomes	chemoRT (N = 36)
Completion of full course of chemoRT	30 (83%)
Reasons for unable to complete treatment	
Arrhythmia	1 (2.8%)
Sepsis	1 (2.8%)
Neutropenic fever	4 (11%)
Posttreatment 6 weeks OGD—complete response (%)	33 (92%)
6 weeks posttreatment mean tumor volume (cm^3)	20 ± 20
3 months posttreatment mean tumor volume (cm^3)	11 ± 12
Mortality from chemoRT (30 days)	0 (0%)
Morbidity from chemoRT	24 (67%)
Anorexia	5
Nausen	6
Neutropenia	8
Fever	5
Salvage surgery performed	
Two-stage esophagectomy	5
Exploratory thoracotomy	1

OGD = esophagogastroduodenoscopy.
Values given in No. of patients (%) unless otherwise specified.

The operative mortality in the standard esophagectomy group was 6.8%, with a morbidity of 38.6%. This is comparable to rates of other studies on the perioperative outcomes for esophagectomy.[4,5,25] Although there was no mortality directly related to chemoradiation, the perioperative mortality in the salvage esophagectomy group was 16.7%. Technically, salvage esophagectomy is more difficult than primary surgery, and extended lymphadenectomy is not advocated because of the increased perioperative morbidity and mortality.[26]

The chemoRT group has a significantly longer hospital stay compared with that of the standard esophagectomy group. This is because concurrent chemoradiation required therapy to be given in divided doses over a period of 6–8 weeks. From the patient's perspective, a longer stay in the hospital could possibly jeopardize the quality of life and satisfaction.[27]

In our study, the disease-free survival was similar for the esophagectomy group and the chemoRT group. The proportion of recurrence at 2 years was also similar in the two groups. The pattern of recurrence, however, differs slightly between the two

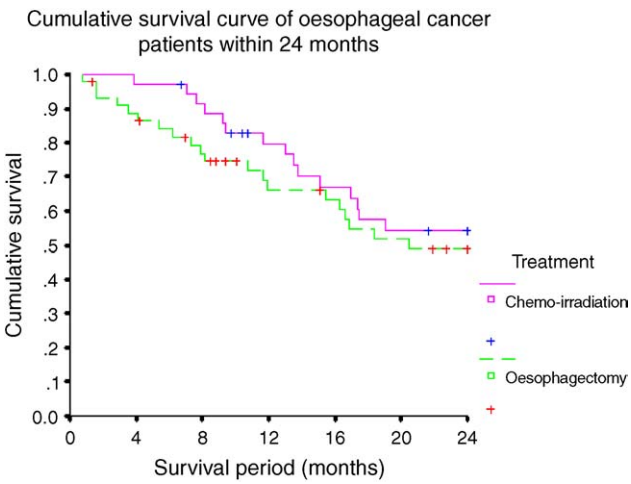

Fig. 1. The Kaplan-Meier curve representing the early cumulative survival of the standard esophagectomy group and the chemoradiation group (RR = 0.89; 95% confidence interval, 0.37–2.17; log-rank test $P = 0.45$).

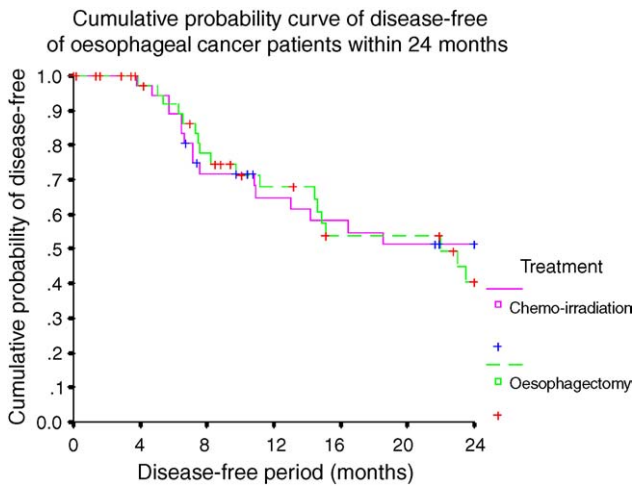

Fig. 2. The Kaplan-Meier curve representing the disease-free survival of the standard esophagectomy group and the chemoradiation group (RR = 1.2; 95% confidence interval, 0.49–2.92).

Table 5. A comparison of the early oncologic outcomes between the esophagectomy group and the chemoradiation (chemoRT) group

	Esophagectomy	chemoRT	*P* Value
Median hospital stay, days	27 (8–215)	41 (14–129)	0.02
Overall survival, mo	24 (55%)	21 (58%)	0.34
Disease-free survival, mo	24	20	
Tumor recurrence	18 (41%)	16 (44%)	0.77
Site of recurrence			
Mediastinal	12	6	
Anastomosis/previous tumor site	6	6	
Paratracheal	4	0	
Other	2	0	0.39
Cervical (neck nodes)	1	3	0.65
Abdominal	2	3	0.32
Distant metastasis	5	5	
Bone	2	1	
Lung	1	2	
Liver	1	1	
Brain	1	0	0.75
Treatment for recurrence			
Chemoradiation	1	0	
Radiotherapy	6	1	
Salvage cesophagectomy	-	6	
Supportive treatment	11	9	

Values given in No. of patients (%) unless otherwise specified.

groups. The esophagectomy group tends to have more mediastinal recurrence, whereas those treated with chemoradiation developed cervical or abdominal recurrence. Squamous cell carcinoma of the esophagus has a high incidence of lymphatic spread to the mediastinal lymph nodes, including paratracheal and recurrent nerve nodes.[5] To further improve the locoregional control and survival, the tumor has to be resected together with the surrounding lymphatics. Extended lymphadenectomy including three-field or en bloc esophagectomy used the theory of radical lymphadenectomy with a resection of a complete sheath of tissue surrounding the esophagus.[28,29] Nationwide results from Japan claimed a significant improvement in 5-year survival results.[30] Lerut et al.[31] reported a 5-year survival of 41.9% after three-field esophagectomy in a Western series, which was apparently better compared than transhiatal or two-field esophagectomy.[4–6] Three-field esophagectomy could be one of the strategies to further improve the locoregional control, and thus survival, for carcinoma of the esophagus compared with chemoradiation.

We reported our experience in the use of spiral CT to predict the clinical response of carcinoma of esophagus to preoperative chemotherapy. We found that spiral CT had an accuracy of 88% in predicting T stage and of 84% in predicting N stage.[32] The use of CT to predict response after chemoradiation, however, is still controversial.[33] Some authors used the wall thickness as a criterion to diagnose residue disease, whereas in our current trial we used the tumor volume after adequate distention and contrast enhancement as a measuring tool. Further refinement in the technique and diagnostic criteria of CT scan is necessary to predict tumor response and detect residue disease after chemoradiation.

EUS is another tool to assess tumor response. However, numerous prospective series reported that EUS is not accurate in predicting tumor response after chemoradiation.[34,35] We shared a similar experience with these authors as there is a lack of diagnostic criteria in EUS concerning residue disease. Recently, positron-emission tomography using 2-[^{18}F]fluoro-2-deoxy-D-glucose is emerging as a highly accurate tool to assess tumor response after chemoradiation.[36]

CONCLUSION

From the early results of a prospective randomized trial, we found that both standard esophagectomy and chemoradiation achieved comparable intermediate-term survival. Standard esophagectomy was associated with perioperative mortality, whereas chemoradiation

required a significantly longer period of treatment and was associated with the risks of salvage surgery. Thus, either standard esophagectomy or chemoradiation can be recommended as a treatment for squamous cell carcinoma of the esophagus.

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Laparoscopic Subtotal Colectomy for Colonic Inertia

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Colonic inertia is an uncommon condition, usually occurring in women in the third decade of life. Severity of symptoms may lead some patients to a surgical consultation. This is a retrospective review of 14 patients who underwent laparoscopic subtotal colectomy for colonic inertia, performed by a single surgeon from August 1993 to November 2002. The mean age of the patients was 38.5 years (range 26–50 years); 93% of the patients were women. The common presenting symptoms included abdominal pain (93%), bloating (100%), constipation (100%), and nausea (57%). Median duration of symptoms before surgery was 4.5 years (range 1–30 years). Subtotal colectomy was completed laparoscopically in 13 patients. There was one conversion (7%) because of adhesions. Eleven patients (78.6%) had undergone previous abdominal surgery. The mean operating room time was 153 minutes (range 113–210 minutes). The median time to full bowel action was 2 days. One patient developed postoperative small bowel obstruction that required open exploration. Complete follow-up was available for 11 patients at a median follow-up of 18 months (range 2–96 months). Ninety-one percent of the patients reported excellent satisfaction with surgery, and their bowel movement frequency changed from 1.2 (±0.2) per week preoperatives to 17.2 (±2.9) per week postoperatively ($P < 0.001$). Three patients (27%) continued to report abdominal pain and 3 patients (27%) continued to require laxatives postoperatively. Laparoscopic subtotal colectomy provides excellent symptom relief in patients with colonic inertia who do not respond to medical measures. (J GASTROINTEST SURG 2005;9:803–808)

KEY WORDS: Colonic inertia, laparoscopic colectomy, outcomes

INTRODUCTION

Colonic inertia is an uncommon condition that occurs most often in women in the third decade of life. It usually presents with symptoms of constipation and abdominal pain with insidious onset often before the age of 10 years. Patients with this disorder have significant alteration of their lifestyle, with up to 75% requiring absences from work for symptoms related to the disorder.[1] The diagnosis of colonic inertia represents the severe part of the spectrum of slow-transit constipation, a clinical syndrome of constipation attributable to ineffective colonic propulsion.

Most patients with constipation can be treated medically with improvement of symptoms. Patients with objective evidence of delayed colonic transit whose symptoms are refractory to medical management may benefit from surgical therapy.

The most commonly performed surgical procedures have been total abdominal colectomy with ileorectal anastomosis, and subtotal colectomy with ileosigmoid anastomosis. More recently, laparoscopic techniques have been applied to the clinical problem of colonic inertia.[2–4]

This study examines the feasibility of applying laparoscopic techniques to colonic inertia and follows

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the results of laparoscopic subtotal colectomy with ileosigmoid anastomosis for colonic inertia.

METHODS

Outcomes were examined for 14 patients with colonic inertia who underwent laparoscopic or robotic-assisted laparoscopic subtotal colectomy, performed by a single laparoscopic surgeon between August 1993 and November 2002. Data from a prospectively administered database were abstracted with respect to demographic information, previous surgery, operating room time, type of resection, complications, length of hospital stay, and duration of ileus. A retrospective chart review was undertaken to gather data regarding duration of symptoms, preoperative treatment, and clinical follow-up.

All patients underwent colonic transit studies (CTS). Colonic inertia was defined as retention of at least 25% of markers in the colon at 72 hours. Patients were assessed with colonoscopy (n = 14) and barium enema (n = 3). All patients were evaluated with anorectal manometry to assess continence and rule out pelvic floor dysfunction. Further investigation with small bowel follow through was completed in 3 patients and defecography was performed in 5 patients.

In all cases, the planned procedure was a laparoscopic subtotal colectomy with ileosigmoid anastomosis. One case was performed with robotic assistance. The patients were placed in the lithotomy position with both arms tucked where possible. Abdominal access was obtained with a Veress needle technique. Four or five trocars were used with the insertion of the primary trocar with an Optiview port (Ethicon Endosurgery, Cincinnati, OH) (Fig. 1). Mobilization of the colon segments was generally started at the right colon. Mobilization was aided by utilization of Endoshears (Harmonic Scalpel, Ethicon Endosurgery). A midline extraction site of 4 to 5 cm was used with the colonic vasculature divided partially extracorporeally (left-sided vessels intracorporeally, right-sided extracorporeally). The colon was resected to the level of the distal sigmoid, leaving approximately 5 to 10 cm of distal sigmoid in situ. The anastomoses were created with a double staple, side-to-side technique. No drain was inserted.

RESULTS

All patients underwent subtotal colectomy with ileosigmoid anastomosis. All procedures were attempted laparoscopically, one with robotic assistance. The mean age of the patients (93% female) was 38.5 years (range 26–50 years) with a mean duration of symptoms of 4.5 years. Seventy-eight percent had previously undergone abdominal surgery, but only one required conversion due to adhesions. Most common presenting symptoms were constipation (100%), abdominal pain (93%), bloating (100%), and nausea (57%), and almost 90% of patients were regularly using enemas in addition to oral laxatives (100%). Eighty-six percent of patients used oral bowel preparatory formulas.

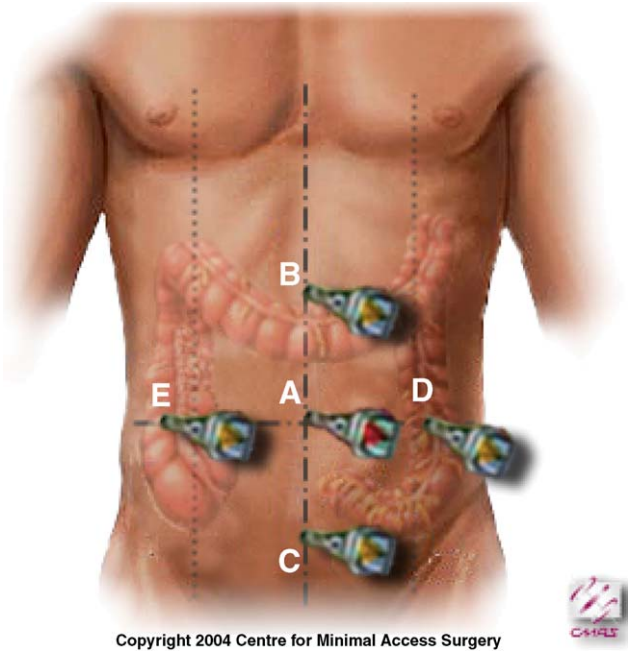

Fig. 1. Placement of trocars. A, B, and C = 5 mm camera ports; D = 5 mm port that may be changed to 10/12 mm for stapler use; E = optional additional 5 mm port for left colon mobilization.

Preoperative workup showed that all 14 patients had delayed transit time during the shape study, confirming the diagnosis of colonic inertia. All patients underwent anorectal manometry, with 13 patients showing normal results and 1 patient with abnormal anorectal inhibitory response. All preoperative results are summarized in Table 1.

Mean operating room time was 153 minutes (range 113–210 minutes). There was one conversion to an open procedure (7%) in a patient with extensive intraabdominal adhesions. The median length of stay was 6 days (range 3–15 days). The median time to resolution of ileus, defined as time to tolerate oral fluids, was 2 days (range 1–9 days). The overall complication rate was 28.6%. There were two major complications. One patient had a significant postoperative intraabdominal bleed, but did not require reoperation. The second patient required early reoperation for small bowel obstruction secondary to

Table 1. Preoperative workup

Study	n	Results
Shape study	14	14 positive
Anorectal manometry	14	13 normal
		1 abnormal anorectal inhibitory reflex
Colonosopy	14	14 normal
Biopsy	13	13 normal
Barium enema	3	3 normal
Small bowel follow through	3	2 normal
		1 decreased
Defecogram	5	3 normal
		1 partial intussusception
		1 anterior rectocele

an internal hernia. This complication involved small bowel herniating through the mesenteric defect. Perioperative outcomes are summarized in Table 2.

Complete follow-up with respect to postdischarge outcomes was available in 11 patients; the remaining three were lost to follow-up. Median duration of follow-up was 18 months (range 2–96 months). In this group of patients, bowel movement frequency increased from 1.2 (±0.2) per week preoperatively to 17.2 (±2.9) per week postoperatively ($P < 0.001$). Three patients continued to require some form of laxative postoperatively. Abdominal pain was experienced postoperatively by 3 of 11 patients (27%), compared with 93% preoperatively. Ninety-one percent of patients reported excellent satisfaction with the surgery.

DISCUSSION

The cause for colonic inertia is unclear. Potential mechanisms for delayed transit include fewer colonic high-amplitude propagated contractions[5] or a reduced colonic contractile response to a meal. Patients with colonic inertia have impaired motor responses to cholinesterase inhibitors and have abnormal expression of serotonin receptors.[6,7] Colons of patients with colonic inertia have been shown to have a decrease in colonic electrical activity when compared with controls, which has been proposed to involve the interstitial cells of Cajal.[8,9]

Table 2. Perioperative outcomes (14 patients)

Mean operative time (min)	153 (range 113–210)
Conversion (n)	1 (7%)
Complications	
All (%)	28.6%
Major (n)	2
Median length of hospital stay (days)	6 (range 3–15)
Median duration of ileus (days)	2 (range 1–9)

The primary investigation for patients with colonic inertia should include a colonic transit study. Several methods to define colonic transit time are available, including indigo carmine, charcoal, barium, radioisotopes, microtelemetry units, and radiopaque markers. Radiopaque marker tests are the least expensive, easiest to perform, and the most informative. The maximum whole gut transit time is 72 hours as measured by plain radiograph on day 4.[10] Workup should also include anorectal manometry to determine the presence of pelvic floor dysfunction. All of our patients were also investigated with anorectal manometry, which revealed an abnormal anorectal inhibitory reflex in one patient. This patient underwent biofeedback therapy preoperatively with a successful surgical outcome. Other testing should include colonoscopy or barium enema to rule out a structural lesion and can include small bowel follow through to identify any abnormalities in small bowel motility.

Medical treatment includes dietary fiber supplements, osmotic laxatives, stimulant laxatives, cathartics, and prokinetics. Most patients have been tried on multiple medical therapies for constipation, including bowel preparatory formulas, before a surgical referral is made. Surgical treatment is appropriate for only a small proportion of those with constipation. Lahr et al. evaluated 2042 patients referred for constipation and found that 9.9% were suitable for surgical therapy. Those patients had no untreated underlying illness, their disease was resistant to medical therapy, and their colonic transit time was consistent with colonic inertia.[11]

Patients in this series all required regular laxatives to have a mean of 1.2 bowel movements per week. Half of these patients also required regular use of enemas, and most also used bowel preparatory formulas (85.7%). As reported in other series,[3,12–22] this disease occurs in a relatively young group of mostly female patients (mean age 38.5, 93% female in our series), but the duration of symptoms in our group was somewhat shorter (4.5 years) than in the other reports. This may represent a shift to earlier referral in the era of laparoscopic colon surgery.

The most common surgical procedures performed for colonic inertia have been total colectomy with ileorectal anastomosis and subtotal colectomy with ileosigmoid anastomosis. Total abdominal colectomy has been performed most frequently for this condition, citing increased rates of recurrent constipation for subtotal colectomy.[23] Total abdominal colectomy does result in incontinence in 4% to 24% of patients

in this young demographic.[15,20,24] Others have suggested that subtotal colectomy will reduce the incidence of postoperative incontinence.[19]

Our choice is to perform a subtotal colectomy with an anastomosis to the distal sigmoid at approximately 5 to 10 cm. We feel this represents a balance in the risks of incontinence vs. recurrent constipation. None of the patients in our series reported incontinence, and only 3 of the 11 patients required any postoperative laxative use. This study shows that the surgery can

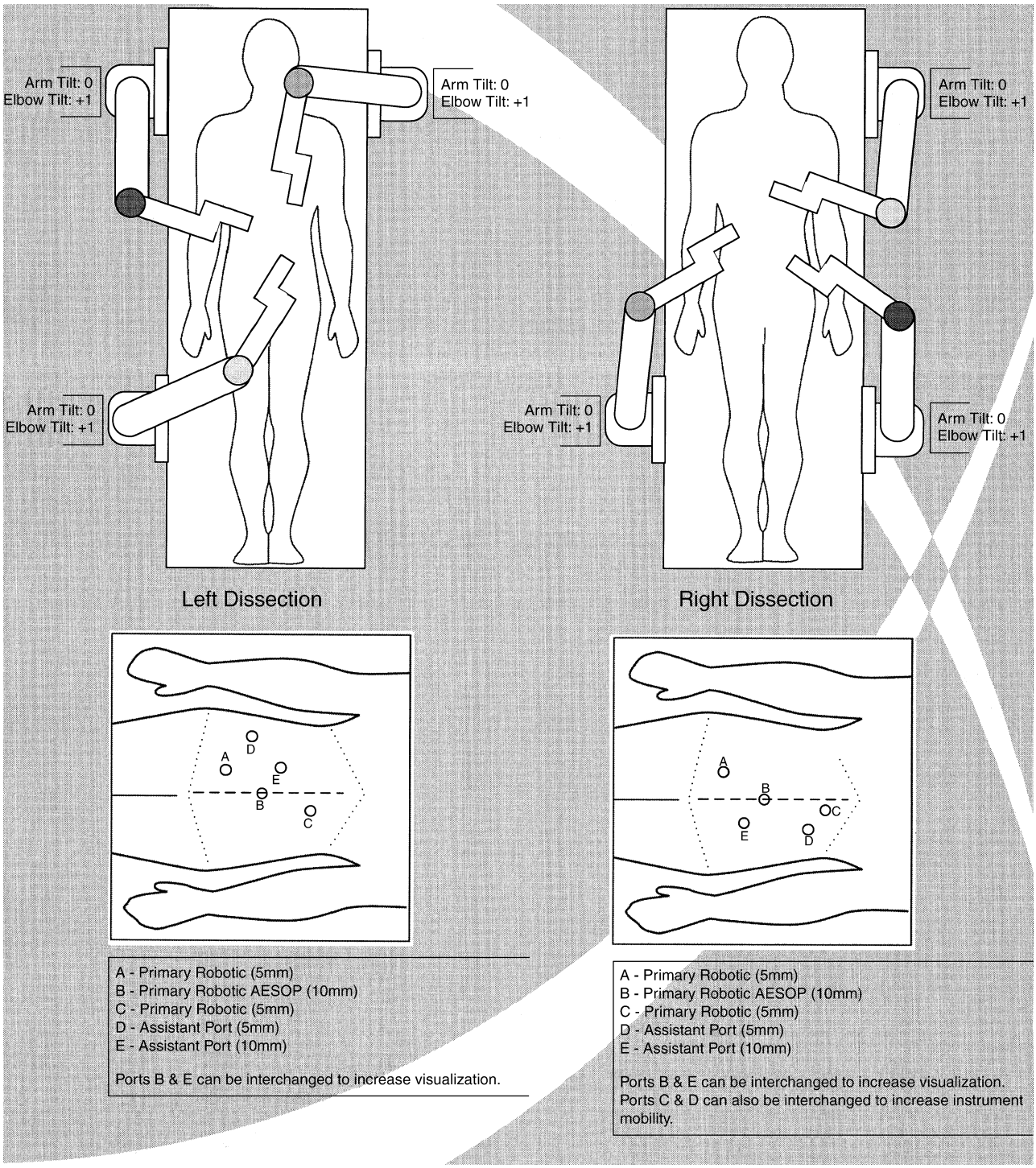

Fig. 2. Setup for left- and right-sided dissection during robotic assisted subtotal colectomy, showing robotic arm and trocar placements.

be completed laparoscopically in a comparable amount of time with good results and limited morbidity.

Several series have shown positive outcomes for surgical treatment with overall success rates of 80% to 100%.[17–22,24–26] Outcomes have generally been measured with respect to frequency of bowel movements improving from 0.5 to 1.4 per week to 15 to 26 per week.[19–22,24,25] Our results mirror those previously published in the open literature with bowel movements increasing from 1.2 per week preoperatively to 17.2 postoperatively ($P < 0.001$) with a subjectively positive result in 91% of patients.

The postoperative course in these patients can be complicated. Length of hospital stay is generally in the range of 7 to 13 days[20,22,25,26] in this young group of patients, with postoperative ileus complicating the postoperative course in many of these patients.[19,20] A review published by Pfeifer et al. revealed a high rate of postoperative small bowel obstructions, occurring in as many as 50% of patients in some series.[23] Our average length of stay was somewhat lower than the open series at 6 days, and the median duration of ileus was quite short at 2 days. Overall morbidity was 28.6%. One patient was readmitted with small bowel obstruction and required reoperation through laparotomy. Overall complication rates in the open literature have generally ranged from 41% to 60%.[13,14,20]

Laparoscopic techniques have been successfully applied to colon surgery with a decrease in hospital stay and morbidity.[27–29] Results of colonic resection for benign disease have shown favorable results.[2] These data have encouraged surgeons to apply minimal access techniques to colonic inertia with the hope that this will decrease hospital stay and reduce postoperative morbidity. Previous published results of laparoscopic resections for colonic inertia have suggested preferable cosmetic results compared with open procedures.[4]

Current robotic technology offers no real advantages to a skilled laparoscopic colorectal surgeon. Although it is safe, robotic use increases operating room time, requires repeated changes of position of the robotic arm because of the inability to cover more than 1 to 2 quadrants of the abdomen at any position, and time wasted during multiple instrument changes. However, future modifications capable of offering multiple-quadrant coverage and ease of tool change with the addition of haptics and three-dimensional imaging may provide a valuable enhancement to the current laparoscopic approach. Figure 2 shows the robotic arm placement and trocar sites for a subtotal colectomy.

CONCLUSION

With careful patient selection, surgical therapy for colonic inertia can have excellent subjective results with objective improvement in bowel function. Subtotal colectomy leaving a short segment of distal sigmoid colon results in improvement in frequency in bowel movements similar to those reported in previously published studies of total abdominal colectomy. Laparoscopic techniques can be successfully applied to colonic inertia with reduction in hospital stay, morbidity, and duration of postoperative ileus.

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Perforated Meckel's Diverticulum Presenting as a Gastrointestinal Stromal Tumor: A Case Report

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Tumors and perforation of Meckel's diverticulum are rare manifestations. A gastrointestinal stromal tumor in a Meckel's diverticulum causing perforation and subsequent peritonitis in a 75-year-old man is presented. The literature on tumors in Meckel's diverticulum is extensively reviewed and discussed. (J GASTROINTEST SURG 2005;9:809–811)

KEY WORDS: Gastrointestinal stromal tumor, GIST, Meckel's diverticulum, perforation

Meckel's diverticulum (MD) is the most prevalent congenital abnormality of the gastrointestinal tract (0.3%–4.0%).[1,2] The lifetime complication rate for MD is around 4%, showing an age-dependent decrease. Of reported complications, perforation occurred in 7.3%–14%.[3] Ulceration of ectopic gastric tissue,[1] ingestion of foreign bodies, Littre's hernia,[4] but rarely tumors were the prevailing pathologies leading to perforation. In detail, since 1978 only nine cases of tumor-associated perforation of an MD (e.g., leiomyosarcoma [4], lymphatic sarcoma [1], and poorly differentiated stromal tumor [1])[5–12] have been reported. We report here a case of a gastrointestinal stromal tumor (GIST) causing MD perforation.

CASE REPORT

A 75-year-old white man with radiologically confirmed pneumoperitoneum indicative of perforation of a hollow organ presented for emergency laparotomy. At 15 cm from the ileocecal valve, a perforated Meckel's diverticulum was found and excised. Macroscopically, the diverticulum measured 2.5 × 2 × 2 cm in its greatest dimensions and showed a pinlike perforation but no features suggestive of a tumor. Specimen for microscopic examination was taken from the perforation site. Microscopic examination revealed a tumor with spindle cell proliferation arranged in a storiform pattern. The tumor involved the entire wall of the small intestine and measured 2 cm in its greatest diameter. Puriform inflammatory and hemorrhagic areas were found at the site of perforation.

Mitotic activity was estimated to be 0–1 mitosis per 50 high-power fields. Immunohistologically, the tumor cells showed strong positive reaction to CD 117 (Fig. 1) and CD 34 and moderate positivity to SMA and CD 99. Ki 67 showed a proliferation rate of 2%. The diagnosis was established as an incompletely resected GIST in a Meckel's diverticulum that caused perforation with subsequent peritonitis.

Computed tomographic (CT) tumor screening was negative except for already known bladder cancer. Atherosclerosis with repeated need for vascular surgical intervention and coronary artery disease with repeated myocardial infarction were additional comorbidities. Due to the compromised general condition, the multimorbidity of the patient, and the low malignancy of the tumor, we refrained from a second-look operation for complete tumor resection or commencement of imatinib therapy.

Because pulmonary embolism, pleural effusion, and gastrointestinal bleeding complicated the postoperative course, the patient was discharged from hospital 4 weeks after laparotomy.

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DISCUSSION

Less than 10% of symptomatic MDs are diagnosed preoperatively,[1] because they can mimic a variety of more common ailments, such as peptic ulcer disease, gastroenteritis, biliary colic, colonic diverticulitis, and milk allergy. Appendicitis, however, is the most common preoperative diagnosis in cases of complicated MD.[2]

Tumors were reported in 0.5%–3.2% of symptomatic MD.[1] A MEDLINE database search of the period November 1965 through August 2002 showed a prevalence of carcinoid tumor (31.5%) followed by leiomyosarcoma (25.5%), adenocarcinoma (11.4%), and leiomyoma (9.4%). The overall malignancy rate of tumors in MD was 77%. Analysis of the occurrence of mesenchymal tumors revealed sarcomas to occur in 34% and benign mesenchymal tumors in 19% of cases. Only two cases of mesenchymal tumor were definitively described as a GIST. The term GIST was originally coined in 1983[13] for entities previously known as smooth muscle cell tumors (e.g. leiomyoma, leiomyoblastoma, and leiomyosarcoma), schwannoma,[14] and spindle cell tumors. Based on this definition, 42% of all tumors and 41% of all malignant tumors in MD would have to be classified as GIST. This definition, however, was revised in 1998, so that now only cellular spindle cell, epitheloid, and pleomorphic mesenchymal tumors of the gastrointestinal tract staining CD 117–positive are termed GIST.[15]

GIST accounts for approximately 0.1%–3% of all gastrointestinal neoplasms.[14] Located in the small intestine, a GIST becomes symptomatic due to abdominal pain (74%), abdominal mass (72%), gastrointestinal bleeding (44%), small bowel obstruction (44%), weight loss (16%), fever or abscess (14%), or urinary symptoms (12%). Perforation of the tumor with subsequent peritonitis has been reported in 8% of GISTs of the small intestine.[16] The case presented here, however, is the first of a GIST of the small intestine causing MD perforation.

The preoperative diagnosis of tumors within MD is rare because of the few characteristic clinical and radiologic features. A range of diagnostic tests can be performed in symptomatic patients, including barium studies, endoscopy, ultrasound, CT scanning, and mesenteric arteriography, but correct preoperative diagnosis is infrequent. Abdominal and pelvic ultrasound examination and CT are helpful in showing a rounded mass. CT images of GIST may show asymmetric focal thickening of the bowel, as is also found in inflammatory conditions such as Crohn's disease and appendicitis.[17] Angiography, which is not routinely used in emergency situations, sometimes shows hypervascularization and feeding vessels. As with other tumors of the small bowel, GIST in this location (e.g.. MD) is difficult to visualize with standard diagnostic modalities. Therefore, most cases are diagnosed at the time of laparotomy and microscopic examination of the specimen.[18]

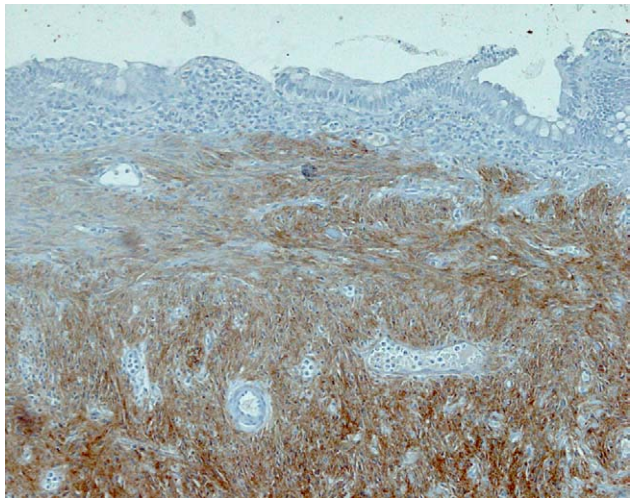

Fig. 1. Gastrointestinal stromal tumor (GIST) in a Meckel's diverticulum staining CD 117–positive and infiltrating the mucosa (original magnification, ×10).

The biological behavior of GIST is difficult to predict. Chang et al.[19] reported significant predictors of malignancy of GIST to be high cellularity, p53 overexpression, size of tumor of 5 cm or greater, 5 or more mitoses per 50 high-power fields, and marginal pleomorphism and necrosis. In addition, the absence of a predominant organoid growth pattern or of skenoid fibers or the presence of mucosal infiltration is a feature indicative of adverse outcome.[20] The present GIST case was characterized by high cellularity and mucosal infiltration. However, a predominant organoid growth pattern with interposed skenoid fibers, a mitotic activity of 0–1 mitosis per 50 high-power fields, and a weak expression of p53 were observed. These factors were indicative for the low malignancy of the present GIST case. This finding was also supported by the absence of necrosis or pleomorphism and a diameter of less than 5 cm.

Especially dense cellularity and mitotic counts are highly correlated with metastasis,[21] but patients with histologically benign lesions and no detectable mitotic figures can also develop metastases and die of the disease. The overall 5-year disease-specific survival rate is reported to be 46% for patients with localized GIST or locally advanced disease, 24% for patients with perforated tumors at diagnosis, but 0% for patients with multiple primary lesions or distant metastases at diagnosis.

The survival rate also depends on the completeness of resection. Patients with complete resection showed a 5-year survival rate of 42%, whereas patients with incomplete resection had a survival rate of only 8%.[16] Because GISTs are unresponsive to conventional chemotherapy or radiation, surgical en bloc resection is the treatment of choice for GIST. Low-malignancy GISTs have an excellent prognosis thereafter, but high-malignancy GISTs show a high rate of recurrence with poor survival after surgical treatment alone. GIST characteristically expresses the c-*kit* receptor tyrosine kinase (KIT), also known as CD 117. GIST generally has a mutation in the *KIT* proto-oncogene. Imatinib, a KIT tyrosine kinase inhibitor, has recently been found to have a dramatic antitumor effect on GIST, above all in the case of recurrence of primarily surgically treated high-malignancy GIST. Long-term follow-up data, however, on imatinib mesylate therapy alone or in combination with surgical therapy, are sparse to date.[22]

In the present case, the resection was incomplete. However, due to the compromised general condition and the multimorbidity (e.g., advanced atherosclerosis, coronary artery disease with repeated myocardial infarction and bladder cancer) of the patient and the low malignancy of the tumor, a second-look operation for complete tumor resection or imatinib therapy was not performed.

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Resection of Mesenteric Inflammatory Veno-occlusive Disease Causing Ischemic Colitis

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Mesenteric inflammatory veno-occlusive disease (MIVOD) is a rare cause of mesenteric ischemia that is diagnosed by histologic examination of the operative specimen. Recurrence of symptoms occurs, but further resection of ischemic intestine is seldom required. We describe the case of MIVOD in a young patient with clinical findings of ischemic colitis. The patient experienced complete resolution of the process, thus confirming the relatively benign course of this disease following resection. This report substantiates resolution of the inflammatory process after resection, colostomy, and reanastomosis. We review the literature and make conclusions regarding the clinical management of this disease. (J GASTROINTEST SURG 2005;9:812–817)

KEY WORDS: Mesenteric, ischemia, phlebitis, colitis

Mesenteric ischemia is classified by vascular etiology as thrombotic or nonthrombotic, venous or arterial. Although venous thrombosis is the least common cause of mesenteric ischemia, it carries the best prognosis.[1] We report the case of a young patient with clinical findings of ischemic colitis that proved to be mesenteric inflammatory veno-occlusive disease (MIVOD) after surgical resection and colostomy. She subsequently underwent colostomy takedown and reanastomosis with follow-up pathology demonstrating resolution of the phlebitis. Little is known about the natural history of this disease, but few patients experience symptoms compatible with recurrent disease and only one case of a second resection has been reported. We discuss the clinicopathologic features and management of MIVOD as well as similar descriptions of intestinal phlebitis and how they potentially relate to its clinical course.

CASE REPORT

A 25-year-old white woman was admitted to the gastroenterology medical service with a 5-month history of lower abdominal pain, bloody diarrhea, and tenesmus. She had initially presented 2 weeks earlier to a gastroenterologist, who performed a colonoscopy that demonstrated colitis from the anal verge to the distal sigmoid colon. She was treated with steroids and aspirin products for the working diagnosis of ulcerative colitis. However, biopsy results were compatible with ischemic injury. She was subsequently admitted to an outside facility for worsening abdominal pain, treated with antibiotics and steroids, and transferred to our institution for further workup and surgical consultation.

The patient's past medical history was remarkable only for appendectomy and atrial septal defect repair during childhood. There was no family history of inflammatory bowel disease or vasculitis. She took no medications and had no known allergies. On admission, she had a temperature of 100°F, blood pressure of 127/68 mm Hg, and sinus tachycardia to 128. Physical examination was remarkable for left mid and lower abdominal tenderness and a palpable mass without rebound. Pertinent laboratory work included a white blood cell count of 16.8 (normal, 4.0–11.0 K/μl), platelet count of 387 (normal, 150–400 K/μl), and normal values for coagulation profile, liver enzymes, electrolytes, and amylase. Repeat endoscopy demonstrated progression of a well-demarcated, confluent colitis to the distal sigmoid colon and biopsy results consistent with ischemic necrosis and inflammation.

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Abdominal computed tomography scan showed extensive sigmoid and rectal wall thickening, pericolonic stranding, and retroperitoneal lymphadenopathy (Fig. 1). Mesenteric arteriogram was normal except for tortuosity and hyperemic arterial circulation over the rectosigmoid region (Fig. 2).

Rheumatologic and hypercoagulability workups were performed that included HIV testing, homocysteine level, anti–thrombin III activity, protein C and S deficiency, lupus anticoagulant, anticardiolipin antibody, C3 and C4 complement levels, ANCA, rheumatoid factor, antinuclear antibody, and prothrombin 20210 mutation. All test results were either normal or negative.

Because the patient experienced no improvement following a trial of bowel rest, antibiotics, and steroids, she was taken to the operating room on hospital day 9 for exploration. Intraoperatively, the sigmoid colon was noted to be hypervascular and in spasm, whereas the rectum was thickened with extensive mesorectal adenopathy. A rectosigmoidectomy was performed with an end-colostomy and Hartmann's pouch. The patient's recovery was uneventful, and she was discharged by postoperative day 6 on an oral steroid taper.

Surveillance endoscopy of the descending colon and rectal pouch showed no further evidence of ischemic colitis. The patient subsequently underwent colostomy takedown with coloproctostomy 9 months after the initial operation and has remained symptom free in 24-month follow-up.

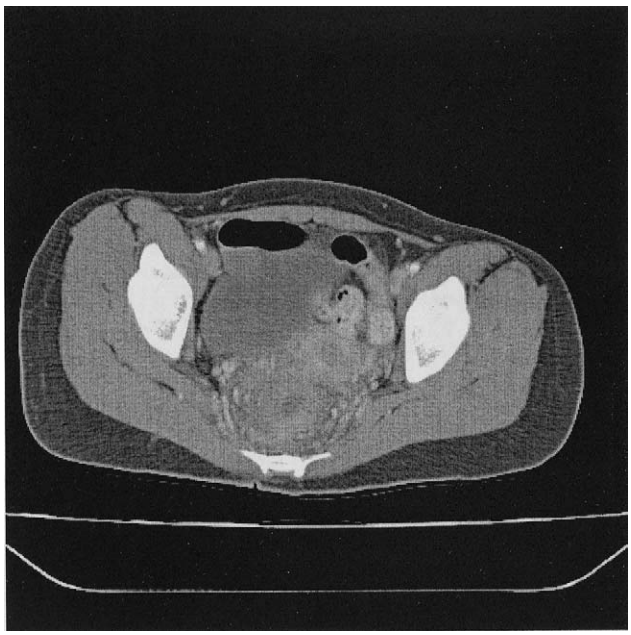

Fig. 1. Computed tomography scan showing rectosigmoid inflammation with bowel wall thickening and enhancing lymphadenopathy.

Histopathologic Findings

Gross examination of the resection specimen showed thickened mucosal areas of yellow discoloration and hemorrhage (Fig. 3). Microscopic examination revealed extensive ulcerations without necrosis of the muscularis propria. There was marked myointimal hyperplasia with mononuclear infiltrate and fibrinoid necrosis of the submucosal and mesenteric veins (Fig. 4A). Numerous venous thrombi were present at varying stages of organization, and Movat staining showed no arterial involvement (Fig. 4B). The vasculopathy was noted to involve the distal resection margin. A diagnosis of MIVOD, or enterocolic lymphocytic phlebitis (ELP), was made.

Specimens from the second operation included some mesenteric scar tissue, a portion of the colostomy, and staple margins from the descending colon and proximal rectum. These tissues were negative for active inflammation and necrosis, although the colon did show focal venous fibrointimal hyperplasia as well as venous occlusion by nonviable material with recanalization.

DISCUSSION

MIVOD[2] is a rare diagnosis that likely describes a spectrum of localized intestinal phlebitis variously termed ELP,[3] intestinal lymphocytic microphlebitis,[4] idiopathic myointimal hyperplasia,[5] granulomatous phlebitis,[6] and intramural mesenteric venulitis.[7] Cases of mesenteric venous thrombosis have been reported throughout the database literature (PubMed) since the 1950s, but the specific syndrome implied by these terms was not formally established until the first report by Saraga and Costa in 1989.[3]

Clinical Features

MIVOD is considered idiopathic, although similar histologic findings have been found in patients with known systemic lupus,[8] antiphospholipid antibody syndrome,[9] and cytomegalovirus infection.[10] The first patients diagnosed with ELP had each used the medication hydroxyethyl rutozide for the treatment of varicose veins[3,11]; thus, it was thought to be a hypersensitivity drug reaction, but subsequent cases have demonstrated no common exposures.

The presenting feature of this disease is subacute to acute visceral ischemia manifested as abdominal pain, hematochezia, and bloody diarrhea. Patients

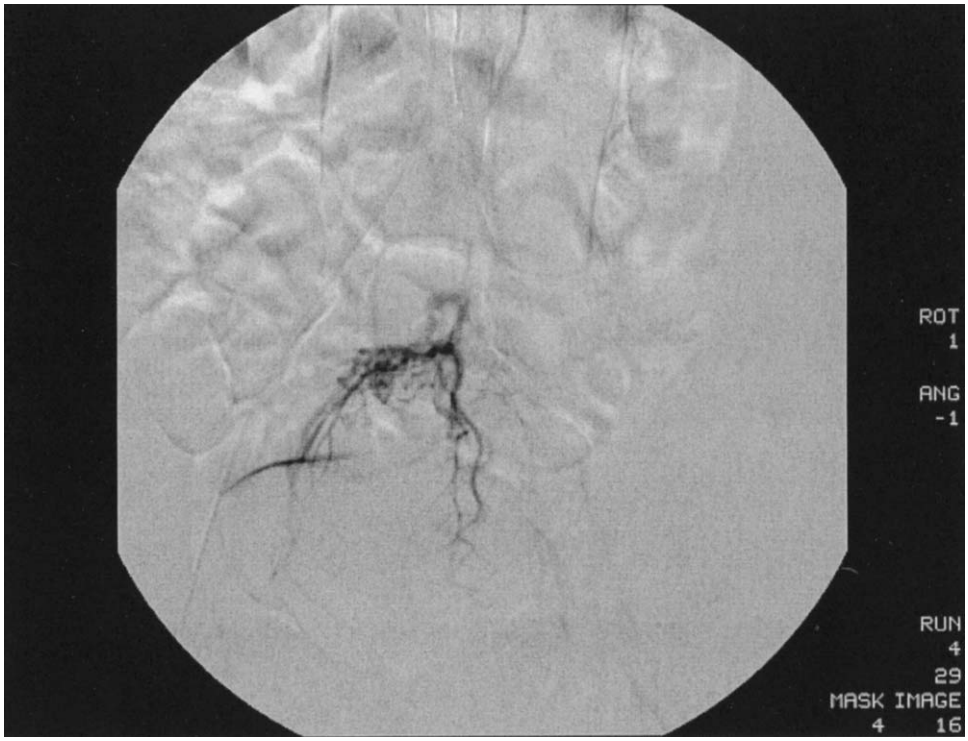

Fig. 2. Arteriogram showing prominent, tortuous superior rectal arteries and a small focal aneurysm.

often first come to the attention of gastroenterologists, and a workup for inflammatory bowel disease is initiated. However, the edema and inflammation associated with local venous outflow obstruction may also appear as an abdominal mass,[12–14] raising concern for a malignant tumor. A massive gastrointestinal bleed without prodrome has also been reported.[15] Of approximately 60 cases in the literature, there is a predominance of male patients, and although most have been older than 50 years, patients as young as 24 years have been diagnosed.

Once the diagnosis of ischemia has been made, typically with endoscopy, further workup to identify an etiology is undertaken. The differential diagnosis includes mesenteric vasculitis and/or thrombosis associated with inflammatory bowel disease and systemic vasculitides that may affect the gastrointestinal tract such as systemic lupus erythematosus, Behçet's disease, Churg-Strauss syndrome, Buerger's disease, and rheumatoid arthritis.[16,17] Hypercoagulable states as well as visceral malignancy (Trousseau's syndrome) must also be considered. Computed tomography scanning and arteriography can identify vasculitis and define arterial pathology but are otherwise nonspecific. Lavu and Minocha[18] observed angiographic findings of local mesenteric hypervascularity with ectatic vessels and an absence of draining veins that may help distinguish MIVOD from IBD. In our case, there were indeed prominent mesenteric arteries on the arteriogram, but this was interpreted as suggestive of localized inflammation only and the venous outflow phase was not examined.

All reported cases have proved refractory to medical management, with persistent symptoms or findings of acute abdomen prompting surgical exploration. Resection of affected bowel, most commonly the large intestine, relieves symptoms. There is no clear predilection for the left or right colon including the terminal ileum. Isolated cases have been reported of involvement of the small bowel as well as descriptions of phlebitis of the gallbladder and omentum.[16,19]

The ischemic inflammation is usually a localized and self-limited process cured by surgical resection. Follow-up has ranged as long as 15 years.[20] Few cases of recurrence have been confirmed, and only one patient required another resection at 15 months.[3,20,21] It is uncertain whether reported recurrences are more the result of inadequate resection of affected mesentery and intestine rather than de novo disease. As in the current case, several authors reported microscopic phlebitis at the resection margins, although the gross surgical specimens at these locations are normal.[3,14] No reported cases had planned second-look laparotomies or required additional bowel resection during the same hospitalization. It is also unclear how frequently patients were diverted at the time of

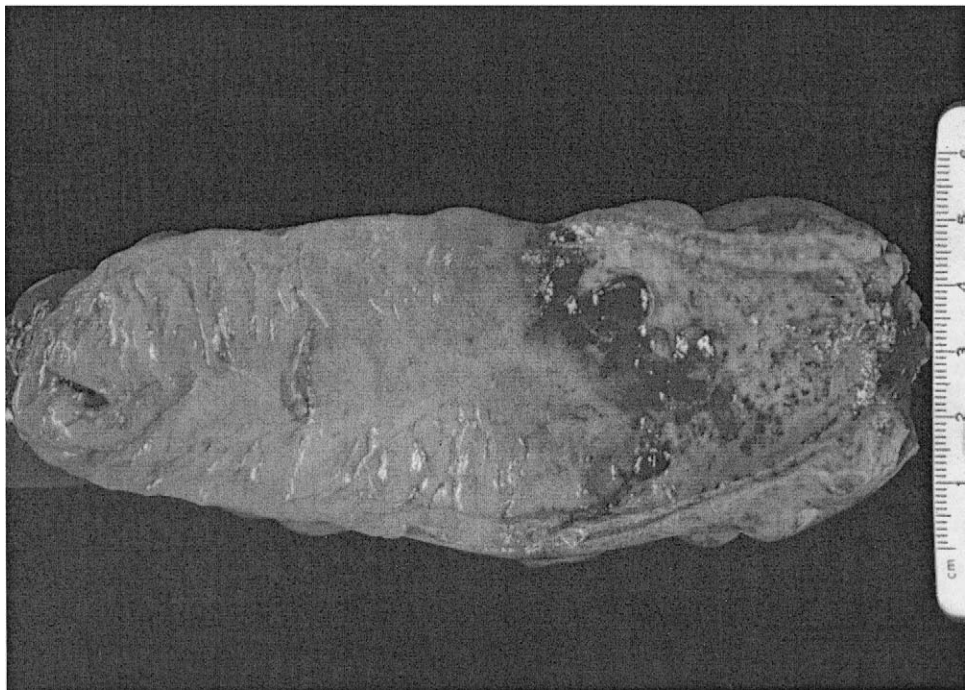

Fig. 3. Rectosigmoid colon, resection (gross photograph), distal well-demarcated and confluent mucosal exudate, and hemorrhage, with gross extension to the distal margin of resection and grossly unremarkable and uninvolved proximal bowel mucosa.

their resection. Based on the histopathologic findings in our patient's second operative specimens, the active inflammation can resolve spontaneously. No evidence exists for postoperative steroid therapy or prophylaxis with systemic anticoagulation, as might be used in mesenteric and portal vein thrombosis.

Histologic Features

MIVOD is a pathologic diagnosis based on findings of isolated mesenteric venous inflammation, particularly of the small submucosal venules, with arterial sparing. Mucosal biopsies are thus inadequate to establish the diagnosis. Thrombotic occlusion of the venous vessels secondary to the inflammation results in localized outflow obstruction and ischemia. The inflammatory infiltrate was originally described as predominantly lymphocytic, belonging in one study to the cytotoxic T-cell lineage.[13] However, proportions of B cells, neutrophils, and giant cell granulomas have also been observed.

The natural history of MIVOD has been hypothesized as a progression from lymphocyte-mediated vascular damage to acute necrotizing vasculitis to venous thrombosis, recanalization, and myointimal hyperplasia in order to account for the various cell types that have been observed on histologic section. In some cases it is difficult to reconcile this proposed evolution of the inflammatory response and the clinical picture. Myointimal hyperplasia without venulitis was first observed in three patients younger than 38 years with no prior intestinal symptoms.[5] Conversely, as might be expected with chronic MIVOD,[11,19] it was the three oldest patients from an early series with an average age of 61 years who demonstrated myointimal hyperplasia and stricture.[2] Recently, a syndrome of idiopathic mesenteric phlebosclerosis was described, although it is unclear whether this entity, characterized by a calcific and fibrotic process involving the small mesenteric veins, also represents part of the spectrum of MIVOD.[22]

CONCLUSION

MIVOD is a rare vasculitis of unknown etiology exclusively affecting submucosal and mesenteric veins. There is no uniform clinical or pathologic pattern to this selective vasculitis as it affects a range of patient ages and both genders and the inflammatory infiltrate is variable. Localized visceral ischemia and its sequelae eventually prompt the patient to seek medical attention and surgical consultation. Surgical management of MIVOD is essentially the management of acute abdomen, with abdominal exploration and resection of affected bowel to grossly normal margins

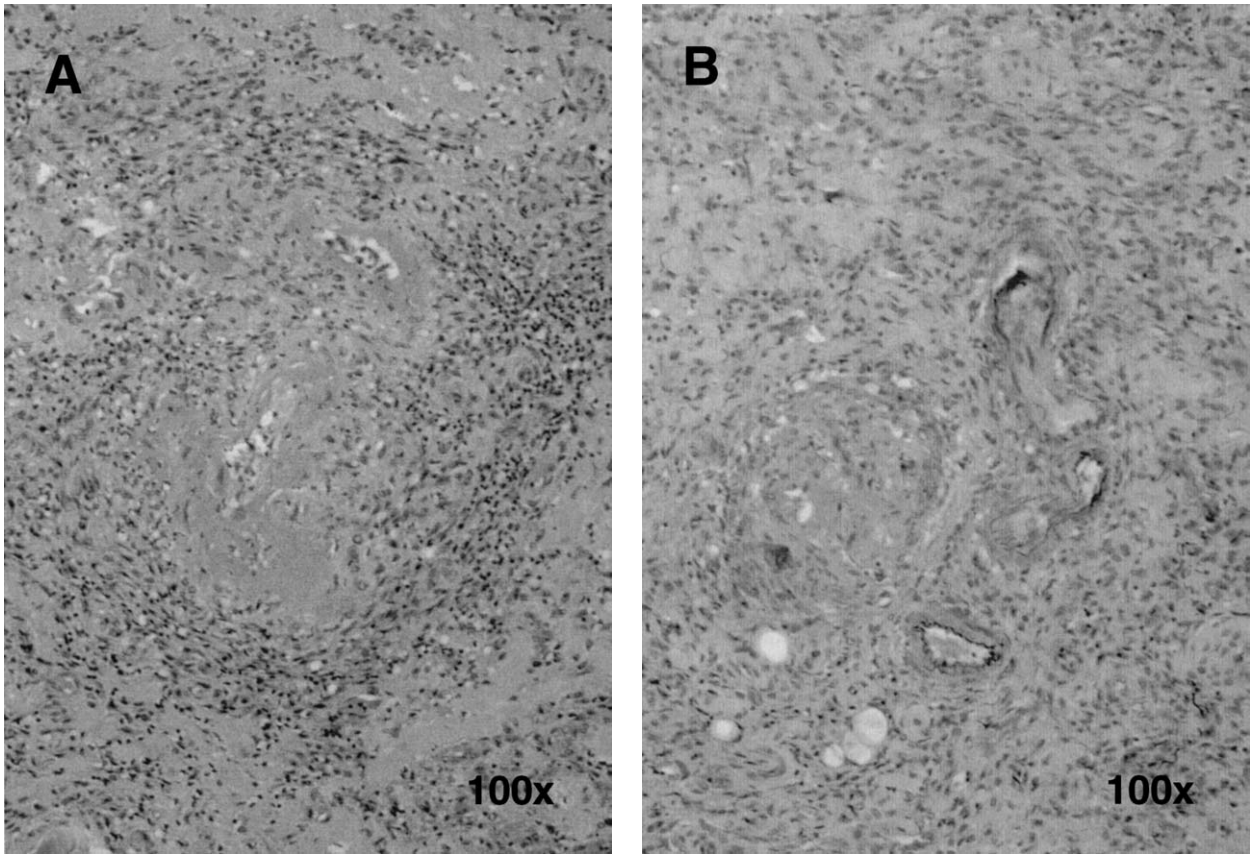

Fig. 4. Rectosigmoid colon, submucosa (**A**) (hematoxylin and eosin stain; original magnification, ×100), necrotizing venous vasculopathy with patchy mural mononuclear cell infiltrate and fibrinoid material in vessel lumens. Same submucosal region, with venous destruction and intact submucosal arteriole elastin (**B**) (Movat's stain; original magnification, ×100).

once the decision has been made to operate. It is unclear whether diversion or immediate reanastomosis is preferable, and this decision is probably best left to the clinical judgment of the surgeon. Once a pathologic diagnosis of MIVOD is established, surveillance appears sufficient and the prognosis favorable, with low probability of recurrence and even less likely need for reoperation.

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Gallbladder Carcinosarcoma: A Case Report and Literature Review

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Carcinosarcoma of the gallbladder is a rare malignancy characterized by both malignant epithelial and mesenchymal components. The clinical behavior of this tumor is extremely aggressive. Only 26 cases have been reported in the world literature to date. We report the case of a 64-year-old woman who had fever associated with a right upper quadrant mass. An exploratory laparotomy through a right upper quadrant incision was performed at another institution, and the patient was thought to have severe acute cholecystitis that would require additional antibiotic therapy before attempted resection. She was referred to our center, where abdominal CT showed a 6.4 × 8.2 cm pericholecystic mass involving the hepatic flexure of the colon. The patient underwent cholecystectomy and hepatic wedge resection, pancreaticoduodenectomy, and right hemicolectomy. Pathologic examination of the surgical specimen revealed two histologic components consisting of squamous cell carcinoma and spindle cell sarcoma of gallbladder origin, consistent with carcinosarcoma. All seven lymph nodes in the pancreaticoduodenectomy specimen were negative for tumor. We present this case and a review of the literature and current treatment recommendations. (J GASTROINTEST SURG 2005;9:818–821)

KEY WORDS: Carcinosarcoma, gallbladder, neoplasm, spindle cell sarcoma, squamous cell carcinoma, treatment

Gallbladder cancer has an exceedingly poor outcome and few effective therapeutic options. In North America, gallbladder carcinoma is the most common malignancy of the biliary tract and, overall, the fifth most common malignancy of the gastrointestinal tract.[1] The annual incidence approaches 3000 new cases. Carcinosarcoma is an extremely atypical subset of gallbladder malignancies. To date, only 26 cases have been reported in the world literature. Carcinosarcomas are defined as malignant tumors that contain both epithelial and mesenchymal components that intermingle.[2] Few data are available about the clinical behavior and the optimal management of these tumors. We report a case of carcinosarcoma of the gallbladder and its subsequent management.

CASE REPORT

A 64-year-old woman was in her usual state of health until she began to experience nausea, vomiting, and right upper quadrant pain. She consulted her physicians, who noted that she was anicteric but had symptoms consistent with early satiety. Acute cholecystitis was diagnosed, and she was given a course of antibiotics. Her condition improved. Several months later, she again presented with similar symptoms. An exploratory celiotomy was performed through a right subcostal incision and an inflammatory mass was encountered. After a failed attempt at cholecystectomy, the incision was closed and antibiotic therapy was initiated. When her discomfort failed to resolve after 1 month, she was referred to our institution for further evaluation and therapy. At presentation, she complained of recurrent fever and right upper quadrant pain.

On examination, the patient was febrile, with an infected, draining right subcostal incision and mild right upper quadrant tenderness. Laboratory investigations at that time showed the following: leukocyte count 15.8 × 10^9/L (normal, 3.5–10.5 × 10^9/L), alkaline phosphatase 223 U/L (103–282 U/L), total bilirubin 0.3 mg/dL (0.1–1.1 mg/dL), and amylase 30 U/L (35–115 U/L); the aminotransferase values were within normal limits. The tumor markers at the time were CA 19-9 of 15.0 U/ml (0–39.9 U/ml) and

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carcinoembryonic antigen 0.9 ng/mL (0–5.0 ng/ml). Chest radiography showed no evidence of parenchymal disease. CT of the abdomen showed a large pericholecystic soft tissue mass that measured 6.4 × 8.2 cm, extended posteriorly to involve the hepatic flexure of the colon, and contained a moderate amount of pericholecystic gas-filled collections (Fig. 1). There was mild prominence of the intrahepatic biliary ducts.

Colonoscopy was performed next, and the findings were consistent with extrinsic compression of the hepatic flexure of the colon. Esophagogastroduodenoscopy demonstrated a large, ulcerated, nearly obstructing necrotic mass in the duodenum at the junction of its first and second portions. The area of involvement appeared to be opposite the ampulla of Vater. Endoscopic forceps biopsy showed squamous cell carcinoma. CT of the chest did not demonstrate any pulmonary lesions.

Because of the condition of the patient's wound, the degree of abdominal discomfort, and the impending obstruction, curative resection was attempted. After standard bowel preparation, antibiotics were given intravenously. The previous right subcostal incision was used. The old wound was excised and the abdomen explored. At exploration, a 12 × 10 cm inflammatory mass that involved the body of the gallbladder was densely adherent to the duodenum and drew up the hepatic flexure of the right colon. There was no evidence of metastatic disease elsewhere within the abdomen. A cholecystectomy with wedge resection of the gallbladder fossa (involving liver segments 4 and 5), extrahepatic bile duct excision, non–pylorus-preserving pancreaticoduodenectomy with excision of 15 cm of proximal jejunum, and right hemicolectomy were performed. The patient had no complications postoperatively. When she was discharged to home on postoperative day 11, she tolerated a postgastrectomy diet and had normal bowel function.

The pathology examination of the surgical specimen revealed carcinomatous and sarcomatous features of gallbladder origin. CT of the abdomen at 2 months follow-up showed neoplastic recurrence involving the inferior aspect of the right and left lobes of the liver, with several small nodules involving the subcutaneous tissues, liver capsule, peritoneum, and external oblique musculature. The patient refused chemoradiation therapy and died 2 months later.

Histology

On gross examination, the surgical specimen included a 12.0 × 10.0 × 7.0 cm focally necrotic tumor mass adherent to the stomach, duodenum, right colon, mesenteric fat, and pancreas. The tumor was of gallbladder origin, with no invasion of the liver parenchyma and minimal superficial invasion of the pancreas. The gallbladder was replaced entirely by

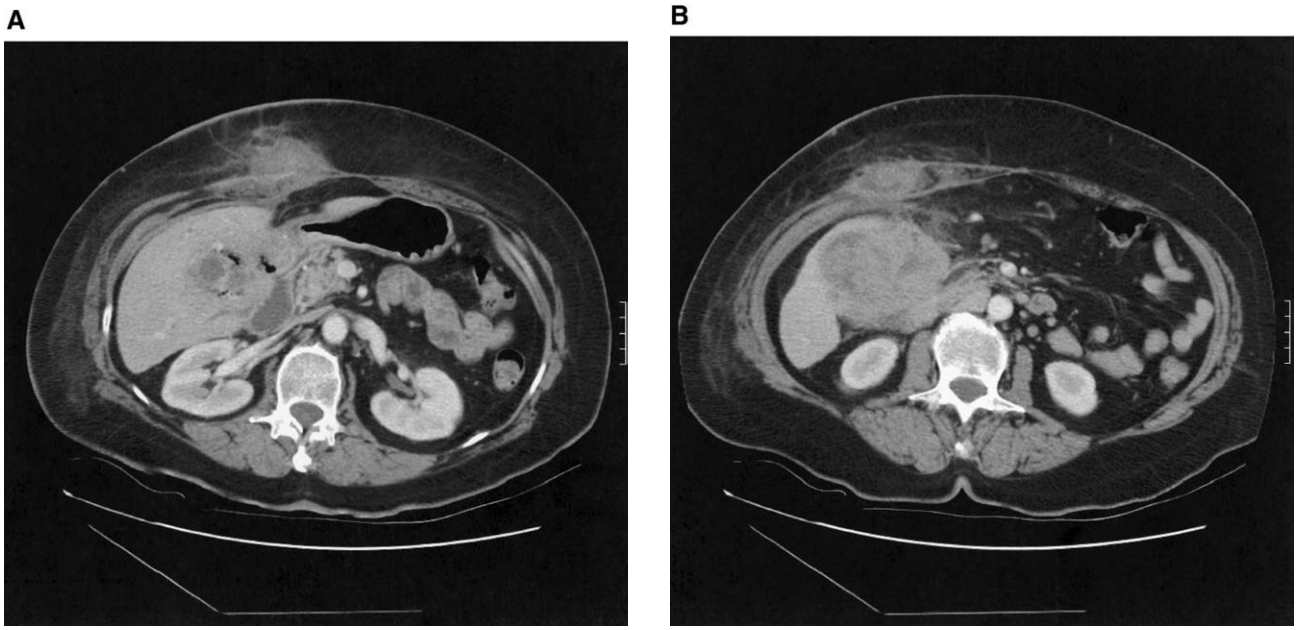

Fig. 1. (A) Abdominal CT with intravenous contrast shows a moderate number of pericholecystic gas-filled collections and mild prominence of the proximal intrahepatic ductal system and extrahepatic ducts. **(B)** This image demonstrates the large pericholecystic heterogeneous soft tissue mass measuring approximately 6.4 × 8.2 cm in maximal transverse diameter.

tumor, which contained two 2 cm calculi. The mass contained two separate histologic components: epithelial and stromal. The epithelial component consisted of well-differentiated squamous cell carcinoma, and the stromal component consisted of poorly differentiated spindle cell sarcoma (Fig. 2). All seven lymph nodes were benign.

DISCUSSION

In most cases, a malignant mass within the gallbladder is adenocarcinoma. The finding of carcinosarcoma in this location is, indeed, unusual. Landsteiner first described carcinosarcoma of the gallbladder in 1907.[3] Various names have been used to describe this tumor, including malignant mixed tumor[4] and sarcomatoid carcinoma.[5] Carcinosarcomas of the gallbladder contain both malignant epithelial and mesenchymal components. The diagnosis requires the presence and intermingling of both histologic components. Carcinosarcoma has been described in several locations, including the lung, kidney, uterus, oropharynx, larynx, salivary glands, thyroid, and thymus, and throughout the gastrointestinal tract.[6–8] Twenty-six cases of carcinosarcoma of the gallbladder have been reported in the world literature. In most cases, the patient presented with right upper quadrant pain with or without jaundice. At laparotomy, most patients had locally advanced disease involving the gallbladder bed or distant metastasis.

The epithelial component in most reported cases of carcinosarcoma was adenocarcinoma, although squamous cell carcinoma was often present as well. The mesenchymal component has varied from homogeneous sarcoma to more heterotopic elements such as malignant bone, cartilage, and other mesenchymal tissues.[9] The homogeneous sarcoma was usually a spindle cell type, as in the current case. It is important to see the stromal and epithelial components intermingled to differentiate carcinosarcoma from a collision tumor. A collision tumor represents synchronous carcinoma and sarcoma from separate sources that arise close by each other and form a tumor front. These tumors have distinct borders between the cellular components, and the components do not intermingle.

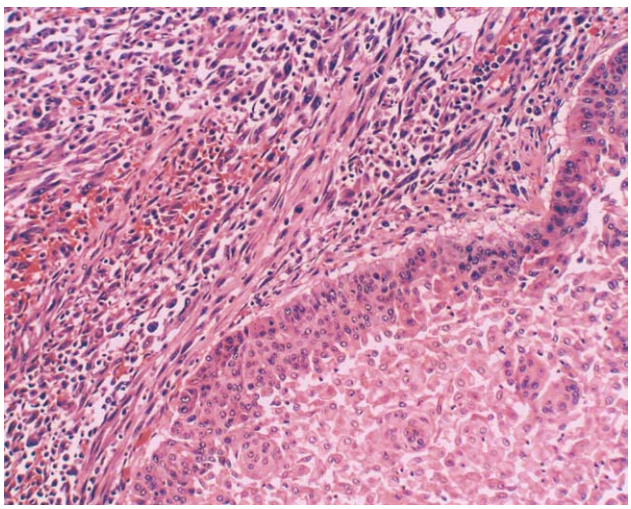

Fig. 2. Carcinosarcoma, with low-grade squamous cell carcinoma and high-grade spindle cell sarcoma components (Hematoxylin and eosin stain, ×100).

The pathogenesis of carcinosarcoma is poorly understood. It has been speculated that these tumors arise from totipotential stem cells,[10] rest cells of mesoblasts that retain the capability of transformation,[11] primitive undifferentiated müllerian stroma, or paramesonephric tissue.[12]

The biologic behavior of carcinosarcoma is very similar to that of an aggressive sarcoma. Most cases of carcinosarcoma of the gallbladder present at an advanced stage and show rapid growth, with a large mass invading adjacent organs. The outlook is grim for most patients with the diagnosis of carcinosarcoma. Born et al.[9] reviewed the world literature in 1984 and found that the longest survival was 8 months after diagnosis and the mean survival was 1.9 months. Since then, 8 additional cases have been reported. Among all reported cases, the mean survival after resection was 4.0 months. Of the 26 reported cases, 3 patients survived longer than 1 year.[9,13,14] In all of these patients, the tumor was confined to the gallbladder wall, with no evidence of serosal invasion. All three patients were treated surgically with cholecystectomy. One patient received postoperative adjuvant radiotherapy. Our patient died of carcinomatosis 2 months after surgical resection.

Because of the limited experience with this disease, there is no consensus about management. Long-term survival after surgical resection for carcinosarcoma is possible if the tumor is confined to the submucosa. However, not many patients with carcinosarcoma fit this category. It appears that simple cholecystectomy with hepatic bed resection may provide adequate treatment for tumors confined to the gallbladder wall. Because most patients present with advanced disease, extensive resection is often required. Previous reports have supported attempts at curative resection for advanced disease. Similar to gallbladder carcinoma, it seems that curative resection for advanced carcinosarcoma is not usually possible.

Our patient presented with an infected pericholecystic mass and intractable vomiting, necessitating resection. Given the absence of clinically involved

lymph nodes or obvious metastatic disease, it was decided to attempt a curative resection. Despite negative surgical margins and negative lymph nodes, our patient died of metastatic disease 2 months after resection. Surgical excision of locally advanced disease provides only marginal improvement in long-term survival, but aggressive resections are still justified to surgically palliate symptoms of jaundice, pain, or gastrointestinal obstruction. What remains to be determined is the role of chemotherapy with or without radiotherapy in the management of this disease. Because of the relative rarity of this malignancy, it is unlikely that any trial will be conducted to test different regimens. Relief of symptoms remains the priority in the treatment of this malignancy, and this usually is best achieved surgically.

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Epithelioid Angiosarcoma of the Gallbladder: Case Report

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A patient with epithelioid angiosarcoma of the gallbladder is described. This is only the second case of an extremely rare but highly aggressive tumor reported in the international literature. Pathophysiological, clinical, and therapeutic aspects are discussed in relation to the available data on angiosarcomas of the gallbladder. (J GASTROINTEST SURG 2005;9:822–825)

KEY WORDS: Epithelioid angiosarcoma, gallbladder, surgery, immunohistochemistry

INTRODUCTION

Angiosarcomas are aggressive neoplasms of vascular endothelial origin. First described by Stout in 1943,[1] they are rare entities, accounting for only 2% of all soft tissue sarcomas.[2] They most often arise in superficial somatic tissues, but sometimes also occur in deep somatic tissues and viscera, such as the heart, lungs, kidneys, urinary bladder, prostate, uterus, and ovaries, and in serous membranes.[3–5] Involvement of the gallbladder has been reported in only four cases in the literature, in three instances by itself and one in combination with squamous cell carcinoma.[6–9] Epithelioid angiosarcoma of the gallbladder, a highly malignant vascular endothelial tumor with epithelial morphology, is extremely rare and to date only one case has been described, by White and Chan in 1994,[10] in an 81-year-old woman who died two weeks after surgical intervention for tumor removal. We describe here what we believe to be the second case of this malignancy in the international literature.

CASE REPORT

A 57-year-old male patient was hospitalized complaining of intense weakness, passage of black stools, occasional rectal bleeding upon defecation, and weight loss over 3 months. He had a clinical history of essential hypertension under satisfactory pharmacologic control, moderate chronic renal impairment, and convulsions in childhood. Clinical examination upon admission revealed a man of medium build, with blood pressure 130/70 mmHg, pulse rate 116 per minute, and normal body temperature, with gross pallor but no jaundice. Abdominal examination showed diffuse tenderness in the upper right quadrant at both superficial and deep palpation with a positive Murphy's sign, i.e., exquisite tenderness upon firm digital palpation at the level of the junction of the 10th rib with the outer margin of the rectus abdominis during inspiration. The inferior margin of the liver was palpable at 2 cm below the costal arc. There was no ascites. Rectal examination revealed no abnormality.

Laboratory investigations showed hemoglobin (Hb), 5 g/dl; erythrocyte count (RBC), 2.170.000/mm^3; hematocrit (HCT), 19.2%; white cell count, 8.500/mm^3 (neutrophils: 80.7%); blood urea, 67 mg%; blood creatinine, 2.12 mg%; blood sugar, 98 mg%; and erythrocyte sedimentation rate, 96 mm/h. Liver function tests revealed bilirubin to be 0.64 mg/dl; alkaline phosphatase, 60 U/L; and total protein, 5.9 g/dl. Examination of urine and stools provided normal results. Three blood transfusions were performed on successive days, after which Hb was 7.7 g/dl, RBC was 3.120.000/mm^3, and HCT was 27.7%.

Small bowel follow-through examination, CT abdominal scan, and abdominal ultrasound were then performed. The small bowel follow-through showed no significant alterations of the intestinal loops. The

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CT scan revealed the presence of a gross dilation of the gallbladder, which had a longitudinal axis of almost 20 cm (Fig. 1). Ultrasound showed a nonhomogeneous content of the gallbladder for the presence of gross echogenic formations and areas of hyperechogenity caused by lithiasis and thin gallbladder walls. It was decided to proceed with surgery for gallbladder removal, through a midline incision extending upward to the xiphoid and downward to the umbilicus. Upon opening of the peritoneum, the gallbladder appeared to have greatly increased dimensions (20 × 10 cm) with gangrenous walls and numerous visceral (duodenal) and omental adhesions. After severance of the adhesions, the gallbladder was aspirated with a thick-bore needle, and the aspirated liquid proved to be hemorrhagic. The cystic duct was then isolated and an intraoperative cholangiography was performed, which showed a regular caliber and trajectory of the choledochus with normal transit of the contrast medium into the duodenum. The gallbladder was then removed. Visual and palpatory exploration was performed of the stomach, duodenum, jejunum, ileum, and colon, which did not reveal any abnormality. A rubber drain was placed in the right subhepatic space and introduced down past the foramen of Winslow into Morrison's pouch; the abdominal wall was then sutured in layers. Upon opening of the gallbladder on the back table, blood mixed with clots, numerous stones, and biliary sludge appeared.

Histology

The walls of the gallbladder showed a necrotic-hemorrhagic appearance. Marked transmural infiltration was found by tumoral cells organized in solid masses. The cells appeared epithelioid with voluminous nuclei and prominent nucleoli, often with intracytoplasmic vacuoles. The neoplastic population tended to form vascular lacunae containing erythrocytes, with interposition of amyloid-like stroma, typical of vascular tumors (Fig. 2).

Immunohistochemically, the tumoral cells were positive for factor VIII-related antigen, CD31, and vimentin; they were negative for epithelial membrane antigen, keratin, CD34, CD117 and S 100.[11] The described pattern was identified as an epithelioid angiosarcoma.

In the postoperative period, upon receipt of the histology analysis, oncologic consultation was carried out. A surgical radical intervention (resection of hepatic segment IV) was recommended, which the patient decided to postpone for personal and family reasons. He was then discharged by the hospital, with the last hematochemical analysis showing Hb, 8.8 g/dl; RBC, 3.360.000/mm^3; and HCT, 31.4%.

Two months later, abdominal CT scans were again performed, which showed no secondary hepatic lesions, no dilation of the biliary ducts, and absence of any adenopathy.

Four months after cholecystectomy, the patient was rehospitalized to undergo resection of the hepatic segment IV. The hematochemical analyses upon admission were Hb, 15.8 g/dl; RBC, 5.540.000/mm^3; and HTC, 47.4%.

Surgery

A right subcostal laparotomy was performed, extending to the xiphoid. The liver was mobilized with section of the suspending ligaments, severance of the adhesions, and freeing of the gallbladder bed. To keep the surgical approach as conservative as possible, only hepatic segment IV was resected in its quadrate lobe.[12] The hepatic parenchyma was divided with a blunt instrument (Kelly clamp) (Fig.3). Intraoperative frozen section histology of the margins of the removed specimen proved to be free of tumor, and thus no further resection was performed. A rubber drain was placed in the right subhepatic space. The abdominal wall was sutured in layers.

Postoperative final histologic examination of the resected hepatic specimen proved to be negative for angiosarcoma at immunohistochemical staining.

Postsurgical recovery was without complications; another oncologic consultation was performed in the postoperative period, and a strict follow-up was recommended without any adjuvant therapy. The patient was discharged by the hospital on the fifth postoperative day in satisfactory health condition. The last hematochemical analyses showed Hb, 11 g/dl; RBC, 3.780.000/ mm^3; and HCT, 34.5%.

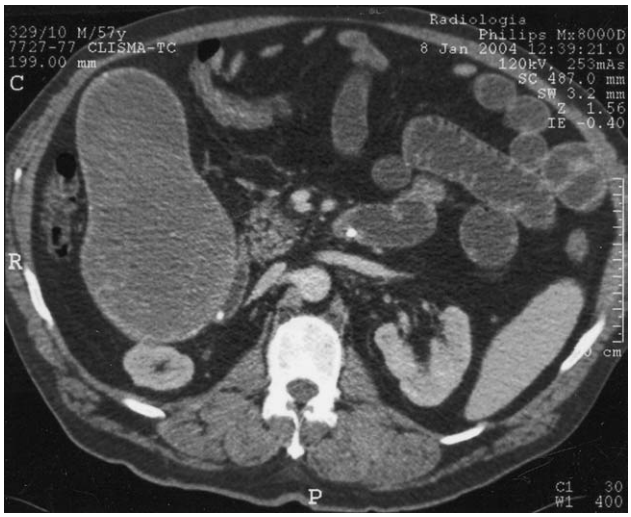

Fig. 1. Preoperative CT scan showing a huge, dilated gallbladder.

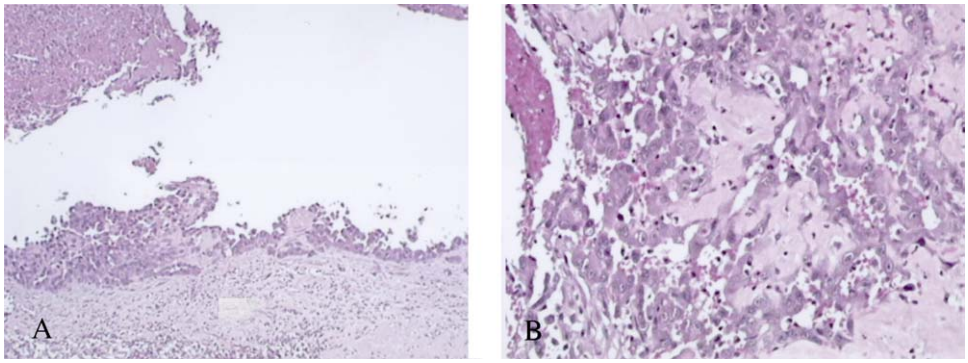

Fig. 2. Specimen from the gallbladder tumor. (**A**) Proliferation is shown of epithelioid elements that become stratified in the lumen of the organ, with invasive aspects. H & E, × 10. (**B**) The neoplastic population tends to form vascular lacunae full of erythrocytes. Amyloid-like stroma, typical of vascular tumors, is located in between. H & E, × 20.

In the 5-month period elapsing since this second intervention, the patient has been asymptomatic and in satisfactory general health. New abdominal CT scans, thoracic CT scans, and total body bone scintigraphy performed during this period were all negative for secondary lesions.

DISCUSSION

Angiosarcomas of the gastrointestinal tract are such rare neoplasms that their exact incidence is still not known.[8,13] Angiosarcomas of the gallbladder, in particular, have been described only four times in the literature,[6–9] and therefore information about their origin, clinical presentation, evolution, and therapeutic approach is still incomplete. A possible role played by cholelithiasis has been advocated for the etiology of gallbladder tumors in general, because of its frequent coexistence with them. Vaittinen, for instance, reported cholelithiasis to be present in 79% of sarcomas of the gallbladder.[9] Though the exact cause-effect relationship remains to be established, it is plausible that the irritation produced by the stones and the frequently accompanying inflammation are a triggering factor for the development of gallbladder tumors, and therefore probably also for the development of angiosarcomas.[14] Symptoms of angiosarcomas of the gallbladder apparently resemble those of carcinomas, but their duration is shorter, as the tumoral progression is reported to be much faster.[7] The specific diagnosis of angiosarcoma can only be established by histopathologic examination, because conventional instrumental examinations, such as CT scans, ultrasound, or X-rays, can at best provide only a general suspicion of a tumoral mass. Because of the very limited experience, no definite treatment guidelines so far exist. Surgery remains the first option: cholecystectomy with or without wedge resection or extended right hepatic resection and regional lymph node dissection when indicated.[15] There are no definite data yet regarding the advisability and/or effectiveness of chemotherapy and/or radiotherapy subsequent to surgery.[7] Of the previously described cases, survival times and treatment approach varied. One case described by Kumar et al. in 1989, for instance, regarded a 56-year-old male patient who underwent cholecystectomy and distal partial gastrectomy with gastrojejunostomy for a distended gallbladder which was infiltrating into the pylorus and omentum.[7] After the diagnosis of angiosarcoma, this patient was advised to receive radiotherapy, which he refused. He was referred to the authors' follow-up clinic 4 months later with jaundice; large, multiple secondaries were detected in the liver and the patient died the next month. In contrast, another

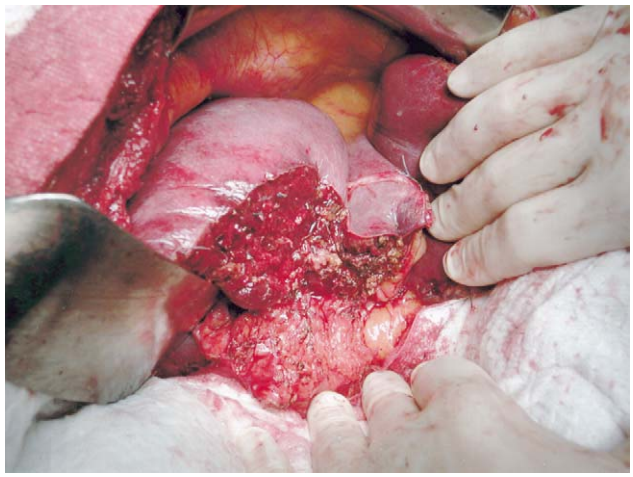

Fig. 3. Surgical intervention for resection of hepatic segment IV (quadrate lobe). Intraoperative view.

case of angiosarcoma, combined with a squamous cell carcinoma, also described by Kumar et al. in 1994, showed a long survival.[8] This 54-year-old male patient survived for 5 years, although no chemotherapy or radiotherapy was performed. The surgical intervention had consisted of cholecystectomy with wedge resection of the liver combined with a regional lymphadenectomy, as there were multiple, small lymph nodes in the cystic, pericholedochal, and supraduodenal areas.

Although limited information exists on angiosarcomas of the gallbladder in general, literature reports specifically on epithelioid angiosarcomas are exceptional. In fact, prior to the present case report, there has been only one case described, in a 81-year-old woman.[10] Symptoms of epithelioid angiosarcomas apparently vary; the patient in the previously described case showed fever and presence of a tender mass in the upper right abdominal quadrant. In the present case only symptoms of severe anemia were observed, caused by continuous bleeding from the gallbladder tumor. In both the previous case and the present one, the specific diagnosis of the tumor could be established only by histopathologic examination, as conventional instrumental examinations, namely, CT scans, ultrasound, and X-rays, provided only a general suspicion for a tumoral mass.

Epithelioid angiosarcomas are considered highly aggressive,[8] with a short survival expectancy. The previously reported case would seem to support this assumption, as the female patient described by Kumar et al.[8] had complained of symptoms for a few weeks before undergoing cholecystectomy and died 2 weeks after the intervention (a perforated thick-walled gallbladder was found, surrounded by omental adhesions and abscesses). Unfortunately no autopsy was performed, so no precise information is available on the exact causes of death and on the progression of the tumor, although the other organs of the abdominal cavity had appeared normal at exploration during surgical intervention.[8]

The patient reported in the present paper has so far shown a fairly longer survival time. A surgical therapeutic approach was followed, performed in two different circumstances. During the first intervention, the gallbladder was removed, which led to histologic identification of the tumor that had involved the whole organ, producing serious anemia as the result of continuous bleeding from the gallbladder walls. During the second intervention, resection of the IV segment of the liver, in its quadrate lobe, was performed as a preventive measure against metastatic occurrences, in accordance with oncologic consultation. Though the follow-up time is still limited (5 months), no metastasis has been detected so far at any level and the patient is in relatively good health. This result would seem to support the notion that ample surgical resection of the gallbladder bed surroundings, in addition to removal of the organ, is a reasonable approach to treatment/control of the progression of the disease without the necessity of adjuvant therapies.

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Pain Persists in Many Patients Five Years After Removal of the Gallbladder: Observations From Two Randomized Controlled Trials of Symptomatic, Noncomplicated Gallstone Disease and Acute Cholecystitis

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After removal of the gallbladder, pain may persist in some patients. To study this condition, 124 patients from two randomized trials, including those with symptomatic noncomplicated gallbladder stones (n = 90) and acute cholecystitis (n = 34), were interviewed, while 139 patients (90%) excluded from both trials responded to a questionnaire 5 years after the operation. Thirty-four patients (27%) of those randomized had pain; 23 (18%) had diffuse, steady pain; and 11 (9%) had pain attacks resembling their preoperative symptoms. A significant dominance of diffuse pain occurred in women ($P = 0.024$), especially those younger than 60 years ($P = 0.004$). A tendency for the diffuse type to be dominant was also present in the group of female patients with symptomatic noncomplicated gallbladder stones ($P = 0.052$). Of the excluded patients, 18% (25/139) had pain, but 88% of them (96% of the men and 87% of the women) were satisfied with the result of the operation. The overall number of patients with postoperative pain was 22% (59/263). We conclude that persisting abdominal pain 5 years after the operation was mainly of a nonspecific type, found mostly in younger women who had had noncomplicated gallstone disease. Eighty-eight percent of the excluded patients declared themselves satisfied with the result of cholecystectomy.
(J Gastrointest Surg 2005;9:826–831)

KEY WORDS: Symptomatic noncomplicated gallstone disease, acute cholecystitis, cholecystectomy, long-term follow-up, postcholecystectomy pain

INTRODUCTION

Although cholecystectomy is considered to be the standard treatment for symptomatic gallstones, far from all patients are relieved of their pain following the procedure. It is still unclear if postcholecystectomy symptoms resemble the pain attacks that led to removal of the gallbladder and to what extent pain persists or occurs de novo postoperatively. According to a recent literature review,[1] 6% to 30% of patients experience the same type of pain after operation. No consistent pathophysiological substrate for such pain has been documented, probably because of the diversity of the indications for cholecystectomy as well as the manner in which studies have been conducted.[2]

Unfortunately, most studies are retrospective, with follow-up periods commonly ranging from a few weeks to a couple of years.[1,3] Additional problems have been lack of a distinct disease definition and separation of symptoms, and differences in the way patients have been examined.[2] Consequently, we will argue that more information on the magnitude and composition of pre- and postcholecystectomy pain is needed in order to gain a better understanding of

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the ability of the operation to cure the preoperative symptoms.

Our aim was to examine the incidence of pain after cholecystectomy in two randomized controlled trials (RCTs) with well-defined entry criteria,[4–6] and to classify such symptoms in two main categories, one resembling acute gallstone attacks, the other a more diffuse type of pain.

MATERIAL AND METHODS

The two trials were carried out simultaneously and a combined follow-up was conducted. Therefore, patients who had undergone cholecystectomy in these trials were amalgamated for the single purpose of studying freedom of pain after removal of the gallbladder. The two RCTs comprised a population of 518 consecutive patients.[4,5] At 5 years, 69% of patients with uncomplicated gallbladder stones (SGBS) and 58% of patients with acute calculous cholecystitis (AC), as well as 54% of all excluded patients, had undergone cholecystectomy. Twenty-four patients (8%) had died, but none of the deaths were the result of gallstone-related disease or postoperative complications. Overall, 278 patients, 124 randomized and 154 excluded patients, were eligible for follow-up.

Timing of Cholecystectomy

Because of our waiting list policy, patients with SGBS who were randomized to surgery had the procedure a median of 3 months (range 0–24 months) after randomization. Those randomized to observation but who dropped out and had cholecystectomy underwent surgery a median of 27 months (range 0–67 months) after randomization. AC patients who were randomized to surgery had the operation a median of 4 months (range 1–13) after randomization and those who were observed but later underwent cholecystectomy, had the procedure a median of 14 months (range 2–67 months) after randomization.

Excluded patients had surgery a median of 2 months (range 0–60 months) after exclusion.

Disease Definitions

The definitions of SGBS and AC and accounts of these two RCTs have been given in previous reports.[4,5] The definition of SGBS pain included at least one of the following features: episodic pain, usually increasing gradually to a peak intensity, at which it normally was quite steady until it subsided similarly; location in the right subcostal or midline epigastric area lasting more than 30 minutes and up to 6 hours for uncomplicated disease; pain often referred to the back in the region under the right shoulder blade; and pain usually accompanied by nausea and anorexia. Attacks appear relatively suddenly and are distinct from and stronger than any steady, continuous, or diffuse type of pain. Preoperative symptoms were defined as severe, moderate, or minimal according to frequency, intensity, and whether they limited daily activities or hampered social life.

AC was defined by acute abdominal pain, commonly in the right subcostal area, with a duration of more than 6 to 8 hours, and tenderness on clinical examination in the right upper quadrant accompanied by signs of inflammation on ultrasonography and in clinical biochemistry data.[5]

Follow-Up

In randomized patients, gallstone-related events were recorded consecutively. Patients answered questionnaires concerning pain patterns at randomization. All 124 eligible patients from the two RCTs were interviewed at a median of 61 months (range 3–91) after cholecystectomy using a structured interview designed to separate pain patterns.

Excluded patients were not followed-up routinely, but hospital notes were checked and all gallstone-related events recorded. These patients were sent a simple questionnaire in which they were asked about freedom from preoperative symptoms and patient satisfaction. Of the 154 excluded patients, 139 patients (90%) replied to the questionnaire at a median of 79 months (range 21–98 months) after surgery.

Consequently, data on the incidence of pain were available for 263 patients having had a cholecystectomy in the past.

Survey Measures

A self-composed, detailed questionnaire, based on the experience gained in the two RCTs and including all the clinical elements of pain attacks described, was used at follow-up. This questionnaire is currently being used in further prospective studies of gallstone disease. A visual analogue scale (VAS) pain score was included. The score point was crossed by the patients on a 100 mm straight horizontal unmarked line on which no pain and unbearable pain was indicated at the left and right ends, respectively.

Statistics

Fisher's exact test was used to compare frequency of pain between different subgroups of patients and a one sample binomial test to compare the different types of pain within a group of patients. A significance level of 0.05 was applied.

RESULTS

Patient Demographics

The demographics of the patients who were interviewed and responded to the questionnaires are given in Table 1.

Pain Incidence and Characteristics in Randomized Patients

The presence of abdominal pain for patients with SGBS and AC is shown in Table 2. Twenty-seven percent of the 124 patients (34/124) experienced pain, and 29% (29/101) of women. The diffuse type dominated in women ($P = 0.024$), especially those younger than 60 years ($P = 0.004$). Five men (22% of 23 patients) had pain but none of the two patterns dominated. Interestingly, although 8 women had pain attacks, 5 of these also had diffuse pain, meaning that only 3 women had pure pain attacks. Thus, 5% (6/124) of all patients had pure pain attacks. There were no significant differences between women and men for the two pain types (pain attacks, $P = 0.42$; diffuse pain, $P = 0.24$; combined, $P = 0.61$).

The duration of the history (more or less than 2 years), randomization outcome (operation vs. observation), and surgical method (open vs. laparoscopic surgery) made no significant impact.

Pain was located in the upper abdomen in 90% of women (26/29) and in all five men. The incidence of pain radiating to the back was equal among women (n = 13; 45%) and men (n = 2; 40%). The frequency of pain attacks per month was a median of 2.8 (range 1–8) for the eight women and 4.5 (range 1–8) for the three men.

When combined for both pain types, the VAS score was a median of 38 (range 2–100) for women and 42 (range 5–56) for men. Analgesic use according to symptomatic group is shown in Table 2. Thirteen of 29 women (45%) reported abdominal pain at follow-up, and 1 of 5 men (20%) used pain medication ($P = 0.38$). Preoperatively, 79% (98/124) of followed up patients had used analgesics. However, of the group that was asymptomatic at follow-up, only 74% (67/90) had used analgesics preoperatively, compared with 91% (31/34) of the symptomatic patients.

Gallstone-Related Events in SGBS and AC Patients

A new gallstone-related event occurred after cholecystectomy in four patients (3%). Two patients (one early and one late) from the AC study had common bile duct (CBD) stones. One SGBS patient was admitted because of a pain attack without evidence of gallstone disease, and one had a CBD stone soon after the cholecystectomy.

Excluded Patients

The incidence of pain at follow-up is shown in Table 3. Twenty-five of 139 patients (18%) had pain. Despite these circumstances, 88% of all excluded patients (96% of the men and 87% of the women) were satisfied with the result of the operation. New gallstone-related events were noted in two patients: one patient had acute pancreatitis shortly after cholecystectomy and another had a CBD stone 2 years after surgery.

The majority of excluded patients who still reported pain (17/25) had originally refused randomization because they were experiencing severe symptoms or wanted an operation, while only two of the symptomatic patients had originally refused to be randomized because they did not want an operation.

Summary

A combined 22% (59/263) of the patients had pain at follow-up. There was no difference between randomized (34/124) and excluded (25/139) patients ($P = 0.076$). Of the 5 patients (2%) of 263 that had a CBD stone or acute pancreatitis following removal of the gallbladder, three were still suffering from pain.

Table 1. Age and gender composition at 5-year follow-up

	Randomized patients (n = 124)		Excluded patients (n = 139)	
	SGBS (n = 90)	AC (n = 34)	SGBS (n = 111)	AC (n = 28)
Women (n = 214)				
No. of patients	78	23	97	16
Median age (range)	53 (26–84)	54 (33–84)	49 (21–88)	59 (34–82)
Men (n = 49)				
No. of patients	12	11	14	12
Median age (range)	55 (34–74)	65 (34–78)	63 (32–70)	75 (42–94)

SGBS = uncomplicated gallbladder stones; AC = acute calculous cholecystitis.

Table 2. Postcholecystectomy pain variables at a median of 61 months after removal of the gallbladder

Parameter	No. of patients (%)			
	Pain attacks*	Diffuse pain	*P* values	Combined
All patients (n = 124)	11^5 (9)	23 (19)	0.058	34 (27)
Women (n = 101)	8^5 (8)	21 (21)	0.024	29 (29)
Men (n = 23)	3 (13)	2 (9)	1.00	5 (22)
SGBS (n = 90)	7^4 (8)	17 (19)	0.064	24 (27)
Women (n = 78)	6^4 (8)	16 (21)	0.052	22 (28)
Men (n = 12)	1 (8)	1 (8)	1.00	2 (17)
AC (n = 34)	4^1 (12)	6 (18)	0.75	10 (29)
Women (n = 23)	2^1 (9)	5 (22)	0.45	7 (30)
Men (n = 11)	2 (18)	1 (9)	1.00	3 (27)
Age <60 (n = 86)	6^3 (7)	20 (23)	0.009	26 (29)
Women (n = 71)	4^3 (6)	18 (25)	0.004	22 (31)
Men (n = 15)	2 (13)	2 (13)	1.00	4 (27)
Pain medication (n = 14)	4 (36)	10 (43)	0.18	14 (41)

*Superscripts show the number of patients who had both pain attacks and diffuse pain.

DISCUSSION

Freedom from pain attacks is a major outcome measure after cholecystectomy and should consequently be assessed separately from other types of pain that might appear. Complete cure of biliary-type pain in contrast to persisting dull aching pain has been reported.[7] Ure et al.[8] found that biliary colic remained in only 8% of patients in contrast to noncolicky pain in 32%. In a prospective Danish study,[9] 21% had persistent pain of the same character as before the operation. This is in agreement with a British randomized trial[10] in which 19% of the patients experienced biliary pain five years after cholecystectomy. The reason for the discrepancies in outcome is not always clear.[1] The indication for surgery may have differed. Another problem may be that the medical community has not agreed completely on a useful definition of "true" biliary pain, as alluded to by Luman et al.[2] A confounding factor is that dyspepsia is often included in the postoperative assessment of satisfactory outcome, including such variables as nausea and vomiting, but these symptoms should be considered part of the pain response elicited by gallstones. Studies of gallstone-elicited symptoms should preferentially be prospective with preoperative symptoms described accurately and in detail.[1]

Ure et al.,[8] who differentiated between colic and other types of pain, reported figures for postoperative pain quite similar to ours. They used a VAS for pain rating and found an average pain score of 68 in all patients with pain (representing 83% of total patients) before the operation. The average score was reduced to 43 in those who still experienced pain; however, they did not separate the results according to the two pain types. A similar result was obtained in another study,[10] with a median score of 67 before and 45 at 5 years after treatment for those who still had pain. McMahon et al.[3] found a lower VAS score of median 35 (range of 10–60), 1 year postoperative. This corresponded almost exactly to the VAS score recorded in our patients. Our median score value indicates moderate to severe pain.[11] Peterli et al.,[12] in a 12 to 25 month follow-up, found the incidence of analgesic use to be 16% in the open group and 15% in the laparoscopic group. This may seem to be in accordance with our figure of 11% at 5 years considering that the pain score decreased with time.[6]

How long after surgery the assessment of pain should take place may be a matter of debate. Patients were followed up from 10 to 25 years in two studies.[13,14] No further gallstone events took place after 5 years in a study from Finland, and still the incidence of abdominal pain was 21% after 25 years.[14] A Dutch study[13] found a minimum of 15% of their patients had complaints at 10 years. In a study of quality of life,[6] we found that the greatest improvement took place during the first 6 months. Bates et al.[15] found

Table 3. Postcholecystectomy pain in 139 excluded patients* at median 79 months after removal of the gallbladder

Parameter	Women	Men	All patients
	n = 113	n = 26	n = 139
Symptomatic patients	23 (20%)	2 (8%)	25 (18%)
Satisfied with outcome	97 (86%)	25 (96%)	122 (88%)

*Symptomatic uncomplicated gallbladder stones, n = 111; acute cholecystitis, n = 28.

that slightly more patients were affected by postcholecystectomy pain at 1 year follow-up than 1 year further on. Ahmed et al.[10] observed that the severity of postcholecystectomy pain decreased slightly from 1 to 5 years following surgery. These results are in agreement with our study; the total number of noncomplicated gallstone disease patients affected by abdominal pain fell from the first to the fifth year, when 27% were affected by abdominal pain.[6] A simple explanation for this may be that postoperative pain symptoms, for whatever reason, improve gradually over time. Coincidentally, it has been reported that 70% of unspecific abdominal pain encountered in general practice will go away after 1 year.[16]

Severity of preoperative symptoms[3] or degree of inflammation seen at histology[2] has been inversely linked to better outcome. There was a tendency toward more reported pain of the diffuse type in uncomplicated disease compared with AC. Thirty-nine percent of patients with AC in our study had only one episode of pain before randomization.[5] Ros and Zambon[7] found that the longer the preoperative history, the higher the frequency of mild postcholecystectomy symptoms. In one study,[2] there was a tendency for a better outcome with a history shorter than 6 months. However, although our patients with a history of less than 2 years had almost significantly more diffuse pain, the total number of patients with pain was unaffected by the preoperative duration of the disease.

Sex did not reach statistical difference in the study of Jørgensen et al.,[9] but there was a tendency for more women to have pain. Others have found that sex matters in disfavor of women when it comes to patient satisfaction,[12,17] or, to the contrary, that it does not matter.[3,13] Konsten et al.[13] also found that age did not influence outcome. Old age, with 50 years the cutoff point, was not important in one study,[9] whereas the opposite was found when 55 years was used.[15] In contrast to these studies, we found that women under the age of 60 years had significantly more pain of the diffuse, more continuous type that is also described in functional dyspepsia. Among excluded patients, more men than women reported a satisfactory outcome. Patients with psychic instability or disorders have been found to have more postoperative complaints.[2,9,18,19] A recent retrospective study[20] found this to be more prominent in women.

No difference has been found in outcome between open and laparoscopic surgery in terms of persistent pain.[3,12] Does some other biliary pathology explain postcholecystectomy symptoms? With a follow-up of 10 years, Konsten et al.[13] found a CBD stone incidence of 2%. These were discovered by a combination of clinical and other signs and not by routine blood tests alone. Similar figures have been reported after more than 1 year of follow-up.[8,12] Two percent of all our patients had been treated for CBD stones, but this occurred some time before the 5-year follow-up.

Sphincter of Oddi dysfunction (SOD), types I and II, has been held responsible by several investigators as a cause of persistent postoperative pain after cholecystectomy. However, consistent evidence for this connection has not been readily produced.[21,22] In SOD type III, duodenal-specific visceral hyperalgesia by distension has been found as a possible cause for pain.[19] There is experimental and clinical evidence that both gallbladder disease itself and cholecystectomy may increase duodenogastric reflux.[7,23] Excessive duodenogastric reflux after cholecystectomy is associated with a high incidence of chronic gastritis.[24] Apparently, the gastric mucosa is vulnerable to bile injury in some but not most persons.[25] Although gastritis or duodenal hypersensitivity may be to blame for some symptoms in patients with gallstones, convincing studies linking duodenogastric reflux to postcholecystectomy pain have not been reported.

Eighteen percent of all excluded patients admitted to having postoperative symptoms. In spite of these figures, 88% were satisfied with the operation. This is in accordance with others who have reported 93% satisfaction after removal of the gallbladder.[3,12,26] This has been independent of surgical approach.[26] Because of the long follow-up, our figures should express true complaints in contrast to a demonstrated placebo effect concerning dyspeptic symptoms that has been seen up to 1 year after treatment.[1]

What remains to be examined in future prospective studies is the reason for "biliary" pain attacks even 5 years after cholecystectomy, especially in female patients with a history of noncomplicated gallstone disease given a proper indication for the operation.

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Novel Bile Duct Repair for Bleeding Biliary Anastomotic Varices: Case Report and Literature Review

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An unusual case of variceal bleeding at the site of a biliary enteric anastomosis is presented. This entity can occur when a high-to-low pressure gradient forms in a variceal field. In this case the anastomotic site was the location of the pressure gradient from the high-pressure small bowel varices to the low-pressure biliary tract. This was successfully treated by disconnection of the anastomosis. The resulting biliary defect was patched with small intestinal submucosa, which functioned successfully as a scaffold for biliary epithelial ingrowth. (J GASTROINTEST SURG 2005;9:832–836)

KEY WORDS: Small bowel varices, biliary strictures, biliary enteric anastomotic

Bleeding secondary to jejunal-biliary anastomotic varices is rare. We report a case of severe gastrointestinal bleeding due to such varices that arose as a complication of extrahepatic portal vein thrombosis. The patient was treated by devascularization with resection of the jejunal loop, and the common bile duct was managed by a novel technique with patch closure, which has not been previously reported in humans. We discuss the management of this case and review the literature on symptomatic jejunal varices.

CASE REPORT

A 42-year-old woman presented with recurrent gastrointestinal bleeding. She had a past history of alcoholic chronic pancreatitis that caused biliary obstruction requiring endobiliary stenting. A Roux-en-Y hepatojejunostomy, gastrojejunostomy, and cholecystectomy had been performed due to frequent stent changes and cholangitis. Portal vein thrombosis was diagnosed preoperatively by computed tomography (CT) (Fig. 1), and periportal varices were confirmed at operation. A liver biopsy at the time of surgery showed normal hepatic architecture. The patient's recovery was uneventful, but 18 months later she developed gastrointestinal bleeding. She presented multiple times with melena requiring multiple-unit transfusions. Her evaluation included upper gastrointestinal endoscopy, colonoscopy, angiography, and tagged red blood cell scans. Angiography confirmed the presence of portal vein and splenic vein thrombosis, but all of the endoscopic studies failed to show a bleeding source. She was empirically placed on a β-blocker. A further episode of bleeding in October 2003 precipitated a referral to our hospital. On admission, she was hemodynamically stable, and a repeat CT scan demonstrated extensive varices around the Roux limb. An angiogram again demonstrated portal and splenic vein thrombosis and jejunal varies at the site of her hepatico-jejunostomy, which were assumed to be the cause of her bleeding (Fig. 2). Devascularization through resection of her Roux limb was planned. Prior to surgery, a percutaneous transhepatic cholangiogram (PTAC) was placed through the bile duct into the duodenum to facilitate surgery and to aid postoperative management. At surgery, the Roux limb was identified and there were obvious varices passing over the anterior surface of the bowel wall and draining into the intrahepatic portal vein (Fig. 3); these were carefully ligated. The biliary stent was palpated, and the side-to-side hepatojejunal anastomosis was taken down.

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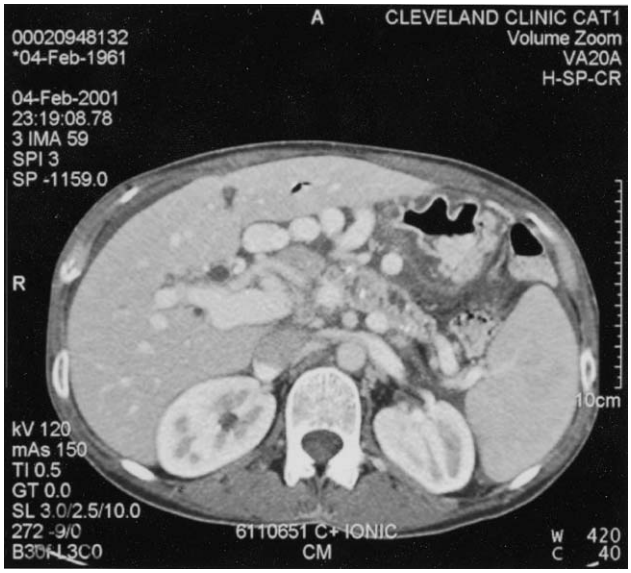

Fig. 1. Computed tomography with intravenous contrast showing large portal venous collateral beneath the left hepatic lobe following proximal portal vein thrombosis due to chronic pancreatitis (note pancreatic calcifications).

The end of the Roux-en-Y was resected, stapled, and then oversewn. The defect on the anterior common hepatic duct was repaired using porcine small intestinal submucosa (SIS) (Surgsis; Cook Surgical, Bloomington, IN) (Figs. 4, 5). The patient had an uncomplicated postoperative recovery. At 14 months of follow-up, the patient has had no further gastrointestinal bleeding and has an indwelling transhepatic stent. She has been entered into an upper gastrointestinal endoscopic surveillance program because she is at high risk of developing gastroesophageal varices following disruption of her preferred decompensatory pathway.

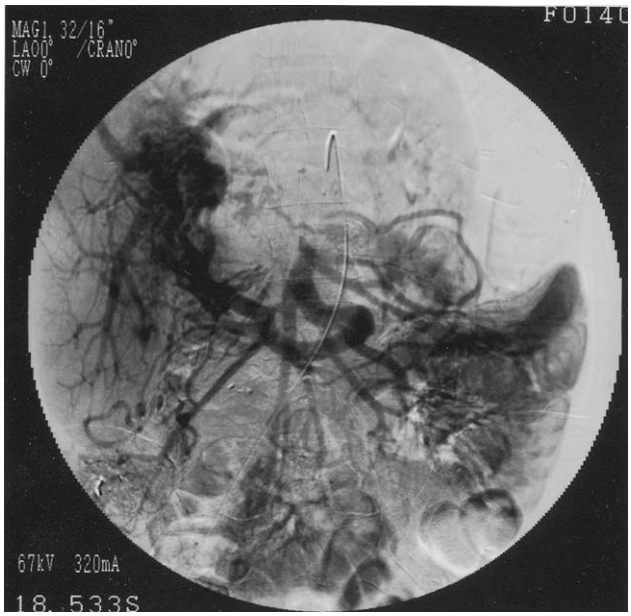

Fig. 2. A mesenteric arteriogram showing the venous phase and varices in the hepatic hilum at the site of the biliary enteric anastomosis.

Fig. 3. Varices passing over the surface of the jejunal Roux limb at the choledochojejunostomy.

DISCUSSION

This is an unusual case of repeated gastrointestinal bleeding due to biliary anastomotic varices as a consequence of extrahepatic portal vein thrombosis, and it demonstrates successful treatment using local devascularization of the varices and a novel method of repair to the bile duct. Portal hypertension causes collaterals to form between portal and systemic circulations. The most clinically important are those at the gastroesophageal junction, although shunting and varices in the hemorrhoidal veins, retroperitoneal

Fig. 4. The defect left in the anterior wall of the common hepatic duct following resection of the Roux limb.

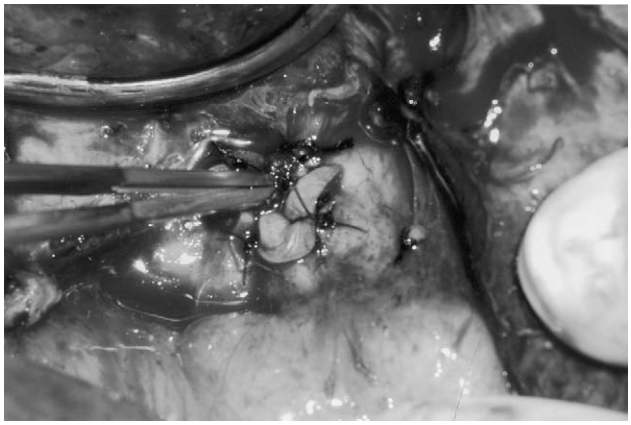

Fig. 5. Patch repair of the common hepatic duct with small intestinal submucosa (SIS).

collaterals, falciform ligament, and at the stoma of an enterostomy are recognized. These "ectopic" varices are estimated to occur in approximately 1%–3% of patients with cirrhosis.[1] The first case of bleeding from varices in the small intestine was described in 1961.[2] Symptomatic jejunal varices are rare; only 20 cases have been reported in the English literature.[3–21] There are two types of jejunal varices: perijejunal varices, which occur in the absence of a high-to-low pressure connection, and jejunal varices, which create a portosystemic shunt. Eight cases have been reported; a summary of clinical, angiographic findings, and treatment in these patients is outlined in Table 1. The syndrome of massive gastrointestinal bleeding secondary to jejunal varices exhibits several characteristic features. Patients often present with melena but rarely with more profuse bleeding per rectum. Hematemesis is characteristically absent unless there are associated gastroesophageal varices. Many patients also have a history of major intra-abdominal surgery. It is postulated that the formation of varices in these patients is higher due to the development of adhesions that bridge high- and low-pressure venous systems. In our case, the chronic pancreatitis is assumed to have caused the thrombosis of the portal vein resulting in "bridging" varices from the high-pressure veins in her jejunal limb to her low-pressure liver sinusoids, which are connected by her choledochojejunostomy. Variceal bleeding associated with pancreatitis usually results from splenic vein thrombosis and the development of portosystemic collaterals in the short gastric veins and gastric fundus trying to form a "bridge" back to the normal-pressure portal vein. An important point in establishing the diagnosis is in the history, particularly to define any prior surgery that may have set up the pathophysiology of an anastomsosis between high-pressure veins in the small bowel to a low-pressure outflow site. Angiography plays a crucial role in the diagnosis of jejunal/ileal varices. The radiographic features include the visualization of abnormal dilated veins on the venous phase of the superior mesenteric artery injection. Injection of a vasodilator such as a calcium channel blocker improves visualization of the varices and occasionally shows active luminal extravasation. Angiography does not always show contrast extravasation, presumably because of a combination of contrast dilution in the venous phase, the slower rate of venous bleeding, and the failure to image for an appropriate period of time during the venous phase of the examination.[7,18]

The treatment of venous thrombosis is symptomatic, with the aim of controlling variceal bleeding or preventing recurrent bleeding with pharmacologic agents. Endoscopic therapy is not an option for small bowel variceal bleeding. Portosystemic shunts are unlikely to be an option because most bleeding in such patients occurs proximal to a vein suitable for such shunts. Nonconventional shunts using peripheral mesenteric veins or the anastomosis of large venous collateral veins with a systemic vein may be considered, but the outcome is often poor.[22,23] In the eight reported cases of anastomotic varices, two were treated using a mesocaval shunt, two by resection of the jejunum with reanastomoses of the jejunal limb, one by ligation of the varix, one by embolization, and one by deployment of an intravenous stent, and one was treated conservatively. All report no recurrence of bleeding, but the follow-up period was limited (2–24 months).

In our case, simple resection with reanastomoses of the conduit or embolization/ligation of the varices would simply result in the same problem arising at a later date—hence, the decision to devascularize the varices by resection of the Roux limb. However, this left the problem of the management of the bypassed bile duct. In this case, a percutaneous transhepatic internal external stent was placed prior to surgery into the duodenum in order to facilitate surgery and aid postoperative management. The defect left after disconnection of the Roux limb was 8 mm in diameter. Simple closure could have resulted in leak or stenosis. Another approach would be to perform a patch repair of the bile duct. A new material, porcine SIS, has been introduced. It is a biodegradable, collagen-based, acellular, nonimmunogenic material harvested from the submucosal layer of porcine intestine, and it has been shown to have regenerative capabilities in various sites.[24,25] In a canine model of bile duct injury, SIS has been shown to be incorporated into the bile duct. At 3 months after implantation, histology

Table 1. Prior series of small bowel varices

Reference	Patient age (yr)/gender	Presenting symptom	Underlying cause	Previous abdominal surgery	Angiographic findings	Treatment	Porto-systematic collateral	Outcome	Follow-up (mo)
5	48/M	Melena	SMV, splenic vein thrombosis	Loop cholecystojejuno-stomy for CBD obstruction	SMV, SV thrombosis	Loop cholecysto-jejunostomy resected; Roux-en-Y preformed	SMV-jejunal branch, proximal PV	No recurrence	2
7	39/M	Hematochezia	SMV thrombosis, pancreatitis		PV,SMV, SV thrombosis	PV recannalization and stent placement	SMV-jejunal branch, proximal PV	No recurrence	6
10	79/F	Melena	PV thrombosis	Cholecystectomy, choledochochectomy and hepatico-jejunostomy	Varices PV	Embolization ethanol and coils	SMV-jejunal branch, proximal PV	No recurrence	13
8	54/F	Melena and Hematochezia	Cirrhosis and SMV thrombosis	Patch repair of duodenum, with jejunal Roux limb	SMV thrombosis	Segmental resection of jejunum and reanastomosis	SMV-jejunal branch, liver and abdominal wall	No recurrence	NK
18	46/M	Melena	Cirrhosis	Esophageal transaction and	Proximal SMV varices	Jejunal resection	SMV-jejunal branch, splenectomy, omentum	No recurrence	36
4	16/F	Melena	PV thrombosis	Laparotomy peritionitis and splenectomy	ND	Varix ligated	SMV-ileal branch, umbilical vein	No recurrence	2
19	48/F	Melena	Cirrhosis	Multiple PU operations BII revised to BI	Ileal varices	Ileal resection	Ileum-right ovary	No recurrence	24
6	53/M	Hematochezia	PV, SMV thrombosis	Multiple gastric operations for PU disease. Hepaticoduodenostomy and cholecystectomy for chronic pancreatitis	PV, SMV thrombosis	Mesocaval shunt	SMV-jejunal branch, proximal PV	No recurrence	24
21	73/F	Melena	Cirrhosis	NK	Varices from SMV connecting to right ovarian vein	Conservative	SMV-right ovarian vein	No therapy	NK
21	47/F	Hematochezia	NK	NK	Varies from SMV connecting to right ovarian vein	Ileal resection portocaval shunt	SMV-right ovarian vein	Perioperative death	-

NK = not known; ND = not done; SMV = superior mesenteric vein; CBD = common bile duct; PV = portal vein; SV = splenic vein; PU = peptic ulcer; BII = Billroth II gastrectomy; BI = Billroth I gastrectomy.

revealed that the SIS graft was replaced with native collagen covered with biliary epithelium.[26] In our case, a patch of SIS was sutured using 5-0 PDS sutures onto the 8-mm defect in the anterior common bile duct wall. A postoperative cholangiogram on day 7 demonstrated no leak. Follow-up cholangiogram has not demonstrated a stricture at this site. The PTHC has been converted into an internal stent as the pancreatic head obstruction remains and will require periodic exchanges.

In conclusion, this case of bleeding biliary anastomotic varices was successfully treated by Roux limb excision and reconstruction of the bile duct using porcine SIS. This case demonstrates another technique that can be used as a treatment option in the management of this difficult and rare clinical entity. Moreover, it demonstrates the porcine SIS can be used as a scaffold for the successful repair of the bile duct.

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The Unsolved Problem of Fistula After Left Pancreatectomy: The Benefit of Cautious Drain Management

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The aim of the study was to identify factors related to the onset of pancreatic fistula and to define the characteristics of the fistula. The study group was composed of 123 patients who underwent left pancreatectomy since 1996. Pancreatic closure was accomplished by a hand-sewn technique (39 patients) or two kinds of mechanical staplers: Proximate (Ethicon Endo-Surgery, Cincinnati, OH) (46 patients) and Endo-GIA (United States Surgical, Norwalk, CT) (38 patients). Fistula was defined as output greater than 5 ml, with amylase × 5, after day 5. In case of fistula, the drain removal was scheduled at a daily output less than 5 ml.

Mortality was 0%, morbidity was 48%, and pancreatic fistula rate was 34%. Fistula rate was 38% after hand-sewn closure, 26% after Proximate, and 39% after Endo-GIA (NS). None of the other factors (separate duct ligation, hand-sewn suture in addition to stapler, spleen preservation, use of pledgetted suture, sex, age, and indication for pancreatectomy) proved to be related to a reduction in the onset of fistula. All fistulas healed spontaneously. Mean fistula duration was 36 days; 92.8% of patients with fistula were discharged with drain. The policy of delayed drain removal allowed a low rate of fistula associated morbidity (16%) and of readmission (4.7%).

In conclusion, fistula is an unsolved problem of left pancreatectomy. However, a careful drain management allows a good outcome in patients with fistula. (J GASTROINTEST SURG 2005;9:837–842)

KEY WORDS: Pancreas, surgery, technique, complications, fistula

The onset of pancreatic fistula after pancreaticoduodenectomy can have dramatic consequences because pancreatic enzymes are activated by contact with bile or intestinal enzymes. Pancreatic fistula after left pancreatectomy is not so frightening for surgeons, because, apart from the infrequent technique of anastomosis between the pancreatic remnant and the jejunum, it is a nonactivated and sterile fistula. Nevertheless, pancreatic fistula after left pancreatectomy can be associated with further complications, such as fluid collections or abscess, or, at the least, it causes discomfort for the patient, who must have a drainage tube in place for days or weeks. There is a great variability in its reported incidence, ranging from 5% to 40% to 50%,[1–3] and a great number of technical variations has been used to obviate to its onset: hand-sewn suture,[1,4–5] different kinds of staplers,[1,4–8] a combination of stapler and suture,[1,4–6] the use of pledgetted suture,[6] pancreaticojejunal anastomosis,[9–10] transection by harmonic scalpel,[11–12] and fibrin sealant.[13–15] The aim of this study was to describe the incidence and the characteristics of pancreatic fistula after distal pancreatectomy and to identify clinical and technical factors that can be related to its onset.

MATERIAL AND METHODS

Between 1996 and April 2004, 141 patients underwent left pancreatectomy at the Pancreas Unit of the S. Raffaele Hospital, Milan. This is a tertiary referral university hospital, with a high-volume pancreatic surgery practice (598 overall pancreatic resections

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during the study period). Data were prospectively collected in our pancreatic surgery database. In 18 cases left pancreatectomy (with or without splenectomy) was associated with further resections (stomach in 8 cases, liver in 4 cases, enucleation of tumours of the pancreatic head in 4 cases, colon in 2 cases). These 18 patients were excluded from the study, because complications and length of stay could be influenced by the associated resection. Therefore, the study population included 123 patients. Demographic factors and indication for the operation are listed in Table 1.

The closure of the pancreatic remnant was accomplished by hand-sewn suture in 39 patients and by mechanical stapler in 84 cases. Hand-sewn suture was performed using interrupted, readsorbable U stitches (Vicryl or Monocryl, from Ethicon, Pratica di Mare, Pomezia, Italy). During the study period we used two different types of staplers: from 1996 to 2001, in 46 patients we used the linear stapler Proximate (Ethicon Endo-Surgery, Cincinnati, OH), 60 mm long, loaded with 4.0×4.5 mm staples, and from 2001 to 2004, in 38 patients we used the Auto Suture Endo-GIA (United States Surgical, Norwalk, CT), loaded with a 60 mm long unit, with 4.8 mm staples. Seven of 38 patients in the Endo-GIA group underwent a laparoscopic resection. The choice of the operation was not randomized. Further technical factors that were considered in the analysis were: the addition of suture to stapled closure, separate main duct ligation, the use of polytetrafluoroethylene (PTFE) pledgets to reinforce the suture, and the preservation of the spleen. The spleen was preserved in case of benign and borderline neoplasm; in all cases, the splenic vessels were preserved.

An open silicone 28 CH drain (wound drainage tube, Redax SRL, Mirandola MO, Italy) was placed in proximity to the pancreatic remnant at the end of the operation. Operative mortality was defined as death occurring within 60 days from the operation (no death related to the operation occurred after this limit); pancreatic fistula was defined as the daily secretion in a drainage tube of more than 5 ml of fluid, with amylase level 5 times higher than serum, after postoperative day 5. In case of fistula, drain was removed when the daily fluid output was lower than 5 ml.

In the absence of other complications, patients with fistula were discharged with the surgical drain and they were seen weekly as outpatients. The presence of fistula was not considered a contraindication for the resumption of oral diet. Octreotide was routinely administered (0.1 mg each 8 hours from day 0 to 7), and in case of fistula it was prolonged until discharge. The healing of fistula was considered to have occurred when the drain was removed, in the absence of a subsequent need for a new drainage.

The χ^2 test or Fisher's exact test were used for comparing categorical variables; the Mann-Whitney-*U* test or Student's *t*-test were used to compare continuous variables; results are reported as mean ± SD or median. A P value <0.05 was considered statistically significant. The analysis was performed with SPSS statistical software (SPSS Inc, Chicago, IL).

Table 1. Demographic factors and indication for surgery of 123 patients undergoing left pancreatectomy

Median age (range)	59 y (19–85y)
Male/female	52/71
Pancreatic adenocarcinoma	59 (48%)
Endocrine neoplasm	24 (19.5%)
Cystic neoplasm	23 (18.7%)
Chronic pancreatitis	5 (4.1%)
Other	12 (9.8%)

RESULTS

Overall Operative Outcome

Mortality was 0%, morbidity was 48.8%, and reoperation rate was 4.1%. Causes of reoperations were early intraperitoneal bleeding in four patients and intestinal perforation in one case. The most frequent complication was pancreatic fistula, occurring in 34.1% of patients undergoing left pancreatectomy. Overall operative results are summarized in Table 2.

Characteristics of Fistula After Left Pancreatectomy

Thirty-nine out of 42 patients with postoperative leak (92.8%) were discharged with drain. Mean ± SD

Table 2. Operative results in 123 left pancreatectomies

	No.	%
Mortality	0	0
Morbidity	60	48.8
Reoperations	5	4.1
Pancreatic fistula	42	34.1
Intrabdominal abscess	6	4.5
Infectious complications	9	7.3
	Mean ± SD	Range
Operative time (min)	246 ± 87	70–540
Blood loss (ml)	635 ± 523	50–2700
Blood transfusions (ml)	193 ± 319	0–1320
Length of stay (days)	11.8 ± 6.1	6–45

daily output of fistula at discharge (in patients discharged with drain) was 31 ± 35 ml (range 5–250 ml); mean ± SD fistula duration was 36 ± 17 days (range 10–95 days). All fistulas healed spontaneously. Fistula-associated morbidity was 16.6% (7 patients): 2 abscess, 2 fluid collection, 2 pleuric effusion, and 1 wound infection. None of these patients required a reoperation; the abscesses and fluid collections were treated by percutaneous drainage. Forty-two patients with fistula had a significantly prolonged postoperative stay in comparison to 63 noncomplicated patients (mean ± SD: 12.0 ± 4.0 days and 9.6 ± 2.4 days, respectively, $P < 0.01$).

The rate of readmission after discharge for patients with fistula was 4.7% (two cases): the first patient had the drain removed on postoperative day 5, after two negative amylase assessments in the drainage fluid. She was discharged on day 9 and readmitted on day 12 because of fever and pain caused by a peripancreatic fluid collection, which was treated by a ultrasound-guided percutaneous drainage (high amylase in the fluid). The second patient was readmitted on day 30 because of pain and mild increase in temperature, 7 days after the removal of drain as a outpatient. Ultrasound revealed a small peripancreatic fluid collection, that was treated conservatively.

Factors Related to Fistula

Results are summarized in Table 3. Patients who underwent hand-sewn suture of the pancreatic remnant had a 38% fistula rate, whereas patients with mechanical pancreatic closure had a 32% fistula rate ($P = 0.6$). The closure by Proximate stapler had a 26% fistula rate compared to 39% in patients who had closure by Endo-GIA ($P = 0.3$). Fifty-two out of 84 patients with mechanical closure received a combination of staple closure and hand-sewn suture, but this technique did not significantly improve the fistula's rate when compared to staple closure alone (31% and 34%, respectively, $P = 0.9$). Fifty-one patients who underwent separate main duct ligation had no reduction in postoperative fistula as compared to 72 patients who did not (35% and 33%, respectively, $P = 0.9$). The group of 18 patients with pledgetted suture had a 22% fistula incidence vs. 37% of 73 patients in whom the suture was not reinforced by pledgets ($P = 0.4$). Spleen preservation allowed a slight reduction of fistula (20% versus 38%, $P = 0.15$); no reduction in the rate of infection was observed in the spleen-preserving group (12% and 6%, $P = 0.5$). None of the patient-related factors (sex, age, indication for the operation) was significantly associated with fistula formation.

Table 3. Incidence of pancreatic fistula according to different factors

	No. of patients	Fistula No. (%)	*P* value
Gender			
Male	52	22 (42.3%)	0.16
Female	71	20 (28.2%)	
Age			
<70 y	93	36 (38.7%)	0.64
>70 y	20	6 (30%)	
Indication for pancreatectomy			
Cancer and chronic pancreatitis	64	23 (35.9%)	0.81
Other	59	19 (32.2%)	
Method of closure			
Hand-sewn closure	39	15 (38.4%)	0.63
Stapler closure	84	27 (32.1%)	
Proximate stapler	46	12 (26.1%)	0.29
Endo-GIA stapler	38	15 (39.5%)	
Further technical factors			
Stapler closure only	32	11 (34.4%)	0.91
Stapler + suture	52	16 (30.8%)	
Separate main duct ligation	51	18 (35.3%)	0.97
No separate main duct ligation	72	24 (33.3%)	
Pledgetted suture (+/− stapler closure)	18	4 (22.2%)	0.36
Suture without pledgets (+/− stapler closure)	73	27 (37%)	
Spleen preservation	25	5 (20%)	0.15
Splenectomy	98	37 (37.8%)	

DISCUSSION

The appraisal of two large recently published series[9,16] shows that postoperative pancreatic fistula affects more patients after left pancreatectomy than after pancreaticoduodenectomy. The reason is unclear, since the preferential drainage of pancreatic juice should be towards the duodenum. There is a great variability in the reported incidence of pancreatic fistula. Table 4 shows the results of studies focusing on left pancreatectomy, enrolling more than 50 patients, published in the last 10 years. Fistula rate varied from 3% to 28.6%, and in the present series it was 34.1%. In these studies there is also a great variability in the definition of pancreatic fistula, and the fistula rate has been shown to be strictly dependent upon the definition used.[21] Lillemoe[1] observed a 5% fistula incidence in the largest published series (235 left pancreatectomies), but the definition of fistula is not reported. Balcom[16] found a 14% incidence of fistula in the second large series (190 patients), defining fistula as the drainage of more than 30 ml of amylase-rich fluid.

In our study we used a strict definition of pancreatic fistula (>5 ml with amylase × 5 after day 5).

Table 4. Incidence of pancreatic fistula after left pancreatectomy*

Author	Year of publication	No. of patients	Pancreatic fistula
Suzuki[15]	1995	56	28.6%
Fabre[17]	1996	128	3%
Ohwada[14]	1998	90	18%
Lillemoe[1]	1999	235	5%
Balcom[16]	2001	190	14%
Sheenan[4]	2002	86	14%
Shoup[5]	2002	125	7%
Bernard[18]	2002	54	9.3%
Fahy[19]	2002	51	26%
Hutchins† [20]	2002	84	3.3%
Bilimoria[6]	2003	126	19.8%
Buchler[9]	2003	88	5.7%
Present study	2004	123	34.1%

*Studies published during the last 10 years, enrolling >50 patients.
†only patients with chronic pancreatitis.

We consider this definition, appropriate because our policy is very careful in the case of a positive amylase level in the drainage fluid. To avoid the potential complications related to an early removal of the drain, such as abscess, fluid collection, or pseudocyst, we maintain the external drain until the daily output has lowered to 5 ml. We do not treat patients with fistula with parenteral nutrition, nor antibiotics, nor prolongation of octreotide after discharge.

The cost of this cautious attitude toward drain removal is discomfort for the patient: 39 out of 42 patients with pancreatic leak (92.8%) were discharged with the drain and maintained it for a mean duration of 36 days. The benefit of this policy is a low rate of fistula-associated complications (16%), a limited prolongation of postoperative stay with respect to patients with no complications (12 days versus 9.6 days), and a very low rate of readmission after discharge (4.7%). In all cases pancreatic fistulas healed spontaneously. Maybe an earlier removal of the drain could reduce the patients' discomfort, but a higher rate of delayed complications could be expected.

Virtually no data on readmissions after early removal of drain in these patients are present in the literature: the study of Balcom, from the Massachusetts General Hospital,[16] described an overall readmission rate of 13% in 190 patients who underwent distal pancreatectomy. It is likely that the readmission rate in the subgroup of patients with fistula was much higher than the 4.7% we observed in our patients with the same complication.

We did not find a relation between the onset of fistula and demographic factors (age, sex), nor with the indication for pancreatectomy; a soft pancreas is a well-known risk factor for fistula after pancreatic anastomosis,[22–23] whereas the relation between consistency and fistula after distal pancreatectomy is less clear. In our patients fistula occurred similarly in patients with adenocarcinoma or chronic pancreatitis, who usually have a more fibrotic pancreas, and in patients with other diseases such as endocrine or cystic neoplasms.

To identify technical factors that could reduce the rate of fistula, we explored all of the technical variations that have been applied to our patients during the study period. As in most of the published reports, we used either suture closure or stapler closure or a combination of both. Manual or mechanical closure can be used indifferently, except when the pancreatic parenchyma is very thick; in these cases, the suture is to be preferred because of the risk of fracturing the pancreas during stapling closure. There was no significant difference in the leakage rate between different groups: onset of fistula was observed in 38% out of 39 patients after suture, in 34% out of 32 patients with stapled closure alone, and in 31% of 52 patients with the combined technique.

During the study period, we used two types of staplers: in the first years the Proximate, and since 2001 the Endo-GIA. Endo-GIA is commonly used during laparoscopic left pancreatectomy; it allows simultaneous transection and closure on both sides of the transected pancreas. This device gave us an impression of safety, placing two triple rows of staples, and therefore we began to use it even during open surgery. Unfortunately, the impression of safety was not confirmed by the results: patients undergoing Endo-GIA transection had a slightly higher rate of fistula compared to patients who underwent closure with the Proximate stapler (39% versus 26%, $P = 0.3$). This means that a high fistula rate is to be expected during laparoscopic left resection, when our criteria for fistula are applied.

A further technical note concerns the separate main duct ligation. A recent paper raised this factor as the most important to reduce the fistula rate.[6] Unfortunately, our results cannot confirm this finding, since 51 patients with main duct ligation had virtually the same fistula rate as 72 patients with no duct ligation (35% and 33% respectively, $P = 0.9$). The last technical factor we considered is the use of pledgets to reinforce the suture: the group of 18 patients with pledgetted suture had a reduction of the fistula rate (22%), but the sample dimension does not allow to draw any conclusion on the use of pledgets.

Spleen was preserved in 25 patients (about 50% of cases with benign or borderline diseases), in all cases with preservation of the splenic vessels. Patients

with spleen preservation had no reduction in the infectious rate, different from what previously reported,[5] but they had less pancreatic leakage compared to patients with splenectomy (20% vs 38%, $P = 0.15$), suggesting a protective effect of splenic vessels preservation.

A final note on the prophylactic use of octreotide: during the study period, according to the results of four European studies,[24–27] we routinely used it, both for pancreaticoduodenectomy and left pancreatectomy. At present, after the publication of more recent studies from North America and France,[22,28–30] we have changed our policy, limiting the use of octreotide to pancreaticoduodenectomy with high-risk pancreatic anastomosis.

CONCLUSIONS

Pancreatic fistula affects more than 30% of patients after distal pancreatectomy, when a strict definition of fistula is applied. Our policy to delay drain removal in patients with amylase-rich fluid allows a low rate of fistula-related morbidity (16.6%), and a low readmission rate in these patients (4.7%). From a surgical point of view, fistula is an unsolved problem, since none of the technical variations we used through the study period seemed useful to significantly reduce its incidence. Basing on these findings, it is difficult to draw any conclusions about the best technique to use to close the pancreatic remnant; our present attitude is to do the most we can do, and therefore to use a stapler, to separately suture the main duct, and to add a further closure with pledgetted U-stitches.

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Intraductal Papillary Mucinous Tumor of the Pancreas Associated With Autosomal Dominant Polycystic Kidney Disease

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A 43-year-old male with a history of autosomal dominant polycystic kidney disease (ADPKD) was admitted to our center with severe abdominal pain and was diagnosed with acute pancreatitis. CT showed multiple cysts in the liver and both kidneys along with ADPKD and a cystic mass, 4 cm in diameter, in the pancreatic head. The main pancreatic duct was dilated to 1 cm in diameter. The patient was diagnosed with acute pancreatitis due to intraductal papillary mucinous tumor (IPMT), and pancreatoduodenectomy was performed. Histologic examination revealed a multiloculated cystic tumor filled with mucin in the head of the pancreas. Microscopically, the tumor was diagnosed as adenocarcinoma and was found to have invaded the main pancreatic duct. Although, in addition to our case, only seven cases with association between ADPKD and malignant neoplasms have been reported, five of these cases had neoplasms arising from the pancreas. Therefore, we suggest that some genetic interactions may exist between ADPKD and pancreatic carcinogenesis. (J GASTROINTEST SURG 2005;9:843–845)

KEY WORDS: Intraductal papillary mucinous tumor, autosomal dominant polycystic kidney disease, pancreatic cancer

Although autosomal dominant polycystic kidney disease (ADPKD) is known to have several manifestations, there have been only a few reports on the relationship between ADPKD and malignant tumors. Intraductal papillary mucinous tumor (IPMT) is a relatively new entity that consists of a cystic tumor of the pancreas with a malignant potential. We report a case of intraductal papillary mucinous carcinoma of pancreas arising in ADPKD. To our knowledge, a relationship between IPMT and ADPKD has never been reported with the exception of two sisters who were reported to have cystadenocarcinoma associated with ADPKD.

CASE REPORT

A 43-year-old man with a history of ADPKD was admitted to our hospital with severe abdominal pain. Laboratory studies showed the serum amylase level was 625 IU/l and the elastase-I level was 2100 U/ml. CT showed not only multiple cysts in the liver and both kidneys but also a cyst, 4 cm in diameter, in the pancreatic head. The main pancreatic duct (MPD) was dilated to 1 cm in diameter (Fig. 1). Endoscopic retrograde cholangiopancreatography showed that a section of the MPD in the head of the pancreas was narrowed and that the duct in the body and tail was dilated. Mucin was observed to be oozing from the gaping orifice of the ampulla of Vater. The patient was diagnosed with acute pancreatitis due to IPMT associated with ADPKD. Pancreatoduodenectomy was performed. Histologic examination revealed a multiloculated cystic tumor filled with mucin in the head of the pancreas. Several nodules were growing from the cyst wall (Fig. 2*A*). Microscopically, these nodules were diagnosed as adenocarcinomas, and some were found to have invaded the MPD (Fig. 2*B*). Two years following the operation, the patient remains alive without recurrence or metastases.

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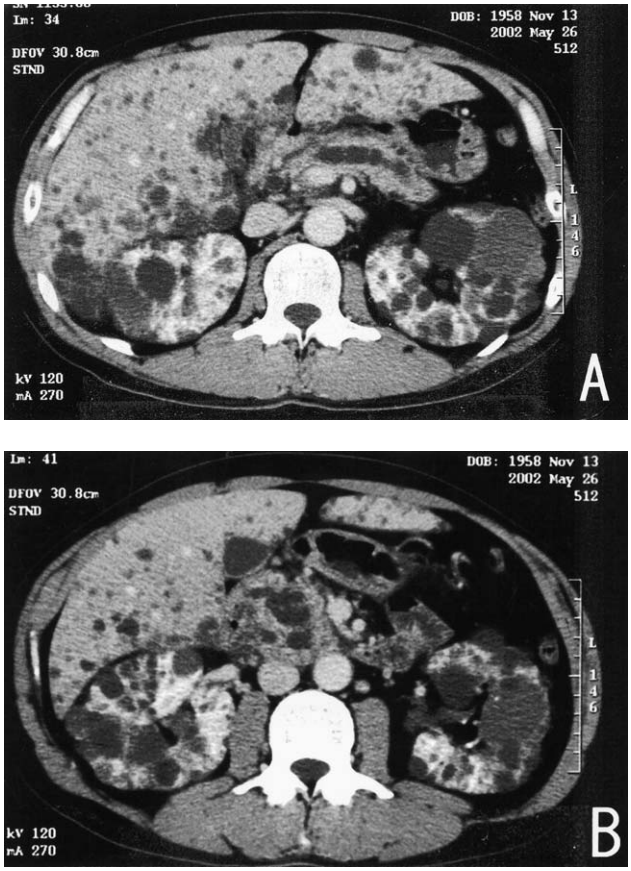

Fig. 1. CT images of the abdomen show (**A**) multiple cysts in the liver and both kidneys, and a main pancreatic duct that is 1 cm in diameter, and (**B**) a cystic mass, 4 cm in diameter, in the head of the pancreas.

DISCUSSION

Among patients with ADPKD, 48% to 74% have associated liver cysts and 5% to 10% have associated pancreatic cysts.[1,2] Mitral valve prolapse and intracranial berry aneurysms are also well-known manifestations of ADPKD. An association with malignancy is rare; we could find only six cases reported in the medical literature written in English.[1–4] Four of these patients had pancreatic malignancies; two of them were sisters with cystadenocarcinoma, reported by Niv et al.[2] The remaining two patients had ductal carcinomas. In our patient, multiple liver cysts were observed, but pancreatic cysts without the IPMT were not detected. Cardiovascular disease, including mitral valve prolapse, and intracranial aneurysms were also not detected. In addition, the patient's father, two uncles, and elder brother were also diagnosed with ADPKD. Although the father died from a subarachnoid hemorrhage and the brother is undergoing dialysis for renal failure, malignant neoplasms have not been detected.

Mucin-producing cystic tumors of the pancreas are presently classified into two main categories; one category comprises mucinous cystic tumor, and the other comprises IPMT. As a result of the development of several types of diagnostic modalities, these tumors are recognized with increasing frequency. IPMT is characterized by intraductal papillary growth, massive mucin secretion, and dilatation of MPD and/or its branches. IPMT is also characterized by the presence of various stages of carcinogenesis ranging from adenomas to invasive carcinomas. It is often difficult to predict the likelihood of malignancy preoperatively. Some predictive factors for malignancy in IPMT have been studied. Sugiyama et al. reported that mural nodules and dilatation of main pancreatic duct (7 mm or more) were independent factors indicative of malignancy in IPMT.[5] Surgical treatment of IPMT usually includes pancreatoduodenectomy, distal pancreatectomy, or total pancreatectomy. However, these surgical procedures result in

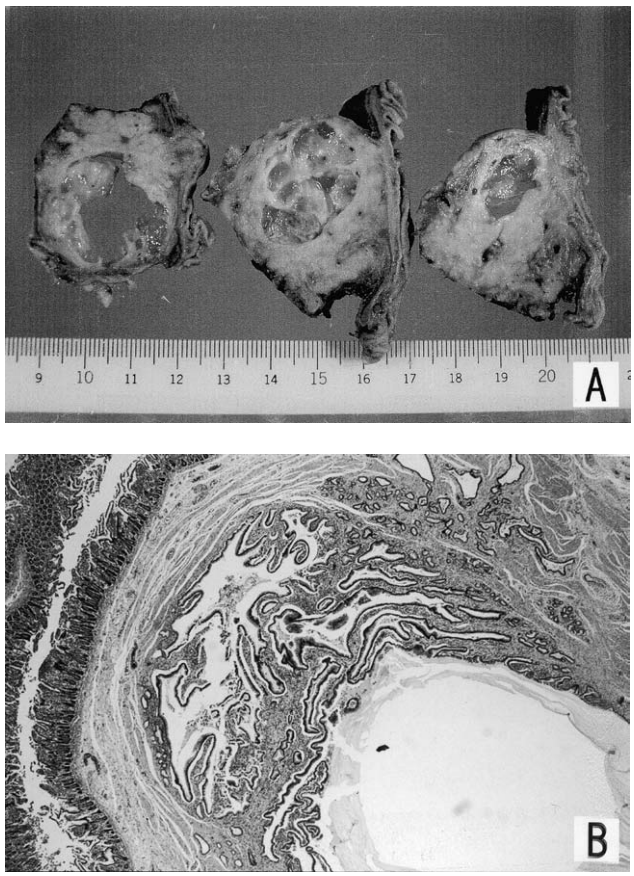

Fig. 2. (**A**) Photograph of the resected head of the pancreas shows a multiloculated cystic tumor filled with mucin and several papillary modules growing from the cyst wall. (**B**) Photomicrograph of the specimen shows these nodules to be adenocarcinomas, some of which invade the main pancreatic duct.

an increased morbidity in the patients. Since the prognosis of IPMT is known to be much better than that of ductal carcinoma of the pancreas, some papers have reported the usefulness of local resection of the pancreas. In the previous 10 years, 10 cases of IPMT have been operated upon in our center. Local resection was performed in 4 of the cases with small lesions (less than 30 mm in diameter) and with abnormal changes in MPD; there were no cases with recurrence. Therefore, in order to select adequate treatment for each patient, more precise and larger studies need to be conducted for estimating the degree of malignancy of IPMT.

It remains uncertain whether ADPKD plays an important role in the development of IPMT. Including the present case, five of the seven cases, which were reported to have an association between ADPKD and carcinomas, had tumors of pancreatic origin. Therefore, as some investigators have previously mentioned,[1,2] we also believe that ADPKD may have some genetic influence on the development of the pancreatic neoplasms.

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Preservation of the Left Gastric Vein in Delayed Gastric Emptying After Pylorus-Preserving Pancreaticoduodenectomy

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The definition of delayed gastric emptying (DGE) after pyloric-preserving pancreaticoduodenectomy (PPPD) varies among surgeons. We compared and evaluated three different definitions reported elsewhere. In addition, we investigated the correlation between multiple surgical factors and recovery of gastric motility. First, 55 consecutive patients were reviewed to assess the three different definitions. Second, surgical factors affecting gastric motility were investigated in 46 patients showing no major complications. All 55 patients underwent PPPD, which was reconstructed with antecolic duodenojejunostomy, with aggressive lymph node dissection and with no mortality. The duration of nasogastric intubation was 2 days, and a solid diet started on the 12th postoperative day (median). Re-nasogastric intubation or emesis was observed in 12.7% of patients. Overall, DGE occurrence rate was 5.5%–29.1%, with striking differences depending on the type of definition. Technically, division of the left gastric vein was accompanied with significantly delayed removal of the nasogastric tube (3 versus 2 days, $P = 0.0002$) and delayed start on a solid diet (14 versus 9 days, $P < 0.0001$) compared with its preservation. Antecolic duodenojejunostomy after PPPD improved DGE occurrence despite aggressive surgery, and preservation of LGV accelerated restoration of gastric motility in our experiments. However, an understanding of a common definition of DGE is needed when discussing the outcome of the various interventions. (J GASTROINTEST SURG 2005;9:846–852)

KEY WORDS: Delayed gastric emptying, pylorus-preserving pancreaticoduodenectomy, left gastric vein, aggressive surgery

Since Traverso reported the pyloric-preserving procedure (PPPD),[1] delayed gastric emptying (DGE) after PPPD has been widely discussed in respect to its occurrence rate. However, controversial opinions lie in the definition of DGE as it appears to differ from author to author.[2–7] These definitions are grossly classified in three types: the first[4,7] refers to the lack of a parameter related to diet; the second[3,5,6] is determined by the duration of gastric aspiration and the period of inability to take a diet; and the third[2] uses multiple parameters, including emesis, re-nasogastric intubation, or the use of a prokinetic drug in addition to the second. To discuss the occurrence rate of DGE by surgical techniques used, it should be evaluated and compared based on its common definition.

On the other hand, pathogenesis of DGE remains unclear in cases without postoperative complications, including disruption of the vagal nerve system around the stomach with antroduodenal ischemia,[8] decreased plasma concentration of motilin,[9,10] gastric dysrhythmia due to peripancreatic inflammation,[11,12] angulation or torsion of the duodenojejunostomy,[5,13] aggressive lymph node dissection in the hepatoduodenal ligament,[14] pancreatic fibrosis,[15] postoperative septic condition,[16] preservation of the right gastric artery,[17] and portal hypertension.[18] However, little attention has been given to the roles of antroduodenal congestion induced by division of the left gastric vein.

This study aimed to compare and evaluate three typical definitions of DGE after pancreaticoduodenectomy based on our knowledge and to demonstrate our reconstruction techniques after PPPD.

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PATIENTS AND METHODS

Fifty-five consecutive patients underwent PPPD using the same surgical technique from October 1998 to October 2004. Of the 55 patients, 29 were men and 26 were women, with a median age of 63 years (age range, 11–84 years). Six patients who underwent hepatopancreatoduodenectomy were excluded. All 55 patients underwent operations with aggressive lymph node dissection based on preoperative diagnosis of malignant tumors; however, postoperative microscopic examination revealed the presence of a mass-forming–type chronic pancreatitis in two patients. Final diagnoses for the remaining 53 patients were pancreatic cancer (n = 20), cancer of the duodenal papilla (n = 16), cancer of the bile duct (n = 15), and other malignant tumors of the pancreas (n = 2).

None of the 55 patients died: 46 patients showed smooth convalescence, and the remaining 9 had major complications. A major complication was defined as a condition requiring invasive treatment or intensive care (n = 5) or pancreatic fistula (n = 5) proved by amylase-rich (>1000 mg/dl) fluid from drains over 7 postoperative days or by radiologic examination. Invasive treatment or intensive care included mechanical respiration for pneumonia (n = 1), reoperation for wound disruption (n = 1), anastomotic stenosis of duodenojejunostomy (n = 1), and percutaneous drainage for intraperitoneal abscess (n = 2).

The nasogastric tube (NGT) was removed if the daily output of the gastric aspiration was below 200 ml. The H_2-blocker was administered early after surgery in all patients. A patient's diet progressed with multiple steps every 1–3 days: water or tea, liquefied rice, water-rich rice gruel, rice-rich gruel, and regular rice food. In this study, the last two types of diet were considered as solid diets. The occurrence rate of DGE was calculated according to three definitions reported[2–4] (Table 1).

Table 1. Definitions of delayed gastric emptying

Reference	Definition
Fabre et al.[4] (A)	Nasogastric intubation ⩾10 days or its reinsertion because of vomiting
Van Berge Henegouwen et al.[3] (B)	Nasogastric intubation ⩾10 days or the inability to tolerate a solid diet on or before POD 14
Yeo et al.[2] (C)	(1) NGT in place ⩾10 days plus one of the following: (a) emesis after NGT removed; (b) use of Prokinetic drug; (c) reinsertion of NGT; (d) failure to progress with diet (2) NGT in place <10 days plus two of (a) through (d) in (1)

POD = postoperative day; NGT = nasogastric tube.

This study reviewed all 55 patients to compare the incidence of DGE according to the three definitions mentioned and the 46 patients without major complications, to investigate multiple clinical and surgical factors affecting restoration of gastric motility after PPPD. Factors evaluated in this study included gender, age, preoperative jaundice, diabetes mellitus, additional operations, intraoperative blood loss, operating time, preservation of the left gastric vein, dissection of neural plexus and lymph nodes, curability of operation, use of a pancreatic stent tube, vascular procedure, and enteral nutrition through catheter jejunostomy (>2 weeks after operation). The log-rank test with Kaplan-Meier graphs, χ^2 test, or Student's t test was used for statistical analyses. A value of $P < 0.05$ was considered statistically significant.

Surgical Techniques

In all patients, aggressive dissection of the regional lymph node around the pancreatic head was routinely carried out using the skeletonizing technique on the common to proper hepatic artery and portal vein. The left gastric vein (LGV) was preserved in cases without bulky nodal metastases near LGV or technical difficulties (n = 22). Dissection of both the neural plexus around the superior mesenteric artery and the celiac axis and of the para-aortic lymph nodes was additionally performed mainly in patients with pancreatic cancer and was categorized in this study as extensive dissection (n = 24 [44%]). The pancreas was transected at the level of the portal vein or superior mesenteric artery. The first portion of the duodenum was dissected 3–4 cm below the pyloric ring. After completing the resection, both pancreaticojejunostomy and hepatico(choledocho)jejunostomy were performed retrocolically, and then duodenojejunostomy was carried out antecolically (Fig. 1). Two procedures were performed to allow for sufficient mobility of the stomach: one involved the dissection of the lesser omentum up to the level of the esophagocardiac junction, and another involved the complete detachment of the greater omentum from the transverse colon. The stomach free from surrounding structures was easily set antecolically and vertically in the left abdomen.

Additional operations were performed simultaneously with PPPD in six patients: portal vein resection (n = 2), partial or hemicolectomy (n = 2), extirpation of benign retroperitoneal tumor (n = 1), and dissection of aneurysms of splenic artery (n = 1).

RESULTS

Overall Assessment

The median duration of nasogastric intubation was 2 days after surgery regardless of the postoperative

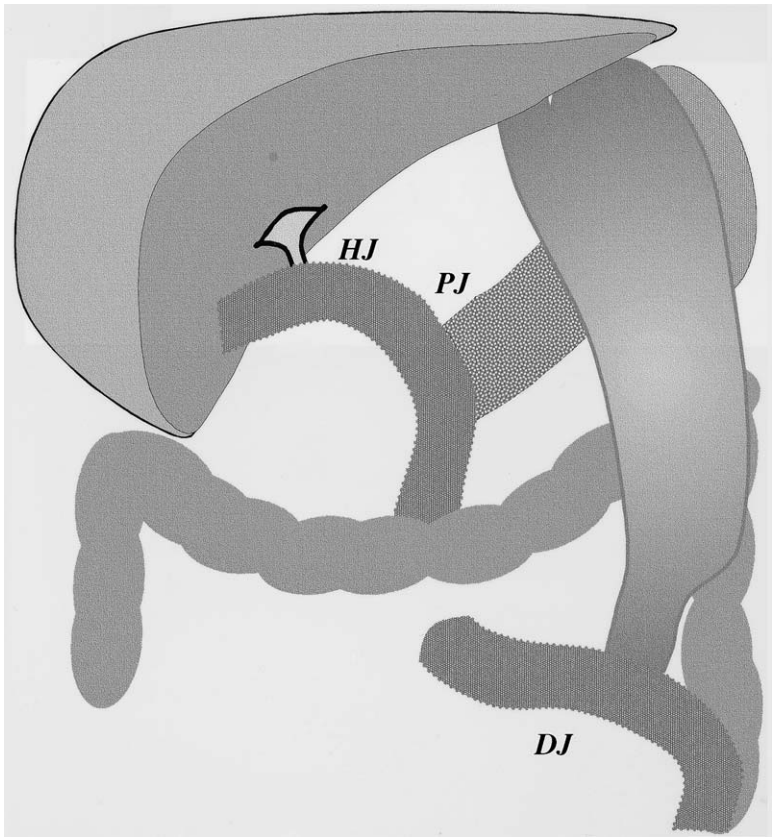

Fig. 1. Reconstruction after pylorus-preserving pancreaticoduodenectomy. Both pancreaticojejunostomy and hepatico(choledoco)jejunostomy are performed moving the single jejunal loop up retrocolically, and then end-to-side duodenojejunostomy is carried out approximately 40 cm distal to the pancreaticojejunostomy. The stomach is set vertically in the anterior aspect of the splenic flexure–descending colon. DJ = duodenojejunostomy; HJ = hepatico(choledocho)jejunostomy; PJ = pancreaticojejunostomy.

course with or without major complications (Table 2). None of the 55 patients required gastric intubation for 10 days or longer. In the 46 patients without major complications, NGT that had been inserted at surgery was removed within 2 days in 58.7%, within 3 days in 80.1%, and within 5 days in 93.5% of patients. Reinsertion of NGT or emesis after NGT removal was noted in seven patients (12.7%), with a

Table 2. Restoration of gastric motility after pylorus-preserving pancreaticoduodenectomy

	All patients (n = 55)	Major complications		*P* Value
		No (n = 46)	Yes (n = 9)	
Duration of gastric aspiration (median) (days)	2	2	3	NS
Reinsertion of NGT or emesis (%)	12.7 (n = 7)	6.5 (n = 3)	44.4 (n = 4)	0.010
Daily output of gastric aspiration [an average of a median value] (ml)	120 ± 107	115 ± 106	137 ± 122	NS
Use of prokinetic drug (%)	10.9 (n = 6)	8.7 (n = 4)	22.2 (n = 2)	NS
Start of diet (median) (days)	7	7	8	0.0381
Progress of solid diet (median) (days)	12	12	20	0.0343
Occurrence of DGE (%)				
Definition A[4]	5.5 (n = 3)	4.3 (n = 2)	11.1 (n = 1)	0.421
Definition B[3]	29.1 (n = 16)	23.9 (n = 11)	55.6 (n = 5)	0.103
Definition C[2]	18.2 (n = 10)	10.9 (n = 5)	55.6 (n = 5)	0.006

NGT = nasogastric tube; emesis = emesis after removal of NGT.

significant difference in its frequency between groups with or without major complications (Table 2). However, reinsertion or emesis was not affected by the duration of nasogastric intubation (a median of 2 days in the group without reinsertion or emesis versus 3 days in the group with no significance).

Major complications significantly affected the start of a diet and the progress with a solid diet (Table 2). In 46 patients without major complications, both time parameters of the diet (start and progress) significantly correlated with the duration of gastric aspiration. Indeed, 27 patients who had nasogastric intubation for 1 or 2 days started the diet and progressed to the solid diet at 7 and 10 days (median), respectively; on the other hand, 19 patients who had nasogastric intubation for 3 days or longer started the diet and progressed to the solid diet at 12 and 14 days (median), respectively ($P < 0.0001$ for start of the diet and $P = 0.0001$ for progression to the solid diet between these two groups of patients, respectively).

Overall, DGE occurrence rate was 5.5–29.1%, with striking differences according to DGE definition (Table 2). In 46 patients without major complications, six patients come under DGE definition B but not under DGE definition C. In these six patients, duration of nasogastric intubation was 2–8 days without reinsertion or emesis but the solid diet started at 16–18 days postoperation. Once they had started a diet, its step-up progressed smoothly to a solid diet. Under definition A, only 4.3% (n = 2) of the 46 patients were judged as having DGE.

Surgical and Postoperative Factors Predicting DGE Without Major Complications

Among multiple factors investigated in this study, four factors were considered as factors affecting the occurrence of DGE ($P < 0.1$): division of LGV, extensive dissection, the duration of nasogastric intubation for longer than 2 days, and its output of more than 400 ml for the first 2 days (Table 3). The division of LGV affected significantly the days of nasogastric intubation and the period of inability to take a solid diet (Fig. 2). In addition, the output of NGT was larger in the division of LGV compared with its preservation (a mean daily output of 146 ml versus 86 ml, $P = 0.0539$). Extensive dissection was also accompanied with significant prolongation of nasogastric intubation: a median of 3 days in patients with extensive dissection versus 2 days in those without, ($P = 0.0073$). However, the start of a solid diet was not affected by extensive dissection.

DISCUSSION

Major complications after pancreaticoduodenectomy are the most important factors predicting DGE occurrence.[3–6] However, it remains unclear whether inability to take a diet due to postoperative complications is entirely consistent with gastric atony. The term "DGE" has been used as related to the presentation of postvagotomy gastric atony.[19–21] DGE was defined as a postoperative condition of the failure of the stomach to empty, which was not secondary to any other well-recognized complications such as infection, pancreatitis, metabolic disorder, pneumonia, or cardiovascular alterations.[19–21] When assessing intraoperative surgical factors or reconstruction techniques used to define DGE occurrence, the inability to take a diet accompanied with major complications should be discriminated and omitted from analyses.

The occurrence rate of DGE is definition dependent as shown in our study. Definition A,[4] without a factor related to a diet, might not reflect the whole restorative process up to re-start of a diet. Definition B[3] was simply defined according to two parameters: the duration of gastric aspiration and the inability period to partake a solid diet. In this definition,[3] the start of a solid diet appeared to be the main determinant of DGE because prolonged gastric aspiration for longer than 10 days appeared to result in delayed progress with a solid diet over 14 days in many cases. Definition C[2] focuses on the time period of nasogastric intubation with a combination of multiple parameters. Although this definition[2] is somewhat

Table 3. Surgical and postoperative factors influencing gastric motility in 46 patients without major complications

Factors with statistical difference of $P < 0.1$	Occurrence rates of DGE (%)	
	Definition B[3]	Definition C[2]
Left gastric vein: preserved (n = 19)/divided (n = 27)	5.3/37 ($P = 0.016$)	0/5 ($P = 0.067$)
Extensive dissection: no (n = 28)/yes (n = 18)	14.3/38.8 ($P = 0.080$)	7.1/16.7 NS
Days of NGI: 1 or 2 days (n = 27)/>2 days (n = 19)	7.4/47.4 ($P = 0.004$)	0/26.3 ($P = 0.008$)
Output of NGI for the first 2 PODs: <400 ml (n = 39)/400 ml (n = 7)	15.4/71.4 ($P = 0.005$)	5.1/42.9 ($P = 0.008$)

Extensive dissection = dissection both of para-aortic nodes and of neural plexus around major arteries; NGI = nasogastric intubation.

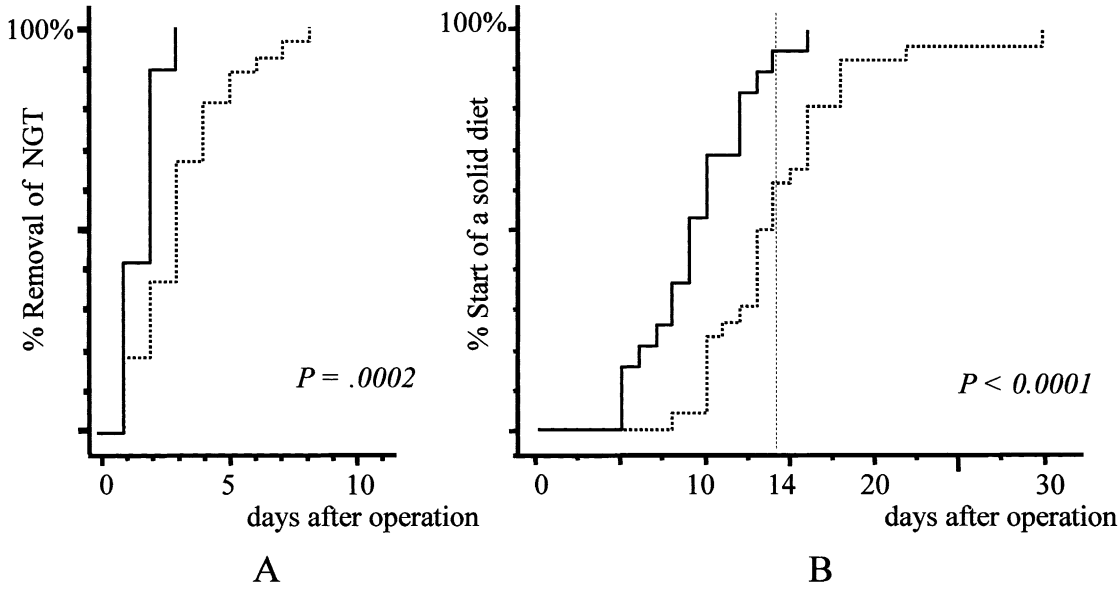

Fig. 2. Removal of nasogastric tube (NGT) and start of a solid diet depending on the status of the left gastric vein. Division of left gastric vein was accompanied with significant delay of NGT removal (**A.** a median of 3 days versus 2 days, $P = 0.0002$) and of the progress with a solid diet (**B.** a median of 14 days versus 9 days, $P < 0.0001$) compared with its preservation. The cumulative curves show the rates attained for the removal of NGT (percent removal of NGT) and for the start of a solid diet (percent start of a solid diet). The black lines refer to the preservation of the left gastric vein (n = 19), and the dotted lines refer to its division (n = 27).

complicated, emesis or reinsertion of NGT without major complications appears to be a suggestive parameter relevant to gastric atony.

In many reports, the duration of nasogastric intubation after PPPD ranged between 5 and 7 days.[2–4,6,22] On the contrary, our reconstruction technique needed only 2 days (median) of nasogastric intubation, compared to the results by Horstmann et al.[5] The duration of gastric aspiration in our experiments was not affected by major complications, and reinsertion of NGT or emesis was observed in only 6.5% of the 46 patients without major complications. The 10-day criterion in the three definitions[2–4] appeared to be too long to decide on an additional drug therapy based on the duration of use of the NGT.

The time period until the initial start of a solid diet was reported as 9–11 days with 6.5–37% overall incidence of DGE.[2,3,6,22] The primary result with definition B reported by Henegouwen et al.[3] showed 37% of overall incidence of DGE, and that with definition C reported by Yeo et al.[2] demonstrated 14% of the incidence in uncomplicated patients under the administration of erythromycin. Horstmann et al.,[5] who used a modification of definition B[3] with gastric aspiration for longer than 7 days, described only 3% of the occurrence because nasogastric suction lasted 2 days and a solid diet started on the 10th day after PPPD. In that study,[5] a period of 8 days was necessary to progress from the removal of NGT to partaking a solid diet. In our present work, this time period was 10 days. On the contrary, this interval was shortened to only 4 days in two previous reports,[6,22] in which a regular or solid diet started on the 9th and 11th postoperative days despite nasogastric intubation requiring 5.3 and 7 days, showing 6.5% and 10% DGE incidence, respectively. There is a striking difference in days of the time period, and this strongly influences DGE incidence. Possible reasons for this are that our study was based on retrospective analyses and that there were some differences in dietary habits. In our department and perhaps in many in Japan, after gastrointestinal surgery in the upper abdomen, the patient's food has usually progressed gradually with multiple steps. Taking into consideration our surgical techniques involving aggressive or extensive dissection and the differences in dietary habits, occurrence rates of DGE in our experiments were 10.9% following definition C and 23.9% following definition B, and they all seemed to improve.

Antecolic duodenojejunostomy described by Traverso and Longmire[1] minimized the occurrence of DGE.[5] In our procedures using a modification of Traverso and Longmire's method, the whole stomach was set freely and vertically in front of the left-side

colon. Isolation of the whole stomach from adjacent organs, setting the anastomotic site out of potential septic focus,[16] and Billroth II duodenojejunostomy[23] without anastomotic angulation appeared to be the main reasons why duration of gastric aspiration was minimized even in operations with extensive dissection.

Malignant diseases[18] and aggressive lymph node dissection[14] are considered to be risk factors causing DGE. In PPPD for malignant diseases, aggressive dissection of regional lymph nodes is routinely performed. In our series, extensive dissection of paraaortic nodes and of neural plexus around the major arteries was added to the routine dissection in half of the patients. Although extensive dissection was thought to be one of the risk factors of DGE, there was no striking difference between extensive and routine dissections for malignant diseases.

However, preservation of LGV showed significant negative values for occurrence of DGE. Anastomosis between the right and left gastroepiploic veins is lacking in approximately 50% of cases.[24] And in these cases, venous drainage from the antroduodenal portion is dependent only on a fine intramural vascular network after division of LGV. In general, portal hypertension with chronic liver diseases is considered to be one important risk factor resulting in DGE in patients without any operations,[25,26] and even in patients who underwent PPPD.[18] Division of LGV impairs only locoregional venous drainage; however, the fact that both duration of gastric intubation and inability period to take a solid diet shortened in the preservation of LGV suggests that the antroduodenal congestion is not irrelevant to the restoration of gastric motility after PPPD. However, its exact role on DGE needs to be confirmed in a randomized trial.

In summary, for management of patients after PPPD, the early discrimination of DGE seems to enable surgeons to choose an appropriate treatment or drug therapy. In that sense, we think that the duration of nasogastric intubation and its output are useful predictive factors for DGE. Furthermore, the factor of emesis or reinsertion of NGT should be added to the definition of DGE. These factors are not affected by any differences in dietary habits. It is suggested that definition C may closely reflect the condition of gastric atony.

CONCLUSION

With regard to defining DGE after PPPD, it seems appropriate to note that the period until a solid diet starts is not always a reflection of true gastric atony. To establish a common definition of clinical DGE, the details of parameters used for determining DGE should also be unified. From a technical point of view, antecolic duodenojejunostomy setting the stomach vertically in the left abdomen is a useful reconstruction technique that improves the occurrence of DGE even in PPPD with extensive dissection of lymph nodes and neural plexus. Furthermore, preservation of LGV accelerated the restoration of gastric motility in our study.

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Management of Hepatic Hemangiomas: A 14-Year Experience

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Hemangioma is the most common primary tumor of the liver and its diagnosis has become increasingly prevalent. Most of these lesions are asymptomatic and are managed conservatively. Large hemangiomas are often symptomatic and reports of surgical intervention are becoming increasingly frequent. We present our experience, over the last 14 years, with diagnosis and management of 249 liver hemangiomas, with special attention to a conservative strategy. Clinical presentation, diagnosis, treatment, and long-term outcome are analyzed. Of 249 patients, 77 (30.9%) were symptomatic, usually with right abdominal upper quadrant pain. Diagnosis was based on a radiologic algorithm according to the size and characteristics of the tumor; diagnosis by this method was not possible in only one case (0.4 %). Giant hemangiomas (>4 cm) were found in 68 patients (27.3%) and in 16 were larger than 10 cm. Eight patients (3.2%) underwent surgical treatment; indications were incapacitating pain in 6, diagnostic doubt in 1, and stomach compression in 1. No postoperative complications or mortality were observed in this series. Patients who did not undergo surgery (n = 241) did not present any complication related to the hemangioma during long-term follow-up (mean = 78 months). Hemangioma is a benign course disease with easy diagnosis and management. We propose a conservative approach for these lesions. Resection, which can be safely performed, should be reserved for the rare situations such as untreatable pain, diagnostic uncertainty, or compression of adjacent organs. (J GASTROINTEST SURG 2005;9: 853–859)

KEY WORDS: Surgery for hepatic hemangiomas

Hemangiomas are the most common primary liver tumor, with a prevalence in the general population estimated to range between 0.4% and 7.3%.[1,2] These vascular tumors have an unknown etiology; however, some studies have suggested a possible relationship with the intake of steroid hormones.[3,4] Hepatic hemangiomas are usually diagnosed unexpectedly during routine abdominal ultrasound and generally present as small-sized, asymptomatic nodules, although they may eventually reach large volumes. Their finding has become increasingly prevalent, becoming a frequent issue in specialized day-to-day clinical practice. Much has been discussed about the natural history of these lesions. Their benign clinical course and rarity of complications, such as rupture and bleeding, are well recognized.[5–7]

In recent years, there has been an increasing enthusiasm with surgical therapy, and some recent publications have shown excellent results after operative treatment.[8–16] However, based on their benign clinical course, we believe that liver hemangiomas should be conservatively managed. Liver resection, although a relatively safe procedure in specialized centers, should be reserved for rare circumstances such as incapacitating pain, compression of adjacent organs, Kasabach-Merritt syndrome, or diagnostic doubt (suspected malignancy).

The aim of this paper is to present our experience with 249 patients with hepatic hemangiomas referred to our institution. We will discuss the diagnostic process, clinical behavior, and management of this highly prevalent liver tumor, with special attention to our conservative strategy.

PATIENTS AND METHODS

From March 1988 to March 2002, 249 patients diagnosed with hepatic hemangiomas were prospectively followed in our unit. Ages ranged between 23

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and 79 years (median = 49 years) with a female predominance of 67.5%. Location, size of the hemangiomas, and the patient's characteristics (e.g., age, sex, and symptoms) were recorded.

Diagnosis was based on a radiologic algorithm as shown in Figure 1. All patients underwent ultrasound liver evaluation. For small lesions (≤1 cm), diagnosis was based solely on ultrasound and patients were observed. In patients with larger nodules, where ultrasound evaluation was not able to establish the diagnosis, the investigation proceeded. Patients with tumors between 1 and 3 cm were submitted to magnetic resonance imaging and those with tumors larger than 3 cm to CT scan, red blood cell scintigraphy, or magnetic resonance imaging. Diagnostic laparoscopy or biopsies from the lesions were not performed in this series.

Surgical treatment was indicated in eight patients of this series (3.2%), for the following reasons: untreatable pain in six, diagnostic uncertainty in one, and tumor growth with compression of the stomach in one. Surgical interventions are shown on Table 1.

Patients were evaluated by liver ultrasonography every 6 months for the first 2 years and annually thereafter. The follow-up period ranged from 12 months to 14 years (mean = 78 months).

The variables were compared by χ^2 test and the statistical significance level was set at 5%.

RESULTS

Solitary nodules were present in 195 patients (78.3%), 32 had two lesions, and 22 presented with three or more lesions. Lesion sizes ranged from 0.2 to 35 cm in diameter (mean = 3.7 cm), and in 152 cases (61%), the hemangioma was located on the right lobe of the liver. Giant hemangiomas, previously defined as lesions larger than 4 cm,[17] were found in 68 cases (27.3%). In 16 patients (6.4%) hemangiomas were larger than 10 cm in diameter. Seventy-nine patients (31.7%) were symptomatic, and the most frequent complaints were right upper quadrant abdominal pain and nonspecific dyspeptic symptoms. Abdominal pain was present in 44.1% (n = 30) of the patients with giant hemangiomas, whereas 27.0% (n = 49) of those with lesions smaller than 4 cm presented with pain. Pain as well as refractory pain were significantly more frequent in patients with lesions larger than 10 cm (Tables 2 and 3). Six patients, all with tumors larger than 14 cm, presented with refractory pain and underwent surgical resection as shown on Table 1.

Abdominal ultrasound was performed in all patients, with an overall diagnostic sensibility of 67.4%. CT scan was performed in 162 patients, defining the diagnosis in 122 (75.3%), and magnetic resonance imaging, indicated in 50 patients, was able to define the diagnosis in 46 (92.0%). Red blood cell scintigraphy was performed in 24 patients with lesions larger than 5 cm, with the results positive in 22 (91.6%).

A diagnosis based on imaging modalities was possible in 248 patients (99.6%). One patient, with an uncharacteristic heterogeneous 18 cm in diameter liver mass was submitted to right hepatectomy and the diagnosis of hemangioma was confirmed by histologic evaluation.

All symptomatic patients, excluding those undergoing surgical treatment, who presented pain were efficiently treated with analgesics, and the ones who had dyspeptic symptoms were investigated with upper digestive endoscopy and then managed according to endoscopic findings. In 20 patients (8%), associated gallstones were found, and all underwent laparoscopic cholecystectomy with further complete relief of the symptoms.

Eight patients (3.2%), all with lesions larger than 14 cm in diameter, underwent surgery: six with

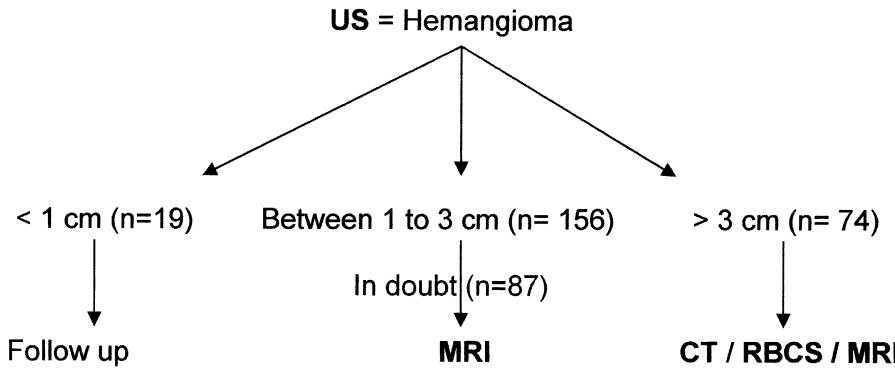

Fig. 1. Diagnostic algorithm for liver hemangiomas. US = ultrasonography; MRI = magnetic resonance imaging; CT = computed tomography; RBCS = red blood cell scintigraphy.

Table 1. Indications, patient characteristics, size of hemangioma, surgical procedure, and follow-up in patients undergoing liver resection

Indication	Gender/Age	Size (cm)	Surgery	Follow-up (months)
Untreatable pain	M / 43	30	Segmentectomy V, VI	Asymptomatic (52)
Untreatable pain	M / 41	24	Left lobectomy	Asymptomatic (28)
Untreatable pain	F / 40	18	Left lobectomy	Asymptomatic (60)
Untreatable pain	F / 39	14	Right hepatectomy	Asymptomatic (72)
Diagnostic doubt	F / 32	18	Right hepatectomy	Asymptomatic (48)
Untreatable pain	M / 47	20	Right hepatectomy	Symptomatic (18)
Untreatable pain	F / 38	16	Segmentectomy V, VI	Asymptomatic (12)
Stomach compression	F / 30	20	Left lobectomy	Asymptomatic (24)

untreatable pain, one with a large tumor of uncertain etiology, and one with tumor enlargement and consequent compression of the stomach. Only one patient (12.5%) required blood transfusion and received 2 units of packed red blood cells during surgery. There were no postoperative complications, and all patients had an uneventful postoperative recovery with a mean hospitalization period of 7 days. The other 10 patients with lesions larger than 10 cm were observed and did not develop any complications.

Among the six patients with incapacitating pain who underwent surgery, five (83.3%) experienced an improvement in symptoms but one had persistent abdominal pain after surgery.

During long-term follow-up (mean = 78 months), none of the 241 patients who had not been surgically treated developed any complication related to the hemangioma. Liver ultrasound follow-up did not show any significant change in the size or characteristics of the lesions.

DISCUSSION

Hepatic hemangiomas are the most frequent hepatic tumors, usually found incidentally during abdominal imaging procedures, laparoscopies, or laparotomies. They are more frequently found in women, usually in the fifth decade, being rare in children. Most of the lesions are asymptomatic, but abdominal pain may be present, especially in patients with large lesions. Pain is the most frequent symptom, usually intermittent and easily controlled with common analgesics, but the investigation of concomitant disorders such as gastritis or biliary stone diseases are sometimes necessary. In our series, biliary stone disease was present in 20 patients (8%).

Lesions larger than 4 cm have been defined as giant hemangiomas,[18] and some authors believe that these lesions are more frequently symptomatic and carry a greater risk of rupture.[5,12,17–19] In our series, pain was reported by 30.9% of the patients, being most commonly seen in those with giant hemangiomas (44.2%), and all patients with untreatable pain had lesions larger than 14 cm in diameter, showing a direct relationship between pain and the size of the hemangioma, as also shown by others.[5,12,17–19] Rupture was not observed in this series. Rarely, large hemangiomas can be responsible for the Kasabach-Merritt syndrome, which is characterized by a consumptive coagulopathy.

Many imaging methods have been employed for suspected hepatic hemangioma investigation. Ultrasound (US) is particularly useful in the identification of small lesions, usually demonstrating a homogeneous, well-delimited hyperechoic lesion (Fig. 2). The accuracy of US depends on the experience of the radiologist; it can reach up to 80% in experienced hands. In this series, typical US findings of hemangiomas were observed in 67.4% of the cases. Larger lesions are usually heterogeneous as the result of intratumoral hemorrhage or thrombosis, and thus lack the typical ultrasonographic characteristics. In these

Table 2. Incidence of symptoms (pain) according to size of hemangioma

Size	Patients (n)	Symptoms
<10 cm	233	63 (27%)
>10 cm	16	16 (100%)*

*$P = 0.0046$

Table 3. Incidence of refractory pain according to size of hemangioma

Size	Patients (n)	Refractory pain
<10 cm	233	0
>10 cm	16	6 (37.5%)*

*$P < 0.0001$

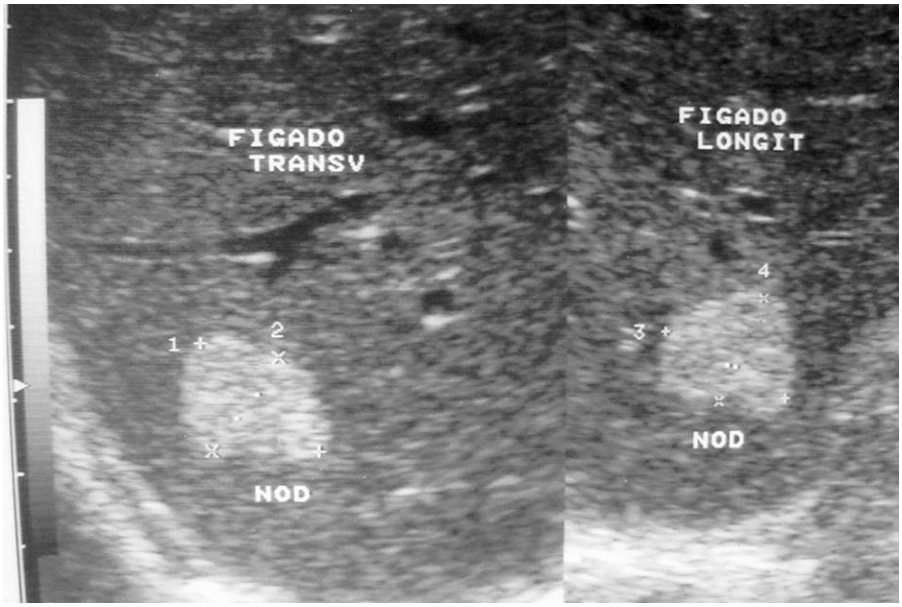

Fig. 2. Liver ultrasound showing a small (1.2 cm in diameter) homogeneous, hyperechoic well-delimited nodule.

cases investigation should be carried out with other methods, such as CT scan or MRI.[20]

On CT, hemangiomas are sharply defined masses, and are usually hypoattenuating compared with the adjacent hepatic parenchyma on unenhanced scans. After intravenous contrast administration, there is a distinctive pattern of enhancement characterized by peripheral nodular opacification proceeding with centripetal filling toward the center of the lesion (Fig. 3). CT scan sensitivity ranges between 75% and 90%[20] and, in our series, confirmed the diagnosis in 75.3% of the cases.

Red blood cell scintigraphy is an excellent diagnostic tool for tumors larger than 3 cm, with a typical radioactive pooling inside the tumor (Fig. 4). Recently, the employment of single photon emission computed tomography (SPECT) has enhanced the diagnostic sensitivity of scintigraphy[21,22] and, in our series, the former was able to establish diagnosis in up to 91.6% of the patients.

MRI has a sensitivity of up to 90%, and is considered by many authors to be the gold standard diagnostic method. On the other hand, it is the most expensive diagnostic tool and should be reserved for small lesions or diagnostic doubt after CT or scintigraphy. In this series, MRI established the diagnosis in 92% of the cases in which it was employed. Hemangiomas appear with low signal on T1 and high-intensity signal on T2 (Fig. 5), demonstrating a relative increase in signal on heavily T2-weighted images.[20,21]

In doubtful cases, some authors indicate a percutaneous needle biopsy.[14,19,23,24] This procedure is hazardous and should not be employed because of the high risk of bleeding.[5,15,25] Fine-needle aspiration may considerably reduce bleeding rates but, on the other hand, provides scarce material for histologic examination. Thus, for undetermined diagnosis, a conventional operative procedure with tumor resection is indicated and, for superficial lesions, a diagnostic laparoscopy could be carried out. Fortunately, with the continuous improvement in diagnostic imaging modalities, these situations are becoming the exceptions.

The natural history of hepatic hemangiomas is sometimes misunderstood. Iwatsuki et al. suggested that lesions larger than 10 cm with central necrosis carry a greater risk of rupture.[19] The risk of spontaneous rupture and bleeding, which is a frequent concern, is actually very low. In an extensive review of the literature published in 1991, only 28 well-documented cases of spontaneous rupture had been reported[7,15]; this is an extremely rare situation taking into account the high prevalence of these tumors. Rapid growth of lesion, which is considered an indication for resection, rarely occurs; some authors report an increase in tumor size in approximately 5% of the patients.[5,14,16,17,26] Nevertheless, in our series, only one patient (0.4%) presented significant growth of the lesion with consequent stomach compression. No other lesion showed any significant change in its dimensions during long-term follow-up.

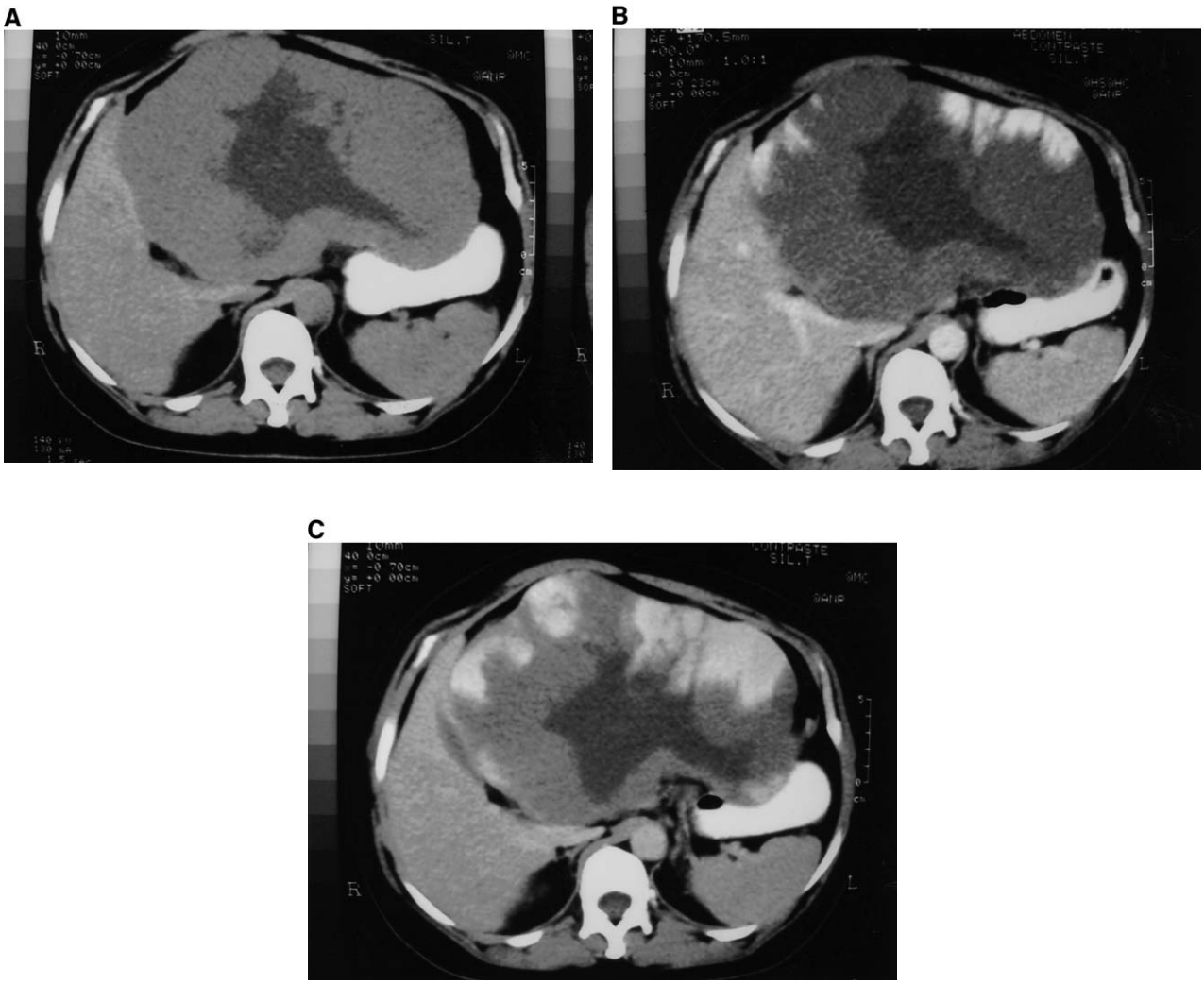

Fig. 3. CT scan disclosing (**A**) a large hypoattenuating mass (20 cm in diameter) in the left lobe of the liver. (**B**) Peripheral nodular opacification. (**C**) Centripetal filling and compression of the stomach.

Pain, the most common indication for resection, should be conservatively treated with analgesics after a thorough search for other concomitant gastrointestinal disorders. Farges et al. reported that, in their experience, pain typically waxes and wanes and, in many cases, may even disappear.[5] In the series from Farges et al. and Terkivatan et al., some patients persisted with symptoms in spite of the hepatic resection.[5,24] In our series, of six patients undergoing resection for untreatable pain, five (83.3%) had complete relief of the symptoms and one had persistent right quadrant abdominal pain after surgery.

Surgical resection is considered the definitive treatment; however, its indications are quite restricted and resection must, indeed, be reserved for situations such as incapacitating pain, compression of adjacent organs, diagnostic uncertainty, and the extremely rare Kasabach-Merritt syndrome. Ozden et al. support operative treatment for patients whose hobby or occupation carry a risk of hepatic trauma, such as football players and boxers, but the validity of this interesting rationale has never been established.[16]

Iwatsuki et al. emphasize that large hemangiomas (>10 cm in diameter) may rupture or bleed and should be resected.[17,19] Tumor size is not a formal indication for resection, although in our patients, pain was more frequently observed than in those with smaller lesions. When pain control is possible with analgesics we, as other authors,[5,24] adopt a conservative approach. In our experience, no patient presented with tumor rupture, and refractory pain was present in 37.5% of the patients with large tumors (>10 cm), which led us to conclude that resection should be indicated only in a selected group of patients with large hemangiomas.

In most of the publications showing the efficacy of hemangiomas resection, surgery was performed based on the following criteria: (1) risk of rupture;

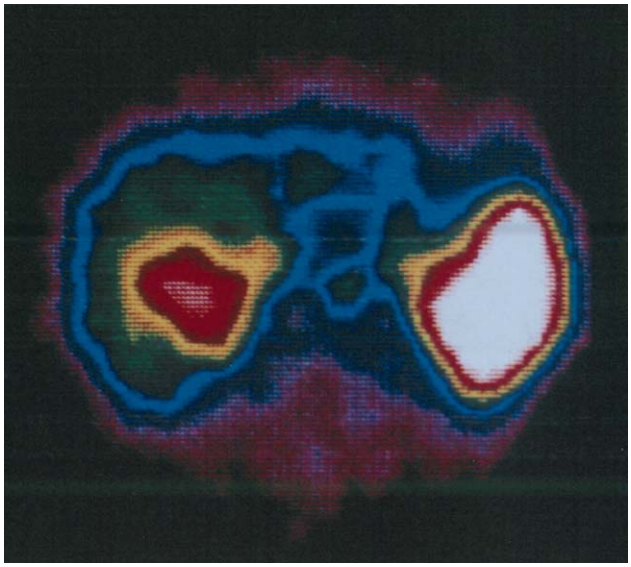

Fig. 4. Red blood cell scintigraphy showing a radioactive pooling area (red) in the right lobe of the liver.

(2) patient's willingness because of the undesirable feeling of living with a hepatic tumor, even if asymptomatic; and (3) the simple presence of a hepatic lesion. In specialized centers, liver resection mortality has dramatically declined lately to rates lower than 3%, and this may explain the enthusiasm with operative treatment of this benign condition. Nevertheless, it is noteworthy that there is a significant risk of intraoperative bleeding, and postoperative complications such as biliary fistula and abscess may follow any hepatic resection, even in experienced hands.[5,24] In Iwatsuki's series of 114 resections of benign liver tumors, there was no mortality[19] but, in other series, mortality rates of up to 2.4% were reported,[16] which should be considered unacceptable considering the benign nature of these lesions.

When surgery is indicated, hemangioma enucleation should be the procedure of choice, even though sometimes it is difficult to find a cleavage plane between the nodule and the surrounding liver parenchyma, which may cause significant bleeding. In Belli et al.'s report,[12] patients submitted to enucleation received an average of 2.8 packs of red blood cell units. In our series we favored classic resections because lesions were larger than 14 cm in diameter, considerably increasing the chance of bleeding, leading us to prefer anatomical resections. Among operated patients, only one (12.5%) required blood transfusion and all had uneventful postoperative recoveries.

Liver transplantation has already been employed for the treatment of the extremely rare cases of diffuse hepatic hemangiomatosis and in patients with the Kasabach-Merritt syndrome, with good postoperative results.[15,27]

A conservative nonsurgical approach is always advised considering that although hepatic hemangiomas are highly prevalent, complications are extremely rare. Surgery should be avoided even in the presence of symptoms like pain, which should be treated with analgesics, because liver resection presents higher morbidity and mortality rates when compared to the natural course of the disease. Special attention should be given to patients with hemangiomas larger than 10 cm in whom refractory pain is significantly more prevalent (37.5%), but the size of the lesion should not be the sole indication for resection. Patients who require surgical treatment should be referred to specialized centers, where resection can be safely performed.

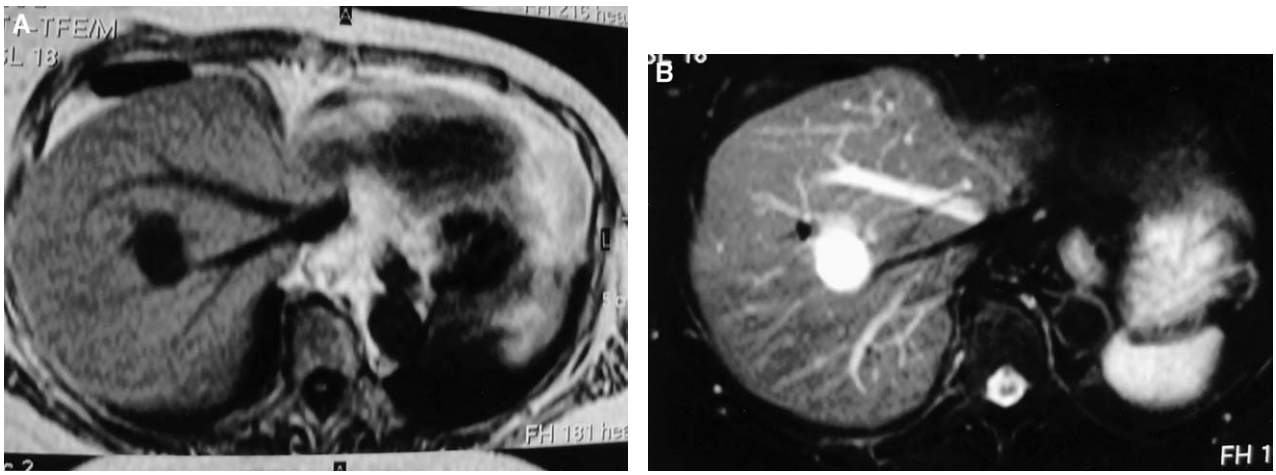

Fig. 5. Magnetic resonance imaging shows (**A**) a low-signal lesion between the middle and right hepatic veins on T1 and (**B**) a high-intensity signal on T2.

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Successful Preoperative Diagnosis and Complete Resection of Biliary Intraductal Papillary-Mucinous Neoplasm of the Liver

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KEY WORDS: Biliary cystic neoplasm, mucin-producing, intraductal papillary-mucinous neoplasm, liver

CASE REPORT

A 59-year-old man was admitted to our hospital for further examination of an asymptomatic cystic tumor in the liver. On admission, he was not jaundiced, and the mass was not palpable in his abdomen. Laboratory evaluation did not demonstrate any abnormalities. Serum carcinoembryonic antigen level was within the normal range, but the carbohydrate antigen 19-9 level was elevated at 221 U/ml (normal range 3 to 25 U/ml).

Abdominal ultrasonography and CT demonstrated a multilocular cystic tumor in the left lobe of the liver measuring 5 cm without mural nodules (Fig. 1). Endoscopic retrograde cholangiography showed a widely opened Vater's ampulla and dilated common bile duct measuring 25 mm with filling defects containing mucus. The left hepatic and intrahepatic bile ducts in the left hepatic lobe were not visualized. No apparent communication was present between the cystic tumor and the bile ducts. Cytology of the biliary juice was examined three times, and diagnosed as showing borderline malignancy.

Under a diagnosis of biliary intraductal papillary-mucinous neoplasm localized in the left lobe of the liver with possible malignant transformation, left hemihepatectomy with lymphadenectomy in the hepatoduodenal ligament was performed. The resected specimen macroscopically showed multiple saccular dilatations of the intrahepatic biliary tree containing mucous fluid in the left lobe of the liver (Fig. 2). Subsequent pathological examination demonstrated that the tumor was a biliary intraductal papillary-mucinous adenocarcinoma. The internal surface of the dilated biliary tree consisted of high columnar epithelium with mucin-producing cells and a partly papillary configuration with carcinoma in situ. No fibrous capsule or mesenchymal stroma was present. Metastases to lymph nodes in the hepatoduodenal ligament were absent. Immunohistochemical study for mucin antigens by the immuno-peroxidase method showed expression of MUC2, MUC5AC, and MUC6 in the neoplastic parts of the tumor.

The postoperative course of the patient was uneventful. He has been doing well for 30 months after surgery without signs of recurrence.

DISCUSSION

The definition and classification of biliary cystic neoplasms of the liver are presently unclear. They are classified, in accordance with World Health Organization criteria,[1] as bile duct cystadenoma and cystadenocarcinoma. Recently, several authors have reported that the clinicopathological features of biliary cystic neoplasms are similar to those of pancreatic cystic neoplasms with mucin secretion, which are classified as mucinous cystic neoplasms (MCNs) or intraductal papillary-mucinous neoplasms (IPMNs). According to previous reports, we consider that biliary cystic neoplasms could be classified into two entities, biliary cystadenoma and cystadenocarcinoma (biliary MCN) or biliary intraductal papillary-mucinous adenoma and adenocarcinoma (biliary IPMN). Additionally, biliary MCNs could be divided into two histologic types: those with mesenchymal stroma and those without mesenchymal stroma.

There are several similarities between biliary MCNs with mesenchymal stroma and pancreatic MCNs. Biliary MCNs usually occur in middle-aged women, demonstrate a multilocular cyst with mural

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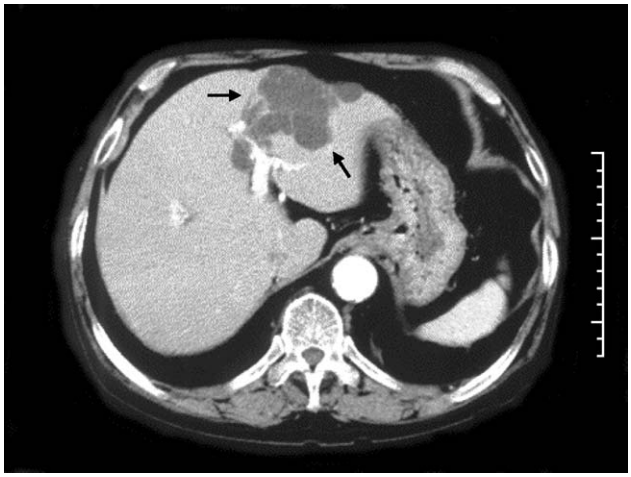

Fig. 1. CT shows a multilocular cystic tumor in the left lobe of the liver (arrows). The tumor measures 5 cm in diameter and has no mural modules.

nodules, are associated with characteristic "cystadenomas with mesenchymal stroma," and have a rather favorable prognosis after surgical complete resection.[2] These clinicopathological features are quite similar to those of pancreatic MCNs that show "ovarian-type stroma." In contrast, biliary MCNs in males and/or without mesenchymal stroma follow a more aggressive course.[2] The histogenesis remain unexplored.

Biliary IPMNs share features with pancreatic IPMNs, such as mucin hypersecretion, predominant intraductal papillary growth, and secondary dilatation of intraductal bile duct.[3] Biliary IPMNs also comprise a histologic spectrum that ranges from dysplasia to invasive carcinoma with different degrees of aggressiveness.[3] Intraductal cholangiocarcinomas, mucin-producing intrahepatic cholangiocarcinomas, and biliary papillomatosis seem to be included in this entity. Several reports from East Asian countries have disclosed that, in hepatolithiasis, biliary papillary neoplastic lesions are frequently detectable in the intrahepatic bile duct and are associated with gastroenteric metaplasia and mucin hypersecretion. Chen et al.[4] reported that mucin-producing intrahepatic cholangiocarcinomas tend to show a favorable outcome compared to non–mucin-producing intrahepatic cholangiocarcinomas.

There have been only a few reports regarding immunohistochemical studies of mucin antigens in biliary cystic neoplasms of the liver. According to these reports, MUC2 was highly expressed in bile duct cystadenocarcinoma, which showed a more favorable

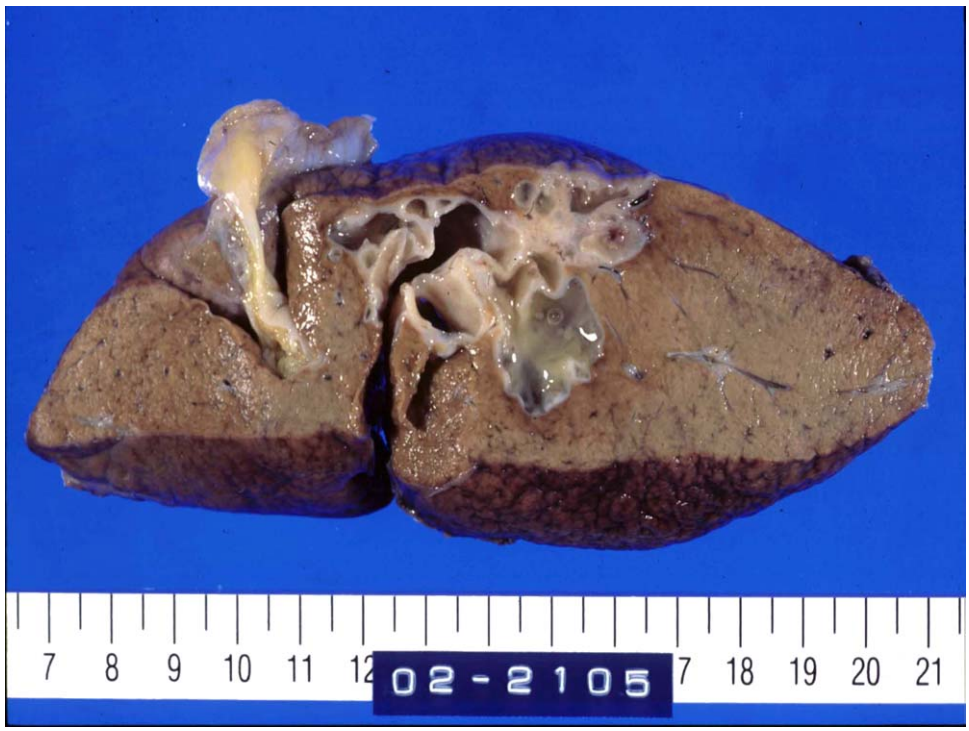

Fig. 2. A photograph of the resected left lobe of the river shows multiple cystic dilatations of the intrahepatic biliary tree that contain mucous fluid.

outcome than intrahepatic cholangiocarcinoma in which MUC2 was absent, suggesting that MUC2 mucin is a favorable prognostic indicator.[5] It was also reported that MUC5AC was expressed in all IPMNs of the pancreas, and MUC2 was expressed in noninvasive IPMNs but absent from invasive IPMNs of the pancreas. In our case, expression of MUC2 and MUC5AC indicated that our case was immunophenotypically similar to noninvasive IPMN of the pancreas and might have a favorable outcome after complete resection.

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Local Resection of the Head of the Pancreas with Pancreaticojejunostomy

Charles F. Frey, M.D., Howard A. Reber, M.D.

The modern surgical management of painful chronic pancreatitis dates back to the 1950s, when Puestow and Gillesby first performed their lateral pancreaticojejunostomy.[1] Subsequent modifications to the original procedure have occurred, but this basic operation is still used widely for patients whose pancreatic ducts are dilated. In those without dilated ducts, some form of pancreatic resection is usually employed, most commonly a Whipple type pancreaticoduodenectomy. The Puestow pancreaticojejunostomy is generally viewed as a safe operation (1% operative mortality rate), and not likely to cause nutritional disturbances in the long term. However, lasting pain relief is achieved in only 50%–60% of patients. Pancreaticoduodenectomy is done today with operative mortality rates of less than 5% in major centers, but nutritional, metabolic, and gastrointestinal side effects, even with the pylorus-preserving modification, may still be problematic for some. Nevertheless, lasting pain relief is achieved in over 90%. Thus, each of these surgical approaches has their drawbacks. This has stimulated ongoing efforts to design newer operations that can relieve pain permanently while minimizing both short- and long-term morbidity.

One such effort to improve upon these results was the 80%–95% distal pancreatectomy, described by Gardner Child in 1965. C.F.F. had the opportunity to perform, follow, and report the results of patients undergoing this procedure at the University of Michigan.[2] Child had hoped that this new operation, by preserving the duodenum and maintaining gastrointestinal continuity, would avoid some of the gastrointestinal side effects associated with the Whipple procedure. Indeed, 80% of patients followed an average of over 6 years continued to have good pain relief. But the drawbacks of this operation were the development of new-onset exocrine and endocrine insufficiency in half the patients and a 40% incidence of short-lived fistulas, fluid collections, or abscesses. For these reasons, this operation never attained wide popularity.

Local resection of the head of the pancreas combined with longitudinal pancreaticojejunostomy (LRPJ) was described by Frey and Smith in 1987.[3] Like the Child operation, it was designed to remove most of the head of the pancreas (the "pacemaker" of the disease), while preserving the body and tail of the gland, the stomach, and duodenum to minimize morbidity. Although drainage of the main pancreatic duct in the body and tail of the gland is usually performed because of the presence of strictures and ductal stones, it may not be an essential part of the procedure if the main duct in the body and tail is open throughout its length. This "coring" of the pancreatic head, consisting of the local resection with preservation of the posterior capsule as performed in the Child procedure, is the essential feature of the LRPJ operation.

The duodenum-preserving head resection (DPHR) described by Beger et al. in 1985[4] has similarities to the LRPJ. Both are directed primarily at the disease in the head of the pancreas, and both preserve gastrointestinal continuity. Not surprisingly, the results of both operations in terms of pain relief and quality of life appear to be similar. These two operations also have significant differences. The posterior capsule of the pancreas is preserved in the LRPJ, which allows the "cored out" head to be drained into a Roux-en-Y limb. The DPHR does not preserve the posterior capsule, which mandates two anastomoses: an end-to-end pancreaticojejunostomy to the body of the divided pancreas and a pancreaticojejunostomy to the remnant of pancreas on the inner aspect of the duodenum. The DPHR, like the LRPJ, also includes drainage of the main pancreatic duct in the body and tail of the pancreas in about 10% of cases. And the

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DPHR requires that the pancreas be divided at its neck overlying the superior mesenteric and portal veins. In the event of portal hypertension and inflammatory changes, this may be technically difficult. This is not necessary in the LRPJ.

GENERAL CONSIDERATIONS

LRPJ is indicated in any patient with painful chronic pancreatitis with a pancreatic duct in the body of the gland that is more than 6–7 mm in diameter, and who would be a candidate for a Puestow-type lateral pancreaticojejunostomy. Often the head of the pancreas is enlarged (A-P diameter >4 cm when seen on CT scan), with multiple cysts and calcifications. But even smaller glands are likely to benefit from removal of some of the tissue in the head of the gland, which improves ductal drainage. When chronic pancreatitis is associated with a duct disruption in the form of a pseudocyst, pancreatic ascites, or a pancreatic fistula, LRPJ is also applicable. The presence of duodenal or bile duct obstruction from the pancreatitis is not a contraindication to the coring procedure. However, a concern about the presence of pancreatic cancer is. These latter patients should undergo a pancreaticoduodenectomy.

We also have a limited experience with patients who have "small" ducts (<3–4 mm in diameter in the head, body and tail of the pancreas), and believe that this group may also benefit from LRPJ. These smaller ducts in the head are either resected (Santorini and its tributaries) or unroofed (Wirsung and duct to uncinate), just as larger ducts within the head would have been. But in the presence of a small main duct in the body or tail of the pancreas, we core out the duct itself, creating a 1 cm diameter "neoduct" throughout the body and into the tail of the gland. The jejunal anastomosis is made to the capsule of the pancreas, rather than to the neoduct wall.

TECHNICAL CONSIDERATIONS

Access

A bilateral subcostal incision is used except in patients with a narrow rib cage in whom a vertical midline incision may be more suitable. After exploration of the abdomen, a self-retaining retractor is placed.

Exposure of the Head of the Pancreas

A Kocher maneuver is performed extending to the aorta medially, thus mobilizing the duodenum and head of the pancreas. The superior mesenteric vein is exposed inferiorly. Thickness, consistency, and presence or absence of a mass in the pancreatic head can then be assessed.

The superior mesenteric vein should be separated from the medial portion of the head and uncinate process by dividing the small venous tributaries that run from the head of the pancreas to the vein. This makes it possible to adequately open the duct to the uncinate prior to local resection of the head, and it exposes enough of the pancreas for later attachment to the Roux-en-Y limb. It is not necessary and, in the presence of inflammation and portal hypertension, may be adding an unnecessary risk of hemorrhage to free the portal vein beneath the neck of the pancreas.

Exposure of the Neck, Body, and Tail of the Pancreas

The anterior surface of the body and tail of the pancreas is exposed and palpated after dividing the gastrocolic ligament to open the lesser sac between the splenic and hepatic flexures of the colon. Adhesions between the stomach and the pancreas are lysed, and the proximal duodenum is separated from the pancreas at least as far as the gastroduodenal artery, where the vessel runs between the two structures. The gastroepiploic vein should be ligated and divided just before it joins the middle colic vein to form the gastrocolic trunk. The gastroepiploic artery may also need to be divided, and we often ligate the pancreaticoduodenal extension of the artery onto the surface of the pancreas. It is important to clean off the anterior surface of the head of the pancreas in this way because the incision into the pancreas as one follows the course of the main duct often follows this line. The inferior border of the body and tail of the pancreas may be mobilized to more completely expose the anterior surface of the gland.

Locating and Opening the Main Pancreatic Duct

Most often the main pancreatic duct in the body of the pancreas near the neck of the gland has an eccentric location, being closer to the superior border and posterior surface of the gland (Fig. 1). When large, the duct may create a visible bulge on the anterior surface of the gland. Smaller ducts may be palpated as a groove running along the gland. Those ducts that are neither visible nor palpable can be identified by needle aspiration with a no. 23 butterfly needle and syringe. Aspiration of clear or calcium-laden juice indicates the site of the duct.

Using electrocautery, the anterior capsule of the pancreas is incised directly over and down onto the guide needle. A right-angle clamp is inserted into

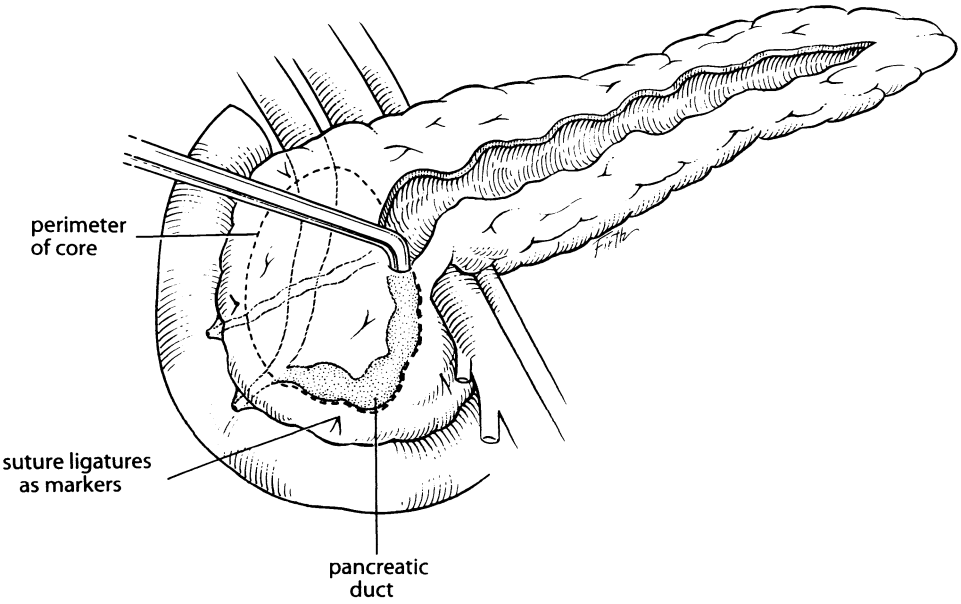

Fig. 1. Prior to locally resecting the head of the pancreas the duct of Wirsung is opened to the duodenum and to within 1.5 cm of the tail of the gland. The local resection of the head is extended outward from the opened Wirsung duct and the duct to the uncinate (duct to uncinate not shown). The dashed line represents the peripheral extent of that portion of the head to be excised.

the duct lumen to probe the direction of the duct both toward the tail and then toward the head of the gland. The incision in the tail of the pancreas is carried to within 1–2 cm of the terminus of the gland. The incision in the head of the pancreas is extended to within 1 cm of the duodenal border.

It is important to note that the main pancreatic duct, after passing over the portal vein in the neck of the pancreas, plunges posteriorly and then inferolaterally in the head of the gland, remaining close to its posterior capsule. In patients with an enlarged head of the pancreas, this can be a distance of 4 cm or more. Ampullary patency should be determined, as should the length of the undrained segment of duct. This is accomplished by passing a 2–3 mm Bakes dilator through the opened pancreatic duct until it passes through the ampulla into the duodenum, where it can be palpated. The duct to the uncinate coming off the duct of Wirsung in the head is also opened using the right-angle clamp as a probe to determine the direction of the incision. Bleeding from surface of the gland may require suture ligation; bleeding from deeper within the parenchyma usually can be controlled by electrocoagulation. All pancreatic calculi encountered in any of the duct systems should be removed.

A common mistake when looking down on the pancreas is to assume that the pancreaticoduodenal junction lies directly above the ampulla and is a guide as to how far the pancreatic duct needs be opened laterally. Because the pancreas is invaginated into the duodenum, the ampulla lies 2–3 cm more laterally and posteriorly than it would appear to be from above using the pancreaticoduodenal confluence as a marker. Failure to open this 2–3 cm portion of the duct will leave a significant portion of the main pancreatic duct and its diseased tributary ducts undrained.

Local Resection of the Head of the Pancreas

Working outward from the opened main pancreatic duct and the duct to the uncinate, slices of pancreatic tissue are taken piecemeal with the electrocautery. This removes pancreatic parenchyma from the anterior capsule down to the opened duct of Wirsung and uncinate posteriorly. The posterior walls of these ducts are within a few millimeters of the posterior capsule of the pancreatic head and mark the posterior extent of resection (Fig. 2). Although the superior mesenteric/portal vein is not seen during this local resection, awareness of its position just medial to the point where the duct dives deeply posterior allows it to be avoided. Thus, we do not excise tissue medial to that part of the duct. Determining how much pancreatic parenchyma to remove requires repeated assessment of the remaining thickness of the shell of the head after each slice is removed by placing ones' fingers behind the head and the thumb in the cavity being created. Palpation of the head as it is being cored out also helps to identify any small cysts or

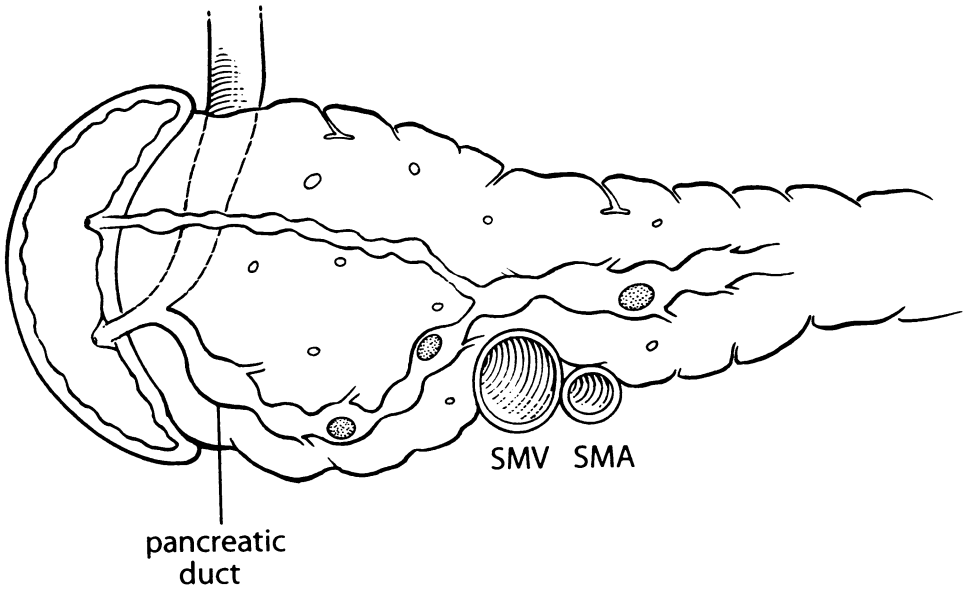

Fig. 2. The anterior location of the duct of Santorini and the posterior location of the duct of Wirsung in the head of the pancreas. The duct of Santorini is excised during the local resection of the head of the pancreas. The duct of Wirsung and duct to the uncinate (not shown) traverse close to the posterior capsule and are unroofed. Attempts to excise either of these posterior lying ducts would compromise the integrity of the posterior capsule of the pancreas and are inadvisable.

impacted calculi in diseased tributary ducts. The duct of Santorini with its tributary ducts lies anteriorly in the pancreatic head and it is excised. In contrast, the unroofed duct of Wirsung remains in place creating the posterior extent of resection. When the local resection is complete, only a rim of pancreatic tissue remains along the inner aspect of the duodenal curve (Fig. 3).

An average of about 6 grams of fibrotic tissue are removed (range, 4–12 grams). These weights underestimate the amount of tissue removed because the electrocautery both desiccates the tissue slices and vaporizes additional tissue. Even though we would not perform this operation in patients with suspected cancer, we always send a piece of the pancreatic tissue that is excised for frozen section examination. A pancreaticoduodenectomy should be performed if cancer is found.

Managing the Common Bile Duct: Avoiding Injury

About half of patients with chronic pancreatitis requiring surgery for relief of pain will have preoperative radiographic evidence of kinking, tortuosity, and narrowing of the intrapancreatic portion of the common bile duct. However, only 20% of patients with an abnormal radiographic appearance of the common bile duct have significant obstruction as evidenced by abnormal biochemical markers or clinical jaundice. The relationship of the common duct to the posterior surface of the pancreas is variable. The duct may lie posterior to the pancreas, it may be partially embedded (palpated as a groove) in the pancreatic parenchyma, or it may traverse entirely within the pancreatic parenchyma (Fig. 4). Indeed, this is the situation associated with the greatest chance for a significant stricture. During the local resection of the head of the pancreas in such patients, the intrapancreatic portion of the common bile duct must be freed from inflamed and fibrotic periductal tissue. In order to identify the common duct, which is often encased in fibrotic scar tissue, and safely free it from the scar, a small Bakes dilator is placed inside the duct where it serves as a guide to the duct's location. In about 70% of cases, coring of the fibrotic pancreatic parenchyma relieves the common duct obstruction. If the obstruction cannot be relieved, a choledochojejunostomy can be performed in addition to the LRPJ.

Reconstruction with Roux-en-Y Drainage of the Head of the Pancreas and the Main Pancreatic Duct

When the pancreatic parenchyma has been sufficiently resected, the ducts opened widely and the calculi removed, the Roux-en-Y limb of jejunum is prepared.

The jejunum is divided about 20 cm distal to the ligament of Treitz. The Roux limb is passed through

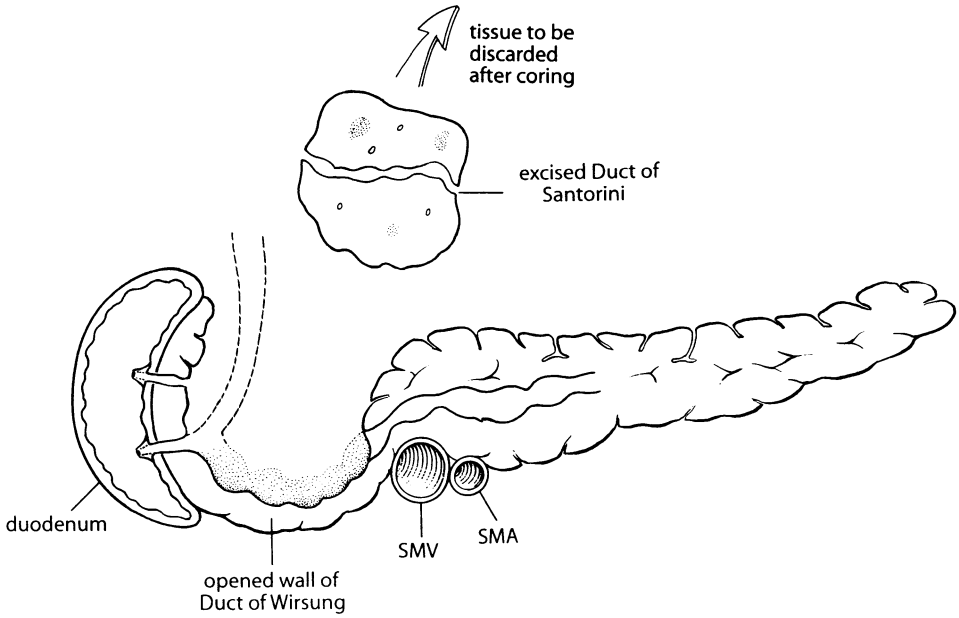

Fig. 3. Tissue removed from the head of the pancreas, including the duct of Santorini. Note that we do not try to remove this tissue as a single specimen as shown here, but rather in piecemeal fashion, taking slices outward from the opened ducts of Wirsung and duct to the uncinate process. This technique allows us to assess the extent of resection by placing the thumb of the left hand within the head of the pancreas and with the fingers behind the Kocherized head.

an opening in the transverse mesocolon to lie over the pancreas. A two-layer pancreaticojejunostomy is performed. The outer layer of the anastomosis consists of interrupted Lembert 3-0 or 4-0 nonabsorbable sutures that approximate the jejunal serosa to the capsule of the pancreas. A running 3-0 or 4-0 absorbable suture attaches the full thickness of the jejunum to the cut surface of the pancreas along the capsule (Fig. 5, *A* and *B*). The defect in the mesocolon is closed around the jejunal limb to prevent internal

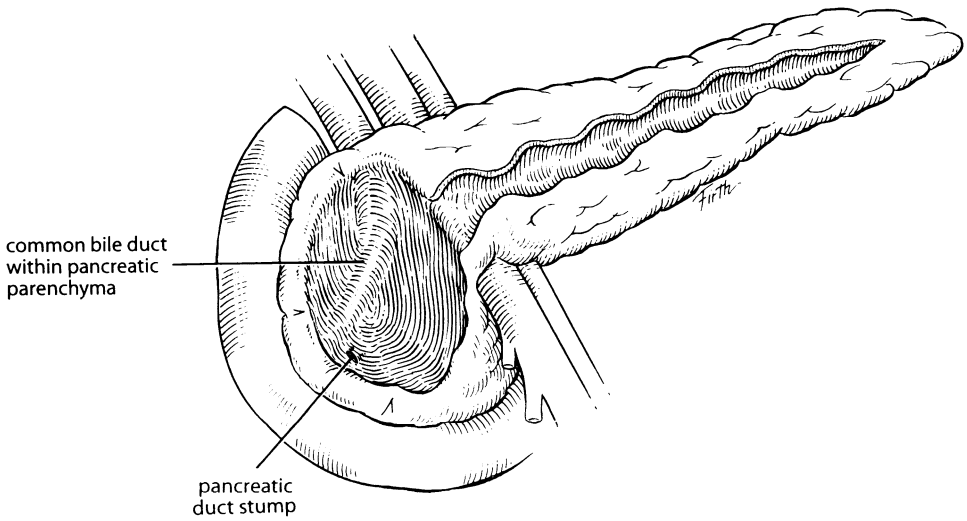

Fig. 4. Completed local resection of the head of the pancreas and decompressed main duct in the body and tail of the pancreas. It is unnecessary to ligate the pancreatic duct stump (Wirsung), shown at the bottom of the cavity created by the coring. The common duct is shown traversing the posterior head within the pancreatic parenchyma. The intrapancreatic location of the common duct is most frequently associated with clinical and biochemical evidence of biliary obstruction. When performing the local resection in such patients, it is best to place a metal Bakes dilator in the common duct, so that its position can be identified and injury prevented while freeing up the bile duct from obstructing scar tissue.

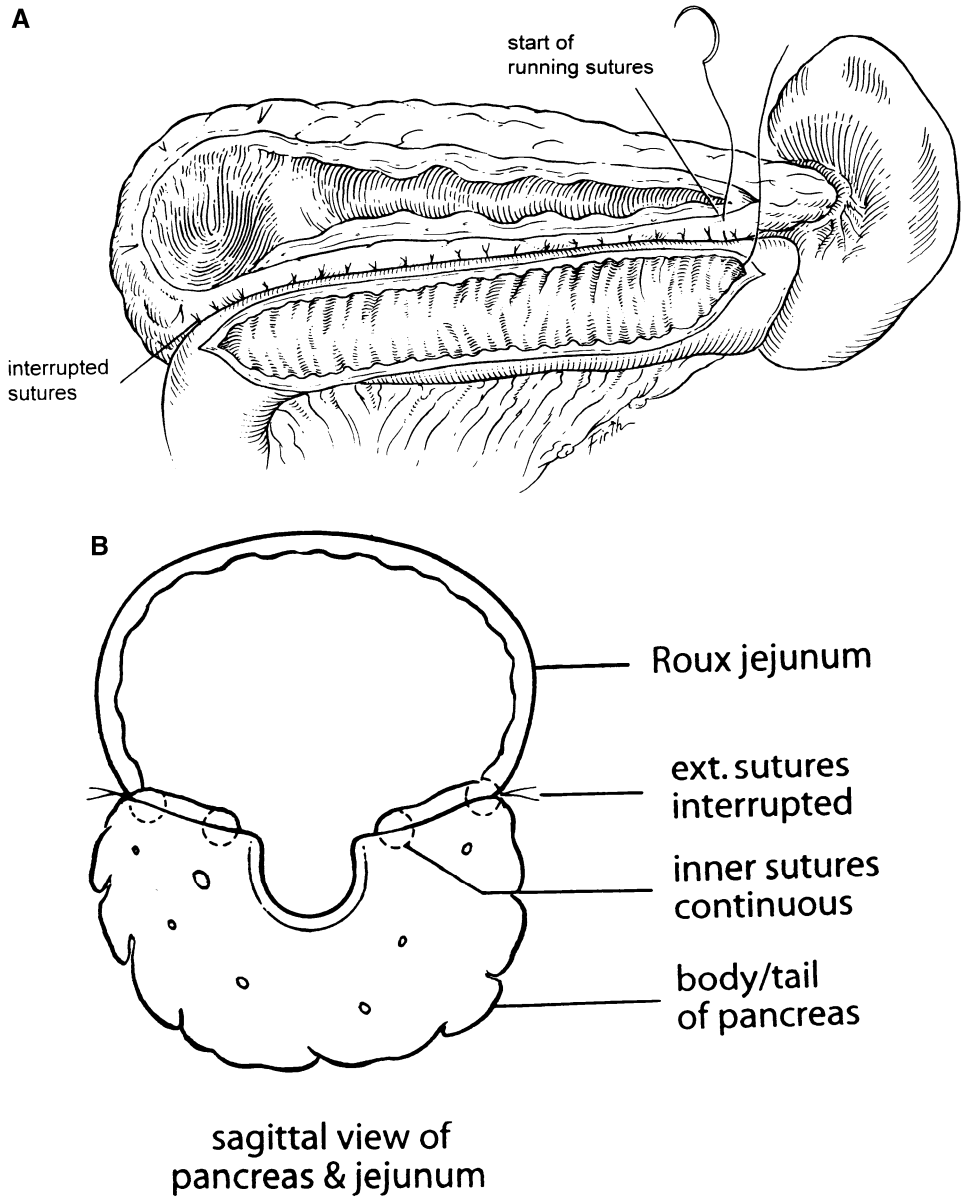

Fig. 5. (**A**) The two-layer anastomosis approximates the opened jejunum to the circumference of the locally resected head and to the decompressed main duct in the body and tail of the pancreas. The inner layer is accomplished with running 3-0 or 4-0 absorbable sutures (e.g., PDS). Note: This layer approximates the *capsule* of the pancreas (not the wall of the duct) to the jejunum. The outer layer consists of 3-0 or 4-0 interrupted nonabsorbable sutures. (**B**) Cross-sectional view of the completed two-layer anastomosis between the opened jejunum and the decompressed main duct in the body of the pancreas.

herniation. The continuity of the gastrointestinal tract is reestablished by an end-to-side jejunojejunostomy 40–50 cm distal to the pancreaticojejunostomy. We place a closed suction drain to the area of the anastomosis.

The nasogastric tube is removed the next morning and feeding begins when postoperative ileus has resolved. Most patients are discharged by the sixth postoperative day.

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Review Article

Changing Concepts in the Management of Liver Hydatid Disease

Christos Dervenis, M.D., F.R.C.S., Spiros Delis, M.D., Costas Avgerinos, M.D., Juan Madariaga, M.D., Miroslav Milicevic, M.D.

Hydatid disease is a rare entity primarily affecting the population of developing countries. The parasite shuttles between the liver and lungs. but almost any organ can be invaded, forming cysts. Septation and calcification of the cysts with a high antibody titre in the patient's serum confirm the diagnosis, although more sophisticated tests have been applied recently. Surgery constitutes the primary treatment, with a variety of techniques based on the principles of eradication and elimination of recurrence by means of spillage avoidance. Minimally invasive techniques and percutaneous drainage of the cysts are now feasible because of progress in the field.

The aim of this review is to collect the experience from three different institutions and to provide practical guidelines for diagnostic and therapeutic strategies. (J GASTROINTEST SURG 2005;9:869–877)

KEY WORDS: Echinococcus, hydatid liver disease, laparoscopic treatment, percutaneous drainage, albendazole

INTRODUCTION

Echinococcosis in humans is a parasitic tapeworm infection, caused by a larval stage (the metacestode) of *Echinococcus* species. The infection can be asymptomatic or severe, causing extensive organ damage and even death of the patient. The metacestodes of all four recognized *Echinococcus* species can infect humans. There are three known forms of echinococcosis in humans: 1) cystic echinococcosis (CE – Hydatid disease) caused by *Echinococcus granulosus*, 2) alveolar echinococcosis (AE) caused by *Echinococcus multilocularis*, and 3) polycystic echinococcosis (PE) caused by *Echinococcus vogeli* or *Echinococcus oligarthus*. The most common sites for cystic echinococcosis infection are the liver and lungs (60% and 30%, respectively), although hydatid cysts may develop, rarely, at other sites, including kidney, bones, brain, and pericardium. In theory, hydatid cysts may develop at any site within the human body. The prevalence of echinococcosis varies considerably but is endemic in the Middle East and Africa.[1–8]

In this review the current concepts in the management of cystic liver echinococcosis (liver hydatid disease) from the perspective of the hepatobiliary surgeon are presented.

MORPHOLOGIC CLASSIFICATION OF HYDATID LIVER CYSTS

Several ultrasound classifications of liver hydatid cysts based on the morphologic characteristics of the cyst have been proposed in the past. The ultrasound classification described by Gharbi et al. seems to be most widely accepted. The pathognomonic characteristics and signs of hydatid liver disease such as the presence of a detached laminated membrane from the pericyst, the presence of daughter cysts, and

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Table 1. Classification for hydatid cysts*

Type	Description
I	Pure(clear) fluid collection (the cyst is similar to the simple liver cysts)
II	Fluid collection with a detached membrane
III	Fluid collection with multiple septa and/or daughter cysts
IV	Hyperechoic cyst contents with high internal echoes
V	Cyst with reflecting calcified thick wall

*Adapted from el-On J, Khaleel E, Malsha Y. Echinococcus granulosus: A seroepidemiological survey in northern Israel using an enzyme-linked immunosorbent assay. Trans R Soc Trop Med Hyg 1997;91:529-536.

calcifications of the cyst wall have all been included in Gharbi's criteria (Table 1).[9]

The need to evaluate the functional state of the parasite, especially in field studies, has resulted in a new, modified ultrasound classification of liver hydatid cysts. Based on cyst characteristics described in the Gharbi classification, the World Health Organization (WHO) Informal Working Group on Echinococcosis[10] proposed a new classification reflecting the functional state of the parasite that facilitates selection of treatment modalities (Table 2).

DIAGNOSIS

In the majority of cases definitive diagnosis of the disease can be established by a combination of imaging techniques (Figs. 1, 2, and 3) and either serological or immunoassay techniques. At least two tests are required to confirm the diagnosis. Immunofluorescence assay, indirect hemagglutination, immunoelectrophoresis, or coelectrosyneresis with antigen 5 identification confirm the diagnosis in 80% to 96% of patients with liver hydatidosis. The tests are less sensitive when the cysts are not in the liver. Special techniques such as ELISA have a high specificity and accuracy independent of disease stage and site of the cyst.[11,12]

MEDICAL TREATMENT

Thirty years after the first attempts to establish effective medical treatment, surgery is still the gold standard for achieving complete cure of liver hydatid disease.

Chemotherapy with benzimidazole compounds (albendazole and mebendazole) is currently indicated for: (1) inoperable primary liver hydatidosis, (2) multiple cysts in two or more organs, (3) multiple small liver cysts, (4) cysts deep in liver parenchyma, (5) prevention and management of secondary hydatidosis, (6) management of recurrent hydatidosis, (7) unilocular cysts in unfit elderly patients, (8) use in combination with surgery and interventional procedures, (9) pulmonary echinococcosis, and (10) long-term administration for cystic echinococcosis at specific sites (bone, brain, eye, etc.).

The effectiveness of preoperative chemotherapy in preventing secondary echinococcosis and recurrence needs further investigation. Chemotherapy is routinely administered prior to interventional procedures, and in some centers it is used preoperatively. It is still unclear whether preoperative chemotherapy is beneficial and many centers do not administer it.

Chemotherapy is contraindicated in the following: (1) large cysts, (2) cysts with multiple septa divisions (honeycomb-like cysts), (3) cysts than are prone to rupture (superficial), (4) infected cysts, (5) inactive cysts, (6) calcified cysts, (7) severe chronic hepatic disease, (8) bone marrow depression, and (9) early pregnancy.[13,14]

Mebendazole (MBZ) is a broad-spectrum antihelmintic drug with poor intestinal absorption that is active against intestinal nematodes. Albendazole (ABZ) has better intestinal absorption, better tissue distribution, and achieves considerably higher cyst fluid concentrations. It undergoes a rapid first-pass metabolism in the liver to albendazole sulfoxide, the antiscolecoidal agent flubendazole. The MBZ fluorinated analog does not penetrate the cyst, and therefore the drug is not an alternative for treatment.[15–17]

Table 2. WHO classification

Type of cyst	Status	Ultrasound features	Remarks
CL	Active	Signs not pathognomonic, unilocular, no cyst wall	Usually early stage, not fertile; differential diagnosis necessary
CE 1	Active	Cyst wall, hydatid sand	Usually fertile
CE 2	Active	Multivesicular, cyst wall, "rosette-like"	Usually fertile
CE 3	Transitional	Detachment of laminated membrane, "water-lily sign," less round—decreased intracystic pressure	Starting to degenerate, may produce daughter cysts
CE 4	Inactive	Heterogenous hypo- or hyper-echogenic degenerative contents; no daughter cysts	Usually no living protoscoleces; differential diagnosis necessary
CE 5	Inactive	Thick calcified wall, calcification partial to complete; not pathognomonic but highly suggestive of diagnosis	Usually no living protoscoleces

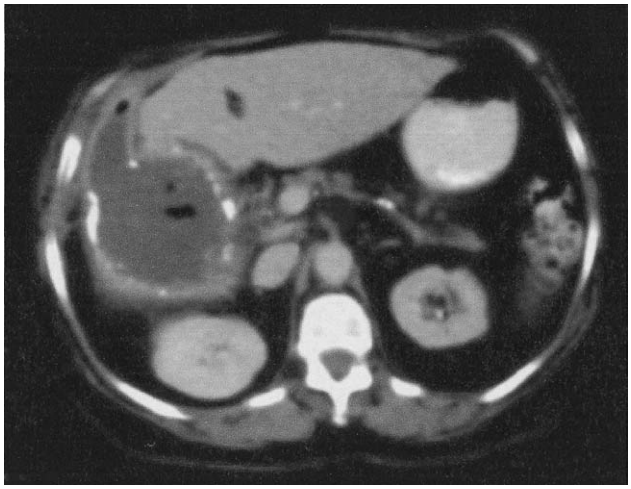

Fig. 1. CT image of hydatid cyst with air-fluid level suggesting infection with abscess formation.

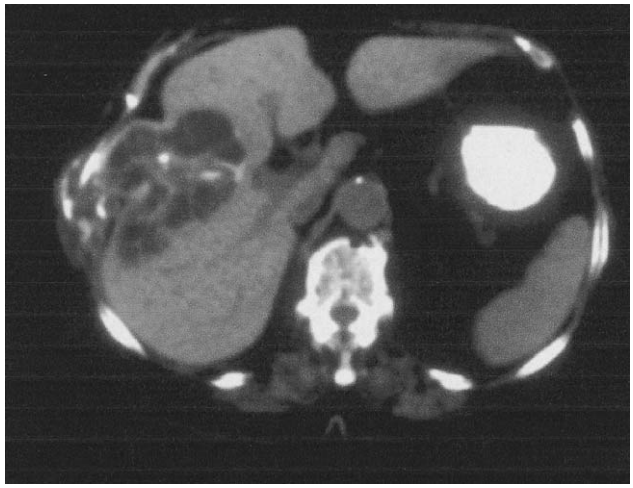

Fig. 3. Multiple daughter cysts in the right liver lobe with extension to the abdominal wall.

The benzimidazole carbamates have a direct effect on the cumulus oophorus and on the wall of the cyst. Younger cysts and cysts with thin walls show a better response. Chemotherapy with ABZ or MBZ may lead to liver enzyme elevation (10%–20% of patients), bone marrow suppression, pancytopenia, agranulocytosis, and alopecia. These adverse effects are reversible once the treatment is stopped.[18–20]

The indicated dosage of ABZ is 10 to 15 mg/kg/day postprandially in two divided doses. The manufacturer suggests a therapeutic cycle of 4 weeks of treatment followed by a 2-week pause. The usual dosage scheme is 3 to 6 or more cycles for liver hydatid disease. For cystic echinococcosis of other organs, duration of therapy is much longer. Recent data have shown equal or improved efficacy of continuous treatment for 3 to 6 months or longer without an increase in adverse effects.[21] Cyclic ABZ treatment seems to be no longer advisable. The equivalent dosage for MBZ chemotherapy is 40 to 50 mg/kg/day in 3 divided doses, for 3 to 6 months. Serum drug levels may vary widely in individual patients, and therefore correlation with oral doses and drug efficacy is inconsistent.

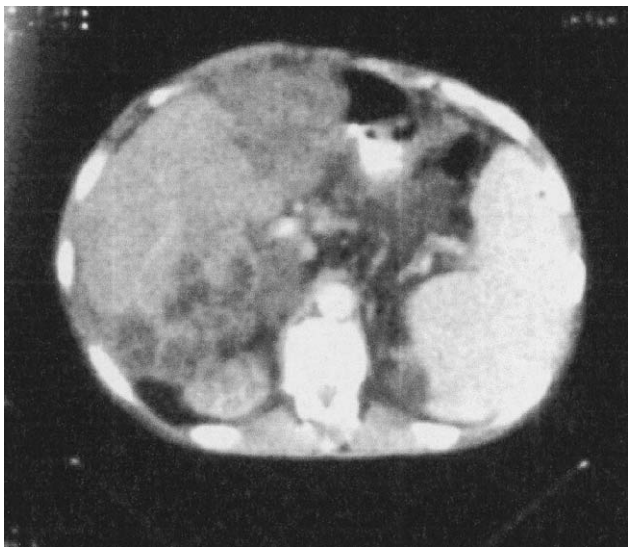

Fig. 2. Multiple daughter cysts invading both right and left liver lobes.

ABZ, the most efficient agent used so far, may induce apparent cure, as indicated by cyst shrinkage or disappearance in 20% to 30% of patients.[22] Some authors have reported degeneration of cysts in up to 50.6% of patients treated with MBZ and 80% of patients treated with ABZ. The interpretation of these studies is difficult because of lack of standardization and interference with the natural history of the disease.[23]

A prospective, controlled, randomized trial has demonstrated the efficiency of preoperative ABZ administration. Following 1 and 3 months preoperative administration, 72% and 92% of cysts were found at surgery to be nonviable, versus 50% of cysts in the control group, which were treated by surgery alone.[24]

According to the WHO guidelines, preoperative administration should begin between 1 month and 4 days before surgery for ABZ and 3 months before surgery for MBZ.[25]

The expected results of adequate chemotherapy are: (1) 10% to 30% cyst disappearance (cure), (2) 50% to 70% degeneration or significant size decrease, and (3) 20% to 30% with no morphologic changes (treatment failure). The rate of relapse after chemotherapy is high (3%–30%), but fortunately relapses are sensitive to retreatment in up to 90% of patients.[26]

Praziquantel, a synthetic isoquinoline-pyrazine derivative, has been used in combination with ABZ. Combined chemotherapy seems to be more effective than ABZ alone.[27–29]

Coordinated, prospective trials are necessary to establish the value of chemotherapy in hydatid disease. All the available data suggest that conservative management of hydatid disease yields poor results, and in the majority of patients the therapy fails or the disease recurs.[30]

SURGICAL TREATMENT

There are many surgical procedures for the management of liver hydatid cysts. Much controversy exists regarding the most appropriate surgical technique, which should effectively eliminate the parasite as well have a low morbidity and mortality rate and a negligible recurrence rate.

Indications for surgery in patients with liver hydatidoses are: (1) large cysts with multiple daughter cysts, (2) single liver cysts situated superficially that may rupture, (3) infected cysts, (4) cysts communicating with the biliary tree, (5) cysts exerting pressure on adjacent vital organs, and (6) cysts in the lung, brain, bones, kidneys, and other organs.

In addition to overall high-risk factors for surgery such as extreme age, pregnancy, and concomitant severe disease, specific contraindications for surgery in liver hydatidoses are: (1) multiple cysts, (2) cysts difficult to access, (3) dead cysts, (4) cysts partially or totally calcified, and (5) very small cysts.

Surgical procedures can be divided into three groups: classic open surgical procedures, laparoscopic procedures, and interventional (minimally invasive) procedures.[31]

Open Surgical Procedures

The classic open surgical procedures can be subdivided into two groups: (1) conservative, tissue-sparing techniques, limited to removing the parasite, with part or most of the pericyst left in situ, and (2) radical procedures that remove the entire pericyst, with or without entering the cyst itself. The choice of surgical technique depends on the size, site, and type of the cyst(s), the existence of complications, and the surgeon's expertise.[32]

The most common conservative, tissue-sparing, techniques are: simple drainage, marsupialization (external drainage—an historical procedure), partial cystopericystectomy (partial resection of the pericyst), and near-total pericystectomy. All of these procedures have some common goals: (1) safe and complete exposure of the cyst, (2) safe decompression of the cyst, (3) safe evacuation of the cyst contents, (4) sterilization of the cyst, (5) management of cyst-bile duct communications, if present, and (6) management of the remaining cyst cavity.[33]

The traditional surgical simple drainage of the cysts is still in use by many surgeons. In this procedure, the abdomen is carefully packed with pads around the cysts to reduce the risk of peritoneal soilage and contamination, the cysts are aspirated by a closed system, and antiscolecoidal agents (e.g. alcohol, chlorhexidine, hypertonic saline, etc.) are infused in the emptied cavity. After repetitive infusions the cyst is unroofed and drained. The recurrence rate following this procedure ranges from 10% to 30%.[34,35] Evaluation of the cyst contents is important. Bile staining implies a communication with the biliary tree and should warn against the injection of antiscolecoidal agents because of the definite risk of sclerosing cholangitis.

Marsupialization was commonly used several decades ago, especially for infected cysts, and it is practically not used anymore due to the high complication rate. In this procedure, following evacuation and sterilization of the cyst, the cavity is drained externally by suturing the opening on the pericyst to the abdominal wall.[36] The management of such patients is prolonged, with suppuration and frequent bleeding from the cyst. The procedure is ideal for infected cysts but convalescence is slow and drainage may persist for months.

Although these techniques are simple, easy, and quick, they are operator dependent and are often accompanied by a high rate of postoperative complications, such as persistence of residual cavity, disease soilage in biliary tract or intraperitoneal, bile leakage, vessel injuries and hemorrhage, sepsis, cholangitis and anaphylactic shock. For that reason several technical improvements have been proposed, such as interrupting all external communications from the cyst and obliterating the remaining cavity with omentum (omentoplasty) or muscle flaps. The omentum is sutured into place and a drain is also placed fixed to the rim of the opening. Other surgeons suggest capitonnage of the remaining cyst's wall to reduce bile leakage.[37,38] This technique involves infolding the redundant cyst wall into the depths of the cyst with successive layers of sutures. Capitonnage is contraindicated when the wall of the cyst is rigid and calcified. Special attention is also required to avoid deep suture placement with subsequent bleeding from hepatic vein injury.[33]

In partial cystopericystectomy, the parasitic foci is eliminated and the surrounding pericyst is removed. Dr. Milicevic, the corresponding author of this study, suggests entailed excision of the exuberant

part of the cyst that protrudes from the liver, especially in small and young hydatid cysts with elastic and thin pericysts.[39]

Subtotal pericystectomy (fere totalis) is an alternative to partial cystopericystectomy. In partial cystopericystectomy, small pericystic areas close to vascular and biliary vessels are not resected because of a high risk of severe complications.[40] The modification proposed by Burgeon et al. includes inner membrane excision with preservation of the outer layer to protect liver parenchyma, biliary ducts, and blood vessels, minimizing postoperative complications such as biliary leaking and hemorrhage.[41]

In radical operations the parasitic content and the entire pericystic membrane is removed. In this subcategory, the main procedures are total pericystectomy and liver resection.

Total pericystectomy, first described in the 1930s, can be performed either with the "open" or the "closed-cyst" method. In the open technique, the cyst is opened, the contained material is removed, antiscolecoidal substances are infused, and then the pericyst is removed. In the closed-cyst method, en block pericystectomy is performed with no other manipulations. During the pericyst's removal, afferent blood and biliary vessels are ligated in order to prevent hemorrhage or postoperative bile leakage. This procedure, although technically more demanding, causes cavity disappearance and prevents relapse of the disease and secondary inflammatory complications.[42,43] There is no doubt that a radical operation in the hands of experts in dedicated centers gives superior results. The operation has the advantage of identifying exogenous daughter cysts adjacent to the main cyst but is to be avoided for cysts impinging on the major hepatic veins, the inferior vena cava, and close to the liver hilum. Closed cystopericystectomy creates no residual adventitia, eliminates the need for antiscolecoidal agents, and avoids biliary fistula, but bleeding can be profuse due to the adjacent vessels in the liver parenchyma.[33,38] Open cystopericystectomy is preferred when the cyst wall is thin and impending rupture is expected and when major vascular structures have been encountered during the closed procedure.[44]

Many authors suggest liver resection for echinococcosis. Although this method seems to be the most complete treatment for hydatid disease, the high postoperative morbidity and mortality rate, and the unknown ability of the remaining liver to regenerate suggest a more skeptical use of this technique. For that reason, liver resection is indicated when other more conservative surgical therapies have failed to eliminate the disease, cysts have destroyed an entire lobe or segment, thus compressing the healthy parenchyma interrupting the bile ducts, or when external cyst-biliary fistula draining zones need to be formatted. In such cases typical left or right hepatectomy or segmentectomy can be performed.[45,46]

In the modern era of radiofrequency (RF) thermal ablation, Brunetti et al. suggest a novel technique for liver hydatid cyst treatment. The RF electrodes were inserted through liver parenchyma into the echinococcal cysts. The cysts were destroyed with a pattern similar to those of hepatic metastases. Histologic examination in the material that was removed with suction showed no live parasites or eggs, and in their small series no recurrence was observed, while no complications have been reported perioperatively. This modification may present a new alternative in liver hydatid cyst treatment, especially in deep cysts, in multiple cysts, or in complicated cases that require severe and multiple operations.[47] RF total cystopericystectomy and RF liver resection are the most recently applied modification. Tissue-desiccating necrosis is limited only to the narrow resection surface layer of the liver parenchyma, providing excellent hemo-, bile and lymphostasis as well as a safe margin, considering exogenous vesiculation as a potential cause of local recidivism.

Management of Bile Duct Communication

Preoperative detection and assessment of cyst-bile duct communication is essential. Large cysts occupying several liver segments and episodes of cholangitis are highly suggestive of cyst-bile duct communications, and a search for the fistula should be meticulous. The direction of the bile duct can be determined by gentle exploration with a thin curved probe. Terminal biliary branches can be sutured with or without T-tube drainage. In some patients with bile-stained hydatid debris, no communication is detected and no additional procedure is done. Bile duct exploration, choledochoscopy, and T-tube drainage is usually done in order to secure and decompress a tenuous closure of a large bile duct in a rigid pericyst. A Roux-en-Y intracystic hepaticojejunostomy may be necessary for large cysts in which major ducts are disrupted, the jejunum being sutured to the duct within the cyst cavity. Choledochoduodenostomy or Roux-en-Y hepaticojejunostomy are performed for massive penetration of hydatid debris and daughter cysts into the common bile duct.[48] Indications for sphincteroplasty are very infrequent and include obstruction of the papilla by calcified hydatid debris or sclerosis.[49]

Laparoscopic Treatment

Laparoscopic treatment of liver echinococcosis has been increasingly popular during the last few decades because of the significant progress in laparoscopic surgery, although no randomized clinical trials comparing laparoscopic with conventional open surgical treatment of hydatid disease have been reported. Laparoscopic treatment includes partial or total pericystectomy and cyst drainage with omentoplasty. A major disadvantage of laparoscopy is the lack of precautionary measures to prevent spillage under the high intraabdominal pressures caused by pneumoperitoneum. Some authors suggest that pneumoperitoneum is beneficial in preventing spillage,[50] while others suggest a decrease in intraabdominal pressure.[51] The most difficult part of the laparoscopic procedure is the initial cyst puncture and aspiration of the cyst fluid.[52] Pre- and intraoperative use of antiscolecoidal factors seems to be of great importance because it ensures the inactivation and clearance of the parasites, while some authors avoid them because of the potential risk of sclerosing cholangiitis.[53,54] Seven et al. suggest that intraoperative spillage can be avoided by fixing the cyst in the abdominal wall with a special umbrella trocar and suction with a specific suction device.[55] Bickel et al. suggest a combination of filling the right subdiaphragmatic suprahepatic space with antiscolecoidal fluid (cetrimide) and Trendelenburg position for decreasing the risk of spillage, although this approach cannot prevent a sudden jet of fluids escaping the cyst.[50] In their study, they propose a new technique with a transparent cannula and vacuum for complete fluid evacuation. The tip of the device is adhered firmly to the cyst wall to prevent spillage in the peritoneal cavity.

The indications for laparoscopic excision of liver echinococcosis has changed through the years. In the past, patients with cysts with a diameter greater than 15 cm and those with recurrent disease were excluded from laparoscopic treatment. Nowadays, the only excluding criteria for laparoscopic intervention are deep intraparenchymal cysts or posterior cysts situated close to the vena cava, more than 3 cysts, and cysts with thick and calcified walls.[56,57]

Conversion to open laparotomy may occur because of unsafe exposure, unsatisfactory access, intraoperative bleeding, or intrabiliary rupture of the cyst. Choledochotomy, irrigation, and T-tube drainage is indicated in these patients, although open laparotomy prolongs significantly hospitalization. A more conservative approach is laparoscopic removal of the cysts and endoscopic sphincterotomy for intrabiliary rupture or external biliary fistulas.[58,59]

Postoperative morbidity in laparoscopic studies ranges from 8% to 25%,[50,60] while in open series varies from 12% to 63%.[43,46] The treatment-related death after laparoscopy is almost zero, while in open series it ranges from 0% to 3%.[39,43,46] Major complications (in the form of allergic reactions) seem to be more common in laparoscopic interventions due to peritoneal spillage during debridement and removal of cysts content.[50] The rate of short-term recurrence varies from 0% to 9% after laparoscopy,[50,55] while in open series it is even higher (0% to 30%).[39,43,46] These favorable results of laparoscopic treatment of liver hydatid disease may be related to not only the advantages of minimally invasive surgery but also the selection criteria for the patients.[61,62]

The well-known advantages and the superiority of laparoscopy are strengthened in the light of the need for a much larger upper abdominal incision for open hydatid surgery and the prolonged hospitalization. Mean hospitalization time ranges between laparoscopic (3–12 days) and open series (9–20 days), and a significant statistical difference seems to exist.[50,56,62]

Criticisms that may be made of the existing studies are that the patients were not randomized into laparoscopic and open intervention, the total number of patients is relatively small, and patients with contraindications for laparoscopic treatment were handled with open surgery.

Percutaneous Drainage

Until recently percutaneous treatment of hydatid liver cyst was contraindicated because of the fear of dissemination, peritoneal spillage, and anaphylactic shock. Since 1989, only a few sporadic, mainly unintentional, percutaneous aspirations followed by drainage of hydatid cysts have been reported.[63]

Nowadays both of these complications are extremely rare and should not be considered as absolute contraindications.[64] The development of fine needles and catheters, the advances in imaging techniques, and the introduction of the intercostal intrahepatic approach minimizes the risk of anaphylactic shock or spillage.[65]

Percutaneous aspiration can be performed either by ultrasound- or CT-guided control. The initial puncture can be established either by a freehand technique with ultrasound guidance or by a needle-guiding device mounted on a probe. After insertion the cyst's content is aspirated, a sample is derived, contrast is injected in order to opacify the cyst, and an antiscolecoidal drug is infused followed by a Betadine infusion. The catheter remains clamped for 30 minutes, and after a second Betadine infusion the

catheter remains for drainage. In addition to Betadine, other antiscolecoidal agents have been used successfully.[66,67]

Percutaneous treatment is indicated for type I and II cysts, some groups of type III that do not involve nondrainable solid material, subtypes of type IV, suspected fluid collections, and infected hydatid cysts. In addition, percutaneous treatment should be considered in patients at high surgical risk, pregnant patients, and patients with multiple or disseminated cysts.

Percutaneous procedures are contraindicated in some subgroups of type III and IV (hydatid cysts with heterogeneous echo pattern) and in liver cysts that have ruptured into the biliary system or peritoneum.[25] It is generally accepted that hydatid cysts of type V do not need any intervention but can be managed with regular follow-up instead.[68]

Treatment failure is defined as recurrence in the same location or complications related with the intervention. For uncomplicated hydatid cysts of type I and II, percutaneous treatment seems to be the optimal treatment. Recurrence ranges between 0% and 4% among several series with a low morbidity rate.[69,70] The overall complication rates in percutaneous drainage varies from 15% to 40%. Major complications such as anaphylactic shock range from 0.1% to 0.2%, and minor complications (urticaria, itching, hypotension, fever, infection, fistula, rupture in biliary system) varied from 10% to 30%.[71]

The overall mortality is 0.9% to 2.5% among several studies and associated with perioperative complications, patient's age, and infection of the remaining cyst cavity.[72]

Percutaneous drainage is gaining wide acceptance because of its low morbidity and easy applicability, but selection of the patients is of paramount importance.[73]

A meta-analysis of percutaneous drainage of liver hydatid cyst showed no significant complications and immediate relief of the symptoms, and no recurrence was observed during 33 months of follow-up.[74]

We suggest that percutaneous treatment has an important role in the treatment of hydatid liver cysts with results proved by several series with long-term follow-up. Therefore, we believe that in indicated cases percutaneous drainage is a very effective and reliable interventional minimally invasive procedure associated with low mortality and morbidity.[75] Surgeons should play a key role in the management of patients with hydatid disease and cooperate with the radiologists using these novel techniques.

CONCLUSION

What are the perspectives in the beginning of the third millennium? The answer can be obtained with the determination of the disease-associated problems. Although several therapeutic procedures have been proposed, no randomized clinical trials for their comparison have been organized. Randomized clinical trials may define the therapeutic strategy to combine both low morbidity and radical elimination of recurrences. Encouraging results have been achieved recently by minimally invasive approaches. Current data suggests that laparoscopic and percutaneous drainage are feasible and in certain cases render open techniques unnecessary or obsolete. More sensitive diagnostic methods should be developed. The radical elimination of the disease can be achieved with improvements in agriculture, educational, social, and economic factors of the endemic regions and vaccine development.

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A Disappearing Hepatic Infusion Pump

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KEY WORDS: Hepatic arterial infusion, complications, metastasis

CASE REPORT

An 81-year-old man underwent right hemicolectomy for a T3 N1 colon cancer complicated by the development of a midline incisional hernia. He completed 6 months of adjuvant systemic chemotherapy. Shortly thereafter, he developed a solitary right hepatic lobe metastasis and was referred to our institution for consideration of resection and hepatic arterial pump placement.

A right hepatic lobectomy, hepatic pump placement, and incisional hernia repair were performed through a right subcostal incision with a left-sided extension. Through this exposure, a suprafascial pocket for the hepatic pump was fashioned in the left lower quadrant. The incisional hernia was observed during creation of the pocket, the sac was removed, and the fascia was closed without undue tension with interrupted Prolene (Ethicon, Somerville, NJ). The catheter was placed through the abdominal wall, the pump was secured to the fascia with Prolene, and the pocket was closed with chromic suture. The pump pocket was created lateral to the hernia repair. A postoperative abdominal roentgenogram demonstrated the pump to be in the expected location (Fig. 1).

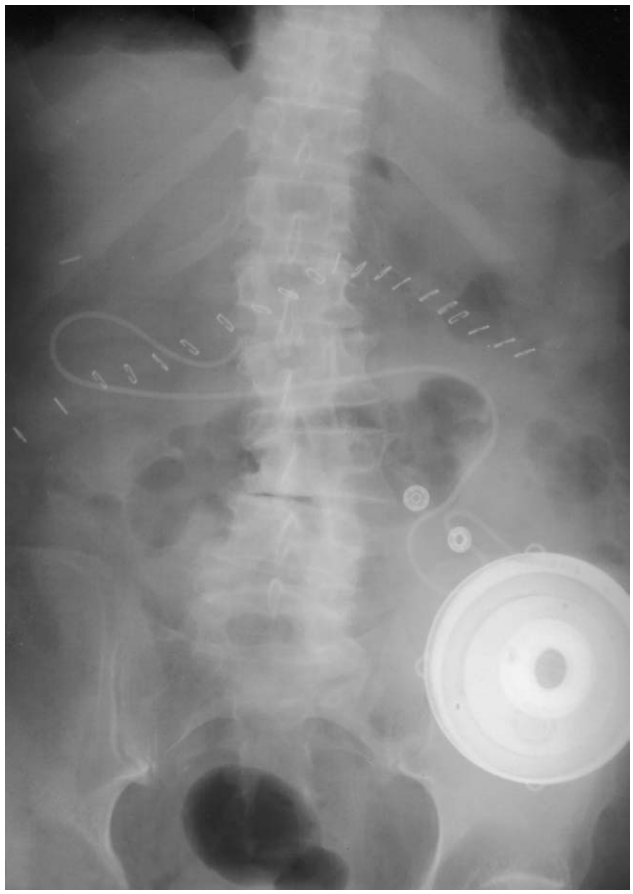

Fig. 1. Abdominal roentgenogram taken immediately after the operation, showing the hepatic arterial infusion pump located in the left lower anterior abdominal wall.

The patient's incisional hernia recurred postoperatively. Despite this, the hepatic pump remained in position, and he received two cycles of fluorodeoxyuridine unremarkably. He began to complain of intermittent abdominal pain in the area of his pump. Four months after placement, the pump could no longer be palpated or accessed. Roentgenograms were obtained (Fig. 2) and demonstrated the pump to be in the patient's true pelvis.

At exploration, a large incisional hernia was found. The pump had subsequently eroded through the midline hernia sac and descended into the patient's pelvis. The catheter remained intact. A new pump pocket was made more lateral to the midline with the

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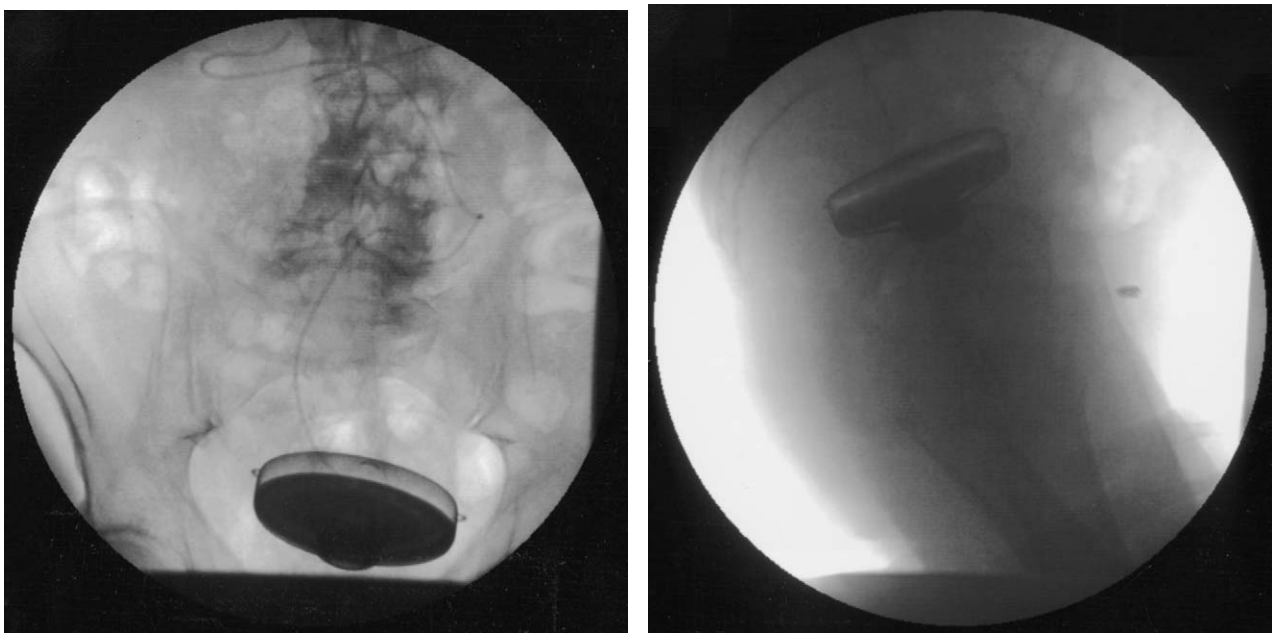

Fig. 2. Anteroposterior (left) and lateral (right) pelvic roentgenograms, taken 4 months after the operation, show the patient's infusion pump now to be located in the true pelvis.

pump resecured. The hernia was repaired with mesh. The patient has done well since then, without hernia or disease recurrence. His pump remains functional.

DISCUSSION

Hepatic arterial infusion of chemotherapy reduces liver recurrence and may provide a survival benefit.[1] However, several factors have limited its widespread application: conflicting data regarding the overall survival advantage; the implementation of newer systemic agents with efficacy such as irinotecan, oxaliplatin, and bevacizumab; and metabolic and technical complications associated with hepatic pump placement and utilization.

Studies specifically addressing technical complications of hepatic arterial chemotherapy using a continuous-infusion pump report complications in 28%[2] to 41% of patients with hepatic pumps, resulting in cessation of therapy in as many as 30% of patients.[3] Complications reported with a greater than 5% incidence are dislodgement of the catheter tip, catheter occlusion, pump failure, and pump pocket hematoma, seroma, and infection.[2,3] This report describes another complication, viz., pump migration from its initial position in the left anterior abdominal wall into the true pelvis.

This case brings attention to several important issues regarding hepatic pump placement and management. It is critical to ensure catheter redundancy during placement to avoid dislodgement and pseudoaneurysm formation should unforeseen catheter tension occur. Generally, a catheter needs only to be tailored at the tip so that it infuses at the junction of the gastroduodenal artery and common hepatic artery. In addition, the creation of a generous pump pocket away from the midline allows for adequate fascial bites for midline closure, which lessens the risk of catheter entrapment and minimizes the risk of pump migration should an incisional hernia occur. Some favor a separate left lower quadrant incision for this purpose, with the added theoretical decreased risk of concomitant pump infection, should the primary operative wound become infected. Finally, the use of interventional radiology services is validated in diagnosing (and often rectifying) a number of complications associated with hepatic pumps and other chemotherapy delivery systems.

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