*Editorial*

# Gastrointestinal Surgery: A Specialty Without Borders

*Keith A. Kelly, John L. Cameron, M.D., Co-Editors, Journal of Gastrointestinal Surgery*

Gastrointestinal surgery is the most common subspecialty practiced by general surgeons in the United States, comprising about 80 percent of a general surgeon's practice. We suspect the same is true in all parts of the world. The type of gastrointestinal surgery done, of course, varies from country to country, mainly because the gastrointestinal diseases treated vary among countries. Esophageal and gastric cancers are more common in Japan, cholangitis is more common in China, hydatid cysts are more common in Turkey, and Chagas' disease is more common in Brazil than in the United States, but we believe that general surgeons in all of these countries do more gastrointestinal surgery than they do other types of general surgery. The need for expertise in gastrointestinal surgery crosses national borders and occurs in every country.

The Society for Surgery of the Alimentary Tract recognized this need at the time our journal, the JOURNAL OF GASTROINTESTINAL SURGERY, was founded six and one-half years ago. This particular title was chosen, rather than the title, "American Journal of Gastrointestinal Surgery," because the Society wished to serve gastrointestinal surgeons throughout the world, not just American surgeons.

We are particularly pleased, therefore, that the International Society of Digestive Surgery (ISDS) has chosen our Journal as its official journal, as of January 2003. Papers from the biannual meeting of the ISDS appear in the Journal for the first time in this issue. These papers were selected by the ISDS as the outstanding papers submitted by young surgeons to be considered for the Grassi Prize at the 2002 meeting of the Society. The Grassi Prize is the highest honor given by the ISDS to a young surgeon. Dr. Lu Wang from China received the 2002 Prize.

We look forward to receiving many more papers from the ISDS and, indeed, from international surgeons everywhere. Currently, international surgeons are writing about one-third of the articles published in our Journal. We believe our Journal offers them an excellent venue for publication. The Journal was recognized in 2001 by the Institute for Scientific Information (Philadelphia, PA) as having an impact factor that placed it in the top one-fourth of all general surgery journals published that year, even though the Journal had only been in existence for five years at that time. Our Journal offers its international authors the opportunity to reach English-speaking audiences worldwide. The Journal is sent by mail all over the world, appears on the World Wide Web (www), and is cited by Index Medicus and other summary publications. We also assure our international authors that their articles will receive prompt and careful attention, and constructive scientific review by two experts in the field and by the Co-Editors. While the originality and scientific rigor of any surgical paper depends on its authors, we do our best to ensure that the English language used in the paper and the format of the publication meets the standard required of a high-quality journal.

We welcome the ISDS into the fold and encourage gastrointestinal surgeons throughout the world to utilize the JOURNAL OF GASTROINTESTINAL SURGERY as the primary way to exchange information pertaining to alimentary tract disease.

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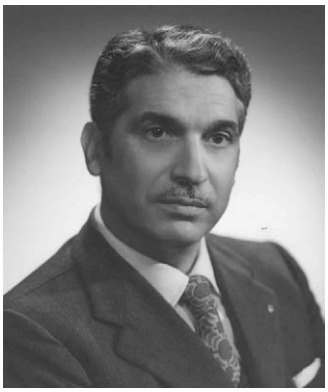
# The Giuseppe Grassi Prize—Comments

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



Dr. Giuseppe Grassi

I am pleased to make a few remarks relative to Dr. Giuseppe Grassi (pictured above), who has been appropriately honored by this named session. Dr. Grassi was born in the year 1913 at Bronte, Catania, Italy. At an early age, his exceptional intelligence was noted. Proof of his continuing hard work and special facility as a surgeon may be found in his successive appointments as Chief of Surgery in major Italian hospitals.

In 1968, during the meeting in Brussels of the Belgium Society of Gastroenterology, Dr. Grassi met Professor Louis Hollender of Strasbourg who, together with Professor Fabiano Benedetti-Valentini of Rome, recognized the need for an international body to study surgery of the gastrointestinal tract. They formed the Collegium Internationale Chirurgie Digestivae (CICD) in 1969 and held its first Congress in San Remo, Italy, during 1970 with Grassi as Congress President.

Dr. Grassi was the original Secretary-General of the CICD until his premature death in 1981.

The CICD established a prize, The Grassi Prize, to be given to a young surgeon who presented the most outstanding paper at the annual meeting of the Society. I know Professor Dr. Giuseppe Grassi would be proud to see his name attached to this Award, given to young surgeon scholars. I excerpt below from a 1996 comment I wrote (Arch Surg 131:1237):

> When Hollender first met Grassi in 1968, he was struck by the wide learning of Grassi, his witty mind and his sparkling eyes. "Isn't this a fine way to remember our esteemed surgeon and colleague from Italy? I understand that he died of a coronary occlusion while performing patient teaching rounds. If Giuseppe Grassi had to leave us prematurely, we can be certain he died happily while teaching and surrounded by the patients he loved."

The name CICD was recently changed by the CICD to the International Society of Digestive Surgery (ISDS).

These comments were presented at the 18th World Congress of the International Society of Digestive Surgery in Hong Kong, China, December 2002.

## 2002 Grassi Prize Winner

The winner of the 2002 Grassi Prize was Dr. Lu Wang (Department of Surgery, Fudan University, Shanghai, Peoples Republic of China), for his paper entitled, "Mechanism of Interferon Alpha on Inhibition of Metastasis and Angiogenesis of Hepatocellular Carcinoma After Curative Resection in Nude Mice," coauthored with Drs. Wei-Zhong Wu, Hui-Chuan Sun, Xiao-Feng Wu, Lun-Xiu Qin, Yin-Kun Liu, Kang-Da Liu, and Zhao-You Tang.

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# Mechanism of Interferon Alpha on Inhibition of Metastasis and Angiogenesis of Hepatocellular Carcinoma After Curative Resection in Nude Mice

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The aim of this study was to examine the mechanism of interferon alpha (IFN-α) on inhibition of metastasis and recurrence of hepatocellular carcinoma (HCC). Nude mice bearing human HCC xenografts with high metastatic potential (LCI-D20) underwent curative resection of tumors on postimplant day 11. IFN-α was begun the next day at different dosages given subcutaneously for 35 consecutive days; normal saline solution was injected into the control mice. The mice were killed 48 hours after the final treatment, and the parameters were evaluated. The HCC intrahepatic recurrence rate, the size of the recurrent lesions, the rate of lung metastasis, the serum vascular endothelial growth factor level, and the microvessel density (immunohistochemistry) were as follows: 100%, 2136 ± 794 $mm^3$ (mean ± standard deviation), 100%, 265.7 ± 154.7 pg/ml, and 144 ± 37/HP, respectively, in the control mice, whereas these same values were 62.5%, 89 ± 45 $mm^3$, 12.5%, 53.3 ± 9.9 pg/ml, and 86 ± 25/HP, respectively, in the IFN-α $1.5 \times 10^7$ U/kg treatment group ($P < 0.05$) and 26.7%, 46 ± 21 $mm^3$, 0%, 65.2 ± 17.9 pg/ml, and 39 ± 14/HP in the IFN-α $3 \times 10^7$ U/kg treatment group, respectively ($P < 0.05$). However, a significant difference was not found in the serum levels of basic fibroblast growth factor among the control and IFN-α treatment groups. IFN-α inhibits metastasis and recurrence of human HCC after curative resection in nude mice mediated by antiangiogenesis through downregulating expression of vascular endothelial growth factor but not basic fibroblast growth factor. (J GASTROINTEST SURG 2003; 7:587–594) 

KEY WORDS: Hepatocellular carcinoma, interferon-α, angiogenesis, metastasis, vascular endothelial growth factor

Hepatocellular carcinoma (HCC), the main type of primary liver cancer, is one of the most common and aggressive malignancies worldwide; HCC ranks fifth in term of number of cases and fourth in terms of mortality.[1–3] In China it is the second most common cause of cancer death.[4] Hepatic resection is the standard treatment for HCC, but the survival rate is still low because of the high incidence of recurrence.[5,6] HCC recurrence occurs in two ways: multicentric occurrence and dissemination of tumor cells. Chemotherapy is ineffective in preventing metastasis and recurrence; therefore new agents and innovative approaches are needed. Interferon alpha (IFN-α) is one of the candidates. In addition to antiproliferative and immunomodulatory effects, IFN-α has been shown to inhibit tumor angiogenesis.[7,8] The progressive growth and metastases of malignant tumors depend on adequate angiogenesis.[9,10] HCC is a typical hypervascular tumor. Marked neovascularization is a hallmark of HCC. Studies have shown that angiogenesis, as assessed by counting of microvessels, is an important prognostic factor in operable HCC, with high microvessel counts being associated with disease spread and poor survival.[11,12]

Previous reports from our institution demonstrated that systemic IFN-α therapy dose dependently inhibits tumor growth and recurrence in nude mice bearing human HCC xenografts with a high metastatic potential. Neovascularization in the eyes of mice bearing corneal micropocket implants

Winner of the 2002 Grassi Prize, International Society of Digestive Surgery, Hong Kong, China, December 11, 2002.
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of HCC tissue was inhibited by treatment of the animals with IFN-α. The growth of the HCC cell lines was unaffected by IFN-α, but the proliferation and migration of vascular endothelial cells were inhibited. Our results suggested that the antiangiogenic activity of IFN-α is an important component of the ability to prevent recurrences of HCC.[13]

Angiogenesis during malignant growth and metastasis is a complex and closely regulated process. The extent of angiogenesis is determined by the balance between the proangiogenic and antiangiogenic molecules released by tumor cells and surrounding host cells.[14,15] Among the known angiogenic factors, vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are potent and representative factors involved in tumor development. VEGF expression has been associated with postoperative recurrence of HCC.[16–20] bFGF is another important positive regulator of HCC angiogenesis.[21–23] It has been reported that bFGF and VEGF show a synergistic effect in murine HCC angiogenesis.[24]

IFN-α has been shown to downregulate the expression of a series of angiogenic factors, but which factors are affected by IFN-α in HCC is unclear. The current study was undertaken to show which angiogenic factors were downregulated by examining serum VEGF, bFGF, and intratumoral vessel development in nude mice treated with IFN-α, and also to determine which angiogenic factors mainly modulate the process of HCC angiogenesis.

## MATERIAL AND METHODS

### Animals

Male BALB/c nu/nu nude mice, weighing approximately 20 g (Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, PR China), were housed in laminar flow cabinets under specific pathogen-free conditions and used at 6 weeks of age. The mice were cared for and handled in accordance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals. The experimental protocol was approved by the Shanghai Medical Experimental Animal Care Committee.

### Metastatic Model of Human HCC in Nude Mice (LCI-D20)

This model was established in the Liver Cancer Institute of Fudan University via orthotopic implantation of histologically intact metastatic tumor tissue. Only one of the 30 implanted surgical specimens demonstrated metastasis. This model has been maintained for more than 90 passages in nude mice. All LCI-D20 models had 100% transplantability and metastatic ability, and manifestations reminiscent of tumor behavior in patients with HCC. Abnormal alpha-fetoprotein and hepatitis B surface antigen were found in this model. The LCI-D20 model represents 100% spreading in the liver, metastasis to the lungs and lymph nodes, and peritoneal seeding.[25]

### Surgical Orthotopic Implantation and Partial Hepatectomy

The animals were anesthetized and their abdomens sterilized with iodine and alcohol. A left subcostal incision was made. The left lobe of the liver was exposed, and a portion of the liver surface was mechanically injured with scissors. Then a piece of LCI-D20 tumor, approximately 2 mm in diameter, was fixed within the liver tissue, the liver was returned to the peritoneal cavity, and the abdominal wall was closed with 8-0 Prolene sutures. On the eleventh day after implantation, through a left upper abdominal subcostal incision, the lobe into which the tumor was implanted was excised. The length between the incisional margin and the tumor edge was $\geqslant$2 mm.

### Interferon-α-1b Treatment and Grouping

Recombinant interferon-α-1b (Sinogen; Kexing Bioproduct Company, Ltd., Shenzhen, PR China) is a highly purified protein with a molecular weight of 194,000 Daltons. The protein is expressed by a gene isolated from the leukocytes of healthy Chinese individuals. The drug is as efficacious as other interferon products but has fewer side effects and induces only a few neutralizing antibodies in Chinese patients.

In the experiment reported here, 51 nude mice underwent curative resection of their tumors and were given subcutaneous IFN-α daily at different dosages ($1.5 \times 10^7$U/kg, n = 16 mice; and $3 \times 10^7$ U/kg, n = 15 mice). A control group of 20 mice underwent curative resection of their tumors and were injected with normal saline solution (0.2 ml). The injections were begun on the day after resection and were continued for 35 consecutive days. All mice were killed 48 hours after the final treatment by cervical dislocation.

### Parameters Observed

At autopsy, intrahepatic recurrent tumor volume was measured for the largest (a) and smallest (b) diameters, and the tumor volume was calculated as $V = ab^2/2$.[26] Paraffin blocks of 10% buffered formalin-fixed samples of lungs were prepared. Serial sections were cut at 5 μm and stained with hematoxylin

and eosin to determine the presence of lung metastases. Blood samples were collected in sterile test tubes and placed on ice, allowed to coagulate at 4° C for a minimum of 30 minutes, and then centrifuged at $2000 \times g$ for 10 minutes at 4° C. The samples were stored in aliquots at −70° C. After thawing, each serum aliquot was assayed only once.

## Quantification of Microvessel Density

Paraffin-embedded tumor tissues were sectioned (4 μm), dewaxed in xylene, and dehydrated in ethanol. Samples were washed three times with phosphate-buffered saline solution (PBS), and incubated with a peroxidase blocking reagent and protein blocker (Dako Corp., Carpinteria, CA). Sections were then incubated with the appropriate dilution (1:100) of rabbit monoclonal antimouse CD34 antibody (Santa Cruz Biotechnology, Inc., Santa Cruz, CA) for 24 hours at 4° C. After the samples were rinsed three times for 5 minutes each with PBS, they were incubated with the appropriate dilution (1:200) of biotin-conjugated goat antirabbit antibody (Santa Cruz Biotechnology) for 1 hour at room temperature in the dark and then with peroxidase-conjugated streptavidin (Dako Corp.) at a 1:200 dilution for 30 minutes followed by three washes with PBS. Finally, 0.02% diaminobenzidine and 1% hydrogen peroxidase were reacted for 10 minutes and counterstained with Mayer's hematoxylin (Dako Corp.). Quantification of blood vessels was then carried out as described previously.[27] Any brown-staining endothelial cell cluster distinct from adjacent microvessels, tumor cells, or other stromal cells was considered a single countable microvessel. The most vascular area of tumors was identified on low-power field (×100), and the vessels were counted in five high-power fields (×200). The data are presented as the mean ± standard deviation (SD) for five high-power fields.

## Cell Culture

Highly metastatic MHCC97 human HCC cells were grown as a monolayer culture in Dulbecco's minimum essential medium (Gibco/BRL, Grand Island, NY) supplemented with 10% human AB serum. The line was established from a subcutaneous xenograft of LCI-D20 by means of alternating cell culture in vitro and growth in nude mice. The line was shown to be of human origin by karyotype analysis. The cells were grown as either compact colonies or a monolayered sheet, exhibited typical malignant epithelial characteristics on morphologic examination, and were positive for alpha-fetoprotein. The rate of metastasis to the lungs was 100% using orthotopic inoculation.[28] Cells were cultured at 37° C in a 5% $CO_2$–95% air environment in humidified incubators.

## Reverse Transcription–Polymerase Chain Reaction

According to results in vivo[13] and in vitro,[29] we determined the dose of IFN-α and the various time intervals used in the experiment. One $\times 10^6$ MHCC97 cells were incubated in medium containing 1000 or 3000 IU/ml IFN-α for 0.5 hours, 2 hours, and 8 hours, respectively. The total RNA was extracted using the RNeasy Mini Kit (Qiagen, Inc., Valencia, CA), and 1 μg of the above-mentioned RNA each was taken for reverse transcription (Gibco/BRL). The expression of VEGF mRNA and bFGF mRNA was analyzed by a semiquantitative polymerase chain reaction whose primers were designed with the use of Primer 3 software (Whitehead Institute, Cambridge, MA). The PCR reaction conditions and primer sequences were shown in Table 1 and Fig. 1 in details. The γ-actin gene was used as the internal standard in our reverse transcription–polymerase chain reaction (RT-PCR) systems.

## Enzyme-Linked Immunosorbent Assay for VEGF and bFGF

Serum, supernatant VEGF, and serum bFGF expression were analyzed by enzyme-lined immunosorbent assay (ELISA) using the Quantikine VEGF and bFGF ELISA kit (R & D Systems, Minneapolis, MN). According to the manufacturer, the assay is designed

**Table 1.** Primers and conditions of RT-PCR to semiquantify bFGF, VEGF and γ-actin genes

| Gene | Sense and antisense primers | Annealing | Cycles | Size (base pairs) |
|---|---|---|---|---|
| bFGF | GTGTGTGCTAACCGTTACCT;<br>GCTCTTAGCAGACATTGGAAG | 57° C | 30 | 237 |
| VEGF | CGAAGTGGTGAAGTTCATG;<br>TTCTGTATCAGTCTTTCCTGGTGAG | 55° C | 26 | 536<br>441 |
| γ-actin | ATGGAAGAAGAAATCGCCGC;<br>ACACGCAGCTCGTTGTAGAA | 55° C | 25 | 287 |

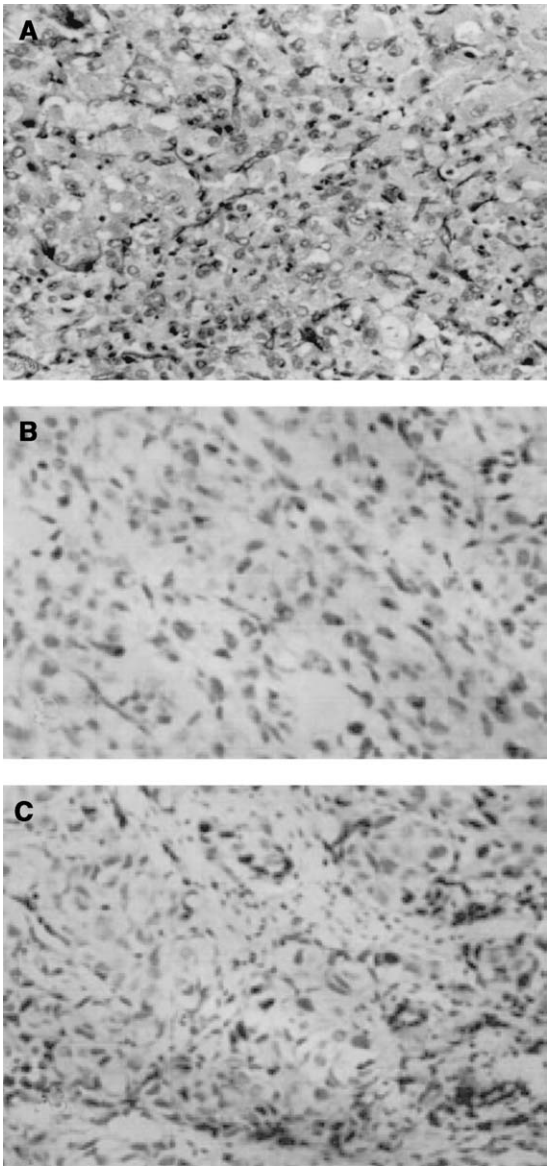


**Fig. 1.** Vascular density. Recurrent LCI-D20 HCC harvested from a saline-treated mouse (**A**) or from IFN-α–treated mice at differing dosages (**B**, $1.5 \times 10^7$/kg/day; **C**, $3 \times 10^7$/kg/day) after curative resection of their tumors. Sections were immunostained for expression of CD34 (microvessel density). Microvessel density was reduced by IFN-α in a dose-dependent manner.

to measure natural VEGF levels in serum. All analyses were carried out in duplicate. The concentrations of VEGF and bFGF in unknown samples were determined by comparing the optical density of the samples to the standard curve. Concentrations are reported in pg/ml.

### Statistical Analysis

Data were analyzed by computer program (SPSS 10.0; SPSS Inc., Chicago, IL), using analysis of variance (ANOVA), Wilcoxon chi-square test, and Fisher's exact test. Differences were considered significant at $P < 0.05$.

## RESULTS

### Inhibition of Recurrence and Metastases After Curative Resection by Systemic Administration of IFN-α

As shown in Table 2, the incidence of intrahepatic tumor recurrence in the control, IFN-α $1.5 \times 10^7$ U/kg, and IFN-α $3 \times 10^7$ U/kg groups was 100%, 62.5%, and 12.5%, respectively; recurrent tumor volume was $2136 \pm 794$ mm$^3$, $89 \pm 45$ mm$^3$, and $46 \pm 21$ mm$^3$, respectively; and the incidence of lung metastasis was 100%, 12.5%, and 0%, respectively. Statistical differences were found among the three groups with regard to the incidence of intrahepatic tumor recurrence, recurrent tumor volume, and incidence of lung metastasis. No animal experienced a weight loss of more than 10%, and none had fever, anemia, neutropenia, or thrombocytopenia during the treatment regimen.

### Intratumoral Vessel Counting

Recurrent tumors in the treatment and control animals were collected and preserved in 10% phosphate-buffered formalin, and sections 4 μm thick were immunohistochemically stained for expression of the endothelial-specific marker, CD 34. Significant reduction in tumor vascularization was revealed. The number of blood vessels in the samples was quantified by counting stained regions in five high-power fields (×200). There was an IFN-α–dependent decrease in the number of countable intratumoral vessels in the LCI-D20 recurrent tumors (Fig. 1).

### IFN-α Inhibits VEGF Expression But Not bFGF in LCI-D20 Mice

To determine whether IFN-α would inhibit the angiogenesis of recurrent HCC by blocking VEGF and bFGF protein, we measured this serum concentration by ELISA. A significant inhibition of VEGF was found. Control mice had high levels of VEGF ($265.7 \pm 154.7$ pg/ml) in comparison to both of the IFN-α treatment groups ($1.5 \times 10^7$ U/day and $3 \pm 10^7$ U/day) (Fig. 2). However, IFN-α therapy did not inhibit the expression of bFGF in vivo. The level of serum bFGF in the untreated control group, the IFN-α $1.5 \times 10^7$ U/day treatment group, and the IFN-α $3 \times 10^7$ U/day treatment group was $137.7 \pm 34.1$ pg/ml, $135.7 \pm 92.3$ pg/ml, and $173.8 \pm 128.2$ pg/ml, respectively ($P > 0.05$) (Fig. 2).

**Table 2.** Systematic IFN-α inhibited both tumor intrahepatic recurrence and lung metastases, downregulated VEGF expression, and decreased microvessel density within tumors in nude mice after curative resection of LCI-D20 tumor xenografts in the liver

| IFN-α (U/kg/day) | Recurrent tumor | | No. of cases of lung metastases | Serum VEGF (pg/ml) | Serum bFGF (pg/ml) | Vascular density |
|---|---|---|---|---|---|---|
| | No. of cases | Volume ($mm^3$) | | | | |
| 0 | 20/20 (100%) | 2136 ± 794 | 20/20 (100%) | 265.7 ± 154.7 | 137.7 ± 34.1 | 144 ± 37 |
| $1.5 \times 10^7$ | 10/16 (62.5%)* | 89 ± 45† | 2/16 (12.5%)† | 53.3 ± 9.9† | 135.7 ± 92.3 | 86 ± 25† |
| $3 \times 10^7$ | 4/15 (26.7%)† | 46 ± 21† | 0/15 (0%)† | 65.2 ± 17.9† | 173.8 ± 128.2 | 39 ± 14† |

*$P < 0.05$.
†$P < 0.01$.

## Effects of IFN-α on VEGF and bFGF In Vitro

To confirm that the antiangiogenic effect of IFN-α on LCI-D20 tumor seen in vivo is by blocking the expression of VEGF but not bFGF and to elucidate the antiangiogenic molecular mechanisms of IFN-α, VEGF and bFGF genes were analyzed by semiquantitative RT-PCR in vitro. The results revealed that MHCC97 cells constitutively expressed a certain level of mRNAs of VEGFs and bFGF. Two different splicings of VEGF mRNA were found to be rapidly suppressed by 3000 IU/ml IFN-α treatment of MHCC97 cells. Densitometric analysis indicated that treatment with IFN-α resulted in a 45% reduction in VEGF mRNA for 0.5 hours and a 60% reduction for 2 hours. However, the transcriptional activities of bFGF were changed little during the experimental period (Fig. 3).

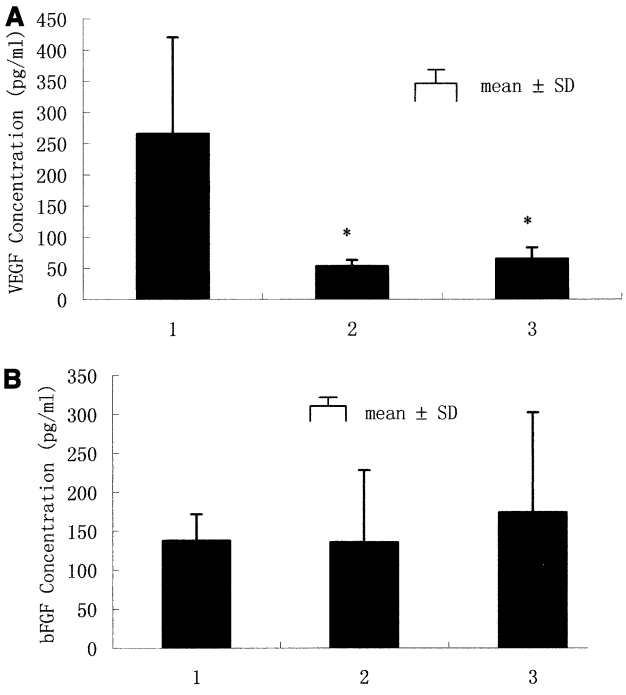


**Fig. 2. A**, IFN-α downregulated serum concentrations of VEGF in nude mice after curative resection of LCI-D20 HCC. **B**, Serum concentrations of bFGF in nude mice were not reduced by systemic therapy with IFN-α.

## In Vitro Inhibition of VEGF Production by IFN-α

We next examined whether IFN-α would inhibit the expression of VEGF by incubating MHCC97 cells (for 2, 8, and 24 hours) in control medium or medium containing IFN-α (1000 IU/ml or 3000 IU/ml). The expression was not reduced by the addition of IFN-α to the medium (at 2 hours or 8 hours). However, the VEGF concentration was significantly reduced after incubation of cells for 24 hours, as determined by ELISA assay (Table 3, Fig. 4).

## DISCUSSION

Angiogenesis is required for tumor growth beyond 1 to 2 mm in diameter and plays an important role in the metastatic spread of malignant disease. It is a highly complex and closely regulated process, and is influenced by the balance between stimulatory and inhibitory factors released by the tumor and surrounding host cells. Elucidation of the process has involved recognition of the role of several angiogenic factors and inhibitory molecules within the tumor.[14,30–33]

Among a series of angiogenic factors, IFN-α has been shown to downregulate expression of the major stimulatory molecules such as bFGF, interleukin-8, MMP-2, and MMP-9, and to inhibit further angiogenesis in most malignant tumors.[15,4–40] However, no reports have appeared showing whether administration of IFN-α modulates the expression of VEGF in HCC.

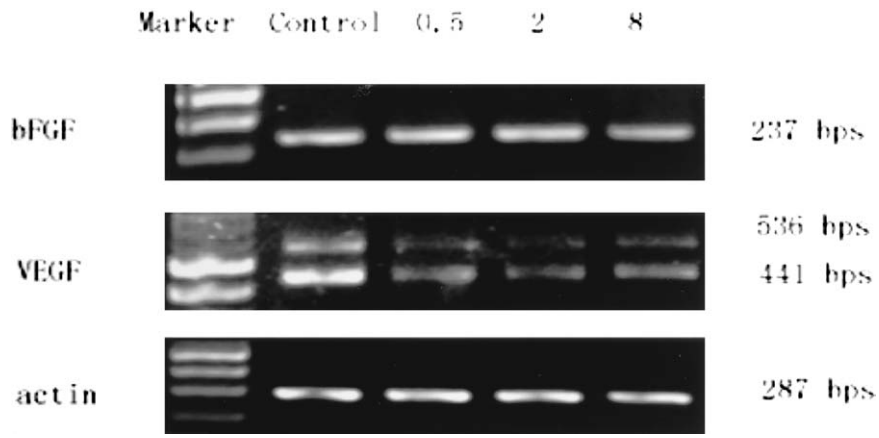


**Fig. 3.** In vitro inhibition of VEGF mRNA but not bFGF mRNA by IFN-α. mRNA was extracted in control MHCC97 cells and cells incubated in medium containing differing dosages of IFN-α for 0.5, 2, and 8 hours. According to densitometric analysis, treatment with 3000 IU/ml quickly downregulated VEGF mRNA expression.

Previous studies from our institution demonstrated that systemic IFN-α therapy dose dependently inhibits tumor growth, tumor recurrence, and metastatic potential in nude mice bearing human HCC xenografts. Our results also suggested that the antiangiogenic activity of IFN-α is the most important factor in inhibiting tumor growth in this particular model.[13]

Our present results showed that the systemic administration of IFN-α to nude mice bearing human HCC with high metastatic potential after curative resection mainly decreased expression of VEGF but not bFGF, reduced vascular density, and inhibited tumor metastasis and intrahepatic recurrence.

The present data also demonstrated that IFN-α can decrease expression of VEGF but not bFGF in highly metastatic human HCC cells. Exposure to 3000 IU/ml IFN-α reduced mRNA transcripts of VEGF in the human HCC cell line MHCC97. We also found that in vitro incubation with IFN-α inhibited the release of VEGF.

The metastatic orthotopic model of human HCC in nude mice LCI-D20 used in this study is a human-like model with high metastatic potential. The highly metastatic MHCC97 cell line originates from the LCI-D20 tumor. VEGF has been investigated as a potent mediator of HCC angiogenesis, metastasis, and recurrence and is known to be upregulated in most cases of HCC. Expression of VEGF correlates with abundant microvessel growth and a poor prognosis in HCC.[16–20,41–43] Our results showed that both VEGF and bFGF expressed during intrahepatic recurrence and metastasis and IFN-α downregulated the expression of VEGF to inhibit angiogenesis within the tumor and further prevent metastasis in our model. VEGF may be a principal preangiogenic molecule that stimulates HCC angiogenesis. The detailed molecular mechanism of how IFN-α downregulates the expression of VEGF must be addressed.

**Table 3.** In vitro inhibitor of VEGF protein expression by IFN-α

| IFN-α (IU/ml) | VEGF concentrations (pg/ml) | | |
|---|---|---|---|
| | 2 hr | 8 hr | 24 hr |
| 0 | 542.4 ± 77.5 | 653.3 ± 75.5 | 1631.6 ± 162.6 |
| 1000 | 361.9 ± 82.6 | 538.8 ± 52.4 | 875.5 ± 111.4* |
| 3000 | 425.8 ± 70.7 | 465.8 ± 93.1 | 702.9 ± 112.9* |

MHCC97 cells were cultured in the presence or absence of IFN-α. The expression of VEGF in supernate was measured by enzyme-linked immunosorbent assay.
*$P < 0.01$.

## CONCLUSION

We have shown that systemic therapy with high-dose and long-term IFN-α downregulates the expression of VEGF. The results suggest a mechanism by which IFN-α inhibits tumor-induced angiogenesis and thus prevents HCC recurrence and metastasis. VEGF seems to have an important role in HCC angiogenesis in preventing recurrence and metastasis of HCC.

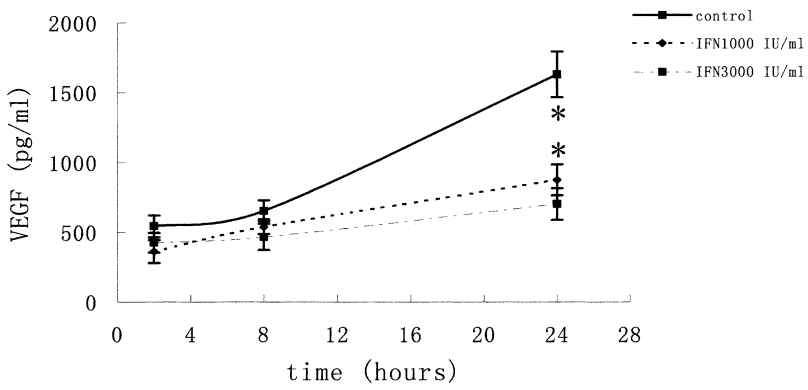


**Fig. 4.** VEGF concentrations were measured in the supernate of MHCC97 cells incubated in medium (control cells) or exposure to IFN-α at differing dosages (1000 IU/ml and 3000 IU/ml) by enzyme-linked immunosorbent assay.

REFERENCES

1. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990. Int J Cancer 1999;80:827–841.
2. Pisani P, Parkin DM, Bray F, Ferlay J. Estimates of the worldwide mortality of 25 major cancers in 1990. Int J Cancer 1999;83:18–29.
3. Parkin DM, Pisani P, Ferlay J. Global cancer statistics. CA Cancer J Clin 1999;49:33–64.
4. Li LD, Lu FZ, Zhang SW, Mu R, Sun XD, Huang-Pu XM, Sun J, Zhao YS, Ou-Yang NH, Rao KQ, Chen YD, Sun AM, Xue ZF, Xia Y. Research on characteristics of mortality spectrum and type composition of malignant tumors in China. Chin J Oncol 1997;19:323–328 (in Chinese).
5. Tang ZY. Surgery of hepatocellular carcinoma with special reference to studies on metastasis and recurrence. Gastroenterol Today 2000;4:191–195.
6. Adachi E, Maeda T, Matsumata T, Shirabe K, Kinukawa N, Sugimachi K, Tsuneyoshi M. Risk factors for intrahepatic recurrence in human small hepatocellular carcinoma. Gastroenterology 1995;108:768–775.
7. Vermeulen PB, Diriz LY, Martin M, Lemmens J, Van Oosterom AT. Serum basic fibroblast growth factor and vascular endothelial growth factor in metastatic renal cell carcinoma treated with interferon-α-2b. J Natl Cancer Inst 1997; 89:1316–1317.
8. Tedjarati S, Baker CH, Apte S, Huang S, Wolf JK, Killion JJ, Fidler IJ. Synergistic therapy of human ovarian carcinoma implanted orthotopically in nude mice by optimal biological dose of pegylated interferon α combined with paclitaxel. Clin Cancer Res 2002;8:2413–2422.
9. Folkman J. Seminars in medicine of the Beth Israel Hospital, Boston. Clinical application of research on angiogenesis. N Engl J Med 1995;333:1757–1763.
10. Fidler IJ, Ellis LM. The implications of angiogenesis to the biology and therapy of cancer metastasis. Cell 1994; 79:185–188.
11. Sun HC, Tang ZY, Li XM, Zhou YN, Sun BR, Ma ZC. Immunohistochemical study of angiogenesis in hepatocellular carcinoma: Its relationship with prognosis. J Cancer Res Clin Oncol 1999;125:419–426.
12. Poon RT, Ng IO, Lau C, Yu WC, Yang ZF, Fan ST, Wong J. Tumor microvessel density as a predictor of recurrence after resection of hepatocellular carcinoma: A prospective study. J Clin Oncol 2002;20:1775–1785.
13. Wang L, Tang ZY, Qin LX, Wu XF, Sun HC, Xue Q, Ye SL. High-dose and long-term therapy with interferon-alfa inhibits tumor growth and recurrence in nude mice bearing human hepatocellular carcinoma xenografts with high metastatic potential. Hepatology 2000;32:43–48.
14. Hanahan D, Folkman J. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. Cell 1996; 86:353–364.
15. Dvorak HF, Brown LF, Detmar M, Dvorak AM. Vascular permeability factor/vascular endothelial growth factor, microvascular hyperpermeability, and angiogenesis. Am J Pathol 1995;146:1029–1039.
16. Poon RT, Ng IO, Lau C, Zhu LX, Yu WC, Lo CM, Fan ST, Wong J. Serum vascular endothelial growth factor predicts venous invasion in hepatocellular carcinoma: A prospective study. Ann Surg 2001;233:227–235.
17. Li XM, Tang ZY, Qin LX, Zhou J, Sun HC. Serum vascular endothelial growth factor is a predictor of invasion and metastasis in hepatocellular carcinoma. J Exp Clin Cancer Res 1999;18:511–517.
18. Qin LX, Tang ZY. The prognostic molecular markers in hepatocellular carcinoma. World J Gastroenterol 2002; 8:385–392.
19. Yoshiji H, Yoshii J, Ikenaka Y, Noguchi R, Yanase K, Tsujinoue H, Imazu H, Fukui H. Suppression of the renin-angiotensin system attenuates vascular endothelial growth factor-mediated tumor development and angiogenesis in murine hepatocellular carcinoma cells. Int J Oncol 2002; 20:1227–1231.
20. Zhou J, Tang ZY, Fan J, Wu ZQ, Li XM, Liu YK, Liu F, Sun HC, Ye SL. Expression of platelet-derived endothelial cell growth factor and vascular endothelial growth factor in hepatocellular carcinoma and portal vein tumor thrombus. J Cancer Res Clin Oncol 2000;126:57–61.
21. Poon RT, Ng IO, Lau C, Yu WC, Fan ST, Wong J. Correlation of serum basic fibroblast growth factor levels with clinicopathologic features and postoperative recurrence in hepatocellular carcinoma. Am J Surg 2001;182:298–304.
22. El-Assal ON, Yamanoi A, Ono T, Kohno H, Nagasue N. The clinicopathological significance of heparanase and basic fibroblast growth factor expressions in hepatocellular carcinoma. Clin Cancer Res 2001;7:1299–1305.

23. Mise M, Arii S, Higashituji H, Furutani M, Niwano M, Harada T, Ishigami S, Toda Y, Nakayama H, Fukumoto M, Fujita J, Imamura M. Clinical significance of vascular endothelial growth factor and basic fibroblast growth factor gene expression in liver tumor. Hepatology 1996;23:455–464.
24. Yoshiji H, Kuriyama S, Yoshii J, Ikenaka Y, Noguchi R, Hicklin DJ, Huber J, Nakatani T, Tsujinoue H, Yanase K, Imazu H, Fukui H. Synergistic effect of basic fibroblast growth factor and vascular endothelial growth factor in murine hepatocellular carcinoma. Hepatology 2002;35:834–842.
25. Sun FX, Tang ZY, Liu KD, Ye SL, Xue Q, Gao QM, Ma ZC. Establishment of a metastatic model of human hepatocellular carcinoma in nude mice via orthotopic implantation of histologically intact tissues. Int J Cancer 1996;66:239–243.
26. Yang R, Rescorla FJ, Reilly CR, Fanght PR, Sanhvi NT, Lumeng L, Franklin TD Jr, Grosfeld JL. A reproducible rat liver cancer model for experimental therapy: Introducing a technique of intrahepatic tumor implantation. J Surg Res 1992;52:193–198.
27. Weidner N, Semple JP, Welch WR, Folkman J. Tumor angiogenesis and metastasis correlation in invasive breast carcinoma. N Engl J Med 1991;324:1–8.
28. Tian J, Tang ZY, Ye SL, Liu YK, Chen J, Xue Q. New human hepatocellular carcinoma (HCC) cell line with highly metastatic potential (MHCC) and its expression of the factors associated with metastasis. Br J Cancer 1999;81:814–821.
29. Wu WZ, Sun HC, Shen YF, Chen J, Wang L, Huang XW, Li Y, Tang ZY, Liu KD. Interferon alpha down-regulated VEGF expression through PI3 Kinase and MAP kinase signaling pathways in MHCC97 cells. J Cell Sci (Submitted).
30. Less JR, Posner MC, Skalak TC, Wolmark N, Jain RK. Geometric resistance and microvascular network architecture of human colorectal carcinoma. Microcirculation 1997;4:25–33.
31. Fox SB, Harris AL. Markers of tumor angiogenesis: Clinical applications in prognosis and anti-angiogenic therapy. Invest New Drugs 1997;15:15–28.
32. Risau W. What, if anything, is an angiogenic factor? Cancer Metastasis Rev 1996;15:149–151.
33. Iruela-Arispe ML, Dvorak HF. Angiogenesis: A dynamic balance of stimulators and inhibitors. Thromb Haemostas 1997; 78:672–677.
34. Indraccolo S, Gola E, Rosato A, Minuzzo S, Habeler W, Tisato V, Roni V, Esposito G, Morini M, Albini A, Noonan DM, Ferrantini M, Amadori A, Chieco-Bianchi L. Differential effects of angiostatin, endostatin and interferon-alpha (1) gene transfer on in vivo growth of human breast cancer cells. Gene Ther 2002;9:867–878.
35. Singh RK, Gutman M, Bucana CD, Sanchez R, Llansa N, Filder IJ. Interferons α and β downregulate the expression of basic fibroblast growth factor in human carcinomas. Proc Natl Acad Sci USA 1995;92:4562–4566.
36. Watanabe H, Iwase M, Ohashi M, Nagumo M. Role of interleukin-8 secreted from human oral squamous cell carcinoma cell lines. Oral Oncol 2002;38:670–679.
37. Oliveira IC, Sciavolino PJ, Lee TH, Vilcek J. Down-regulation of interleukin-8 gene expression in human fibroblasts: Unique mechanism of transcriptional inhibition of interferon. Proc Natl Acad Sci USA 1992;89:9049–9053.
38. Ma Z, Qin H, Benveniste EN. Transcriptional suppression of matrix metalloproteinase-9 gene expression by IFN-gamma and IFN-beta: Critical role of STAT-1 alpha. J Immunol 2001;167:5150–5159.
39. Kato N, Nawa A, Tamakochi K, Kikkawa F, Suganuma N, Okamoto T, Goto S, Tomoda Y, Hamaguchi M, Nakajima M. Suppression of gelatinase production with decreased invasiveness of choriocarcinoma cells by human recombinant interferon-β. Am J Obstet Gynecol 1995;172:601–606.
40. Ulisse S, Gionchetti P, D'Alo S, Russo FP, Pesce I, Ricci G, Rizzello F, Helwig U, Cifone MG, Campieri M, De Simone C. Expression of cytokines, inducible nitric oxide synthase, and matrix metalloproteinases in pouchitis: Effects of probiotic treatment. Am J Gastroenterol 2001;96:2691–2699.
41. Ng IO, Poon RT, Lee JM, Fan ST, Ng M, Tso WK. Microvessel density, vascular endothelial growth factor and its receptors Flt-1 and Flk-1/KDR in hepatocellular carcinoma. Am J Clin Pathol 2001;116:838–845.
42. Li XM, Tang ZY, Zhou G, Lui YK, Ye SL. Significance of vascular endothelial growth factor mRNA expression in invasion and metastasis of hepatocellular carcinoma. J Exp Clin Cancer Res 1998;17:13–17.
43. Baek JH, Jang JE, Kang CM, Chung HY, Kim ND, Kim KW. Hypoxia-induced VEGF enhances tumor survivability via suppression of serum deprivation-induced apoptosis. Oncogene 2000;19:4621–4631.

# Achalasia and Chest Pain: Effect of Laparoscopic Heller Myotomy

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Some patients with achalasia complain of chest pain in addition to dysphagia and regurgitation. Chest pain is said to be most common in young patients who have been symptomatic for a short time, and who often have vigorous achalasia (distal esophageal amplitude ⩾37 mm Hg). Although pneumatic dilatation is reported to improve chest pain in 20% of patients, the effect of laparoscopic Heller myotomy on chest pain is unknown. The aim of this study was to determine the following in achalasia: (1) the prevalence of chest pain; (2) the clinical and manometric profiles of patients with chest pain; and (3) the effect of laparoscopic Heller myotomy. Between 1990 and 2001, a total of 211 patients with achalasia were studied (upper gastrointestinal series, esophagoduodenoscopy, and manometry). A total of 117 patients (55%) had chest pain in addition to dysphagia and regurgitation; 63 (54%) of these 117 patients underwent laparoscopic Heller myotomy and Dor fundoplication. Median follow up was 24 months. Age (49 ± 16 years vs. 51 ± 14 years [mean ± SD]), duration of symptoms (71 ± 91 months vs. 67 ± 92 months [mean ± SD]), and presence of vigorous achalasia (50% vs. 47%) were similar in those with and without chest pain. Ten (16%) of the 63 patients with chest pain who underwent Heller myotomy had vigorous achalasia. Postoperatively chest pain resolved in 84% and improved in 11% of patients. There was no difference in clinical outcome between patients with and without vigorous achalasia. These data demonstrate the following: (1) chest pain was present in 55% of patients with esophageal achalasia; (2) chest pain was not related to age, duration of symptoms, or manometric findings; and (3) laparoscopic Heller myotomy improved chest pain in 95% of patients, regardless of the manometric findings. Thus laparoscopic Heller myotomy was highly effective in treating achalasia with chest pain. (J GASTROINTEST SURG 2003;7:595–598) 

KEY WORDS: Esophageal achalasia, vigorous achalasia, chest pain, esophageal manometry, pneumatic dilatation, Heller myotomy

Some patients who have achalasia complain of chest pain in addition to dysphagia and regurgitation. Chest pain has been reported to be more common in young patients who have been symptomatic for a short time[1] and who have vigorous achalasia (distal esophageal amplitude ⩾37 mm Hg).[2,3] Although pneumatic dilatation is reported to improve chest pain in approximately 20% of such patients,[1] the effect of laparoscopic Heller myotomy on chest pain is unknown. The aims of this study were to determine in achalasia (1) the prevalence of chest pain, (2) the clinical presentation and manometric profile of patients with chest pain, and (3) the effect of laparoscopic Heller myotomy.

## PATIENTS AND METHODS

Between January 1990 and October 2001, a total of 211 patients with esophageal achalasia were evaluated in the Swallowing Center at the University of California San Francisco. There were 114 men and 97 women, whose mean age was 50 years (range 14 to 97 years). Symptoms had been present for an average of 69 months (range 1 to 480 months). Eighty patients (38%) had been treated by pneumatic dilatation (average of 2 per patient, range 1 to 13), four patients (2%) had been treated by intrasphincteric injection of botulinum toxin (average of 2 per patient, range 1 to 3), and 13 patients (6%) by a combination

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of pneumatic dilatation and botulinum toxin. Fifty-four percent of patients had been treated only with medications, mostly calcium channel blockers or proton pump inhibitors. Complaints included dysphagia in 173 patients (81%), regurgitation in 147 patients (69%), heartburn in 121 patients (57%), and chest pain in 117 patients (55%).

Sixty-three (54%) of the 117 patients who had chest pain underwent laparoscopic Heller myotomy and Dor fundoplication. There were 34 men and 29 women whose mean age was 44 years (range 14 to 80 years). The preoperative complaints included chest pain and dysphagia in all patients (100%), regurgitation in 43 patients (68%), and heartburn in 36 patients (57%). Symptoms had been present for an average of 77 months. Thirty-five patients had failed to respond to other forms of treatment before being referred for surgery. Specifically 25 patients (40%) had pneumatic dilatation (average of 2 per patient) and 10 patients (16%) had intrasphincteric botulinum toxin injections (average of 2 per patient), either alone (2 patients) or in conjunction with pneumatic dilatation (8 patients). Fourteen patients (22%) had been treated with calcium channel blockers or proton pump inhibitors.

### Clinical, Radiographic, and Endoscopic Findings

Patients scored the severity of their dysphagia, regurgitation, heartburn, and chest pain before and after the operation using a five-point scale ranging from 0 (no symptoms) to 4 (disabling symptoms). A barium esophagogram was performed to evaluate the gastroesophageal junction, and to assess the axis (straight/sigmoid) and diameter of the esophageal body. Endoscopy was performed to rule out the presence of peptic ulcer or neoplastic stricture.

### Esophageal Manometry

Medications that interfere with esophageal motility were discontinued 3 days before the study. The patients were studied after an overnight fast using an eight-lumen manometry catheter continuously perfused by a pneumohydraulic capillary infusion system connected to a polygraph. Position, pressure, and length of the lower esophageal sphincter (LES) were measured using the station pull-through technique. Esophageal body function was assessed by giving 10 wet swallows of 5 ml of water at 30-second intervals.[4] The following variables were assessed: (1) resting pressure of the LES (normal 14 to 24 mm Hg); (2) relaxation of the LES in response to swallowing; and (3) amplitude and propagation of peristalsis. Vigorous achalasia was defined by the presence of esophageal contractions with an amplitude of 37 mm Hg or higher.[5]

### Ambulatory Esophageal pH Monitoring

Patients were studied after an overnight fast. Acid-suppressing medications were discontinued 3 ($H_2$ blocking agents) to 14 (proton pump inhibitors) days before the study. During the study, patients consumed an unrestricted diet and took no medications for gastroesophageal reflux disease. The pH probe was placed 5 cm above the upper border of the manometrically determined LES.

### Surgical Treatment

Laparoscopic Heller myotomy and Dor fundoplication (180-degree anterior fundoplication) were performed in 63 patients with chest pain and in 61 patients without chest pain. The myotomy was 7 to 8 cm long and extended for 1.5 to 2.0 cm onto the gastric wall.[6]

### Follow-up

All patients were seen in follow-up 2 and 8 weeks postoperatively. Subsequently they were interviewed by phone at 3- to 4-month intervals. Mean length of follow-up was 26 months.

### Statistical Analysis

Student's $t$ test, Wilcoxon signed-rank test, and analysis of variance (ANOVA) were used for statistical evaluation of the data. All results are expressed as mean $\pm$ standard deviation (SD). Differences were considered significant at $P < 0.05$.

## RESULTS

### Prevalence of Chest Pain

At the time of presentation 117 patients (55%) complained of chest pain, whereas 94 patients (45%) did not. Ninety percent of patients had episodes of chest pain at least once a week and 10% every day. The pain was felt mostly in the retrosternal area and lasted from a few minutes to a few hours. It occurred mostly during the day and was often relieved by drinking water. Cardiac disease was excluded by clinical assessment by the primary physician in 98 patients (84%) and by specific testing by a cardiologist in 19 patients (16%). No patient described chest pain as the major complaint but rather in association with more bothersome and typical symptoms such as dysphagia or regurgitation.

**Table 1.** Clinical, radiologic, and manometric profiles of patients with and without chest pain

| | Patients with chest pain ($n$ = 117) | Patients without chest pain ($n$ = 94) | $P$ value |
|---|---|---|---|
| Age* | 49 ± 16 | 51 ± 14 | NS |
| Sex (F/M)* | 56/61 | 41/53 | NS |
| Duration of symptoms* | 71 ± 91 | 67 ± 67 | NS |
| Dysphagia (score 0–4)* | 2.7 ± 1.4 | 2.6 ± 1.5 | NS |
| Regurgitation (score 0–4)* | 1.8 ± 1.4 | 2.0 ± 1.5 | NS |
| Esophageal diameter (cm)* | 4.5 ± 0.7 | 4.3 ± 0.8 | NS |
| LES pressure (mm Hg)* | 15 ± 9 | 17 ± 11 | NS |
| LES relaxation (% of patients) | | | |
| Absent | 46 | 37 | NS |
| Partial | 44 | 52 | NS |
| Complete | 10 | 11 | NS |
| Vigorous achalasia (% of patients) | 50 | 47 | NS |

NS = not significant.
*Values are means ± standard deviation.

### Clinical and Manometric Profile of Patients With and Without Chest Pain

Age (49 ± 16 years vs. 51 ± 14 years [mean ± SD]), duration of symptoms (71 ± 91 months vs. 67 ± 92 months {mean ± SD]), and presence of vigorous achalasia (50% vs. 47%) were similar in patients with and without chest pain (Table 1).

### Ambulatory Esophageal pH Monitoring

Ambulatory pH monitoring was performed in 57 (49%) of 117 patients. A pathologic amount of reflux was found in eight patients (14%) who had already undergone pneumatic dilatation. The distinction between chest pain and heartburn was based on the patient's description of each symptom (often patients described heartburn and chest pain independently).

### Outcome of Laparoscopic Heller Myotomy and Dor Fundoplication

Sixty-three (54%) of the 117 patients who had chest pain underwent laparoscopic Heller myotomy and Dor fundoplication. All operations were completed laparoscopically. The patients were allowed an unrestricted diet after 25 ± 10 hours, and they left the hospital after 38 ± 24 hours. Postoperatively chest pain resolved in 84% and improved in 11% of patients (Table 2). Ten (16%) of the 63 patients with chest pain who underwent Heller myotomy had vigorous achalasia. There was no difference in the outcome of the operation between patients with and without vigorous achalasia. In addition, there was no difference in the postoperative swallowing status in patients with and without chest pain (% excellent/good results 94% vs. 93%; $P$ = NS).

## DISCUSSION

These data show that (1) chest pain was present in 55% of patients with esophageal achalasia; (2) chest pain was not related to age, duration of symptoms, or manometric findings, and (3) laparoscopic Heller myotomy improved chest pain in 95% of patients, regardless of the manometric findings.

### Clinical Presentation and Manometric Profiles of Patients With Achalasia

Dysphagia and regurgitation are the typical symptoms of achalasia, and the effect of therapy is usually measured by the control of these symptoms. Traditionally, less emphasis has been placed on the incidence of chest pain in patients with achalasia and the effect of therapy on this symptom. Chest pain has been reported in 48% to 64% of patients with achalasia,[1,5] and it was present in 55% of our patients. It is unclear why some patients have dysphagia alone, whereas others also experience chest pain. It has been said that chest pain occurs more often in young patients with a short duration of symptoms and high-amplitude, nonpropulsive contractions in the body of the esophagus typical of vigorous achalasia.[2,3,7] As the

**Table 2.** Effect of laparoscopic Heller myotomy on symptoms of achalasia

| | Preoperative* | Postoperative* | $P$ value |
|---|---|---|---|
| Dysphagia (0–4) | 3.5 ± 0.6 | 0.4 ± 0.9 | <0.05 |
| Regurgitation (0–4) | 1.9 ± 1.5 | 0.1 ± 0.4 | <0.05 |
| Chest pain (0–4) | 2.7 ± 0.9 | 0.3 ± 0.9 | <0.05 |

*Values are means ± standard deviation.

disease progresses and esophageal dilatation develops, esophageal contractions decrease in amplitude and chest pain eventually subsides in most patients.[8] Our findings contradict this commonly held scenario. There were no differences in age, duration of symptoms, or esophageal diameter in patients with and without chest pain. In addition, vigorous achalasia affected a similar percentage of patients in each group, suggesting that the high amplitude of contractions is not the cause of the pain. Similar findings comparing classic and vigorous achalasia have been reported by others.[5,7]

## Effect of Laparoscopic Heller Myotomy and Dor Fundoplication on Chest Pain

The therapeutic options for esophageal achalasia include intrasphincteric injection of botulinum toxin, pneumatic dilatation, and surgery. Traditionally, these treatment modalities have been judged in regard to their effect on dysphagia,[9–15] but the effect on chest pain has not been thoroughly studied.

The effect of intrasphincteric botulinum toxin on esophageal pain is unknown. Pasricha et al.[13] reported that dysphagia responded to botulinum toxin in patients with vigorous achalasia, but there was no mention of the effect on chest pain. In the most optimistic reports, pneumatic dilatation relieved dysphagia in approximately 70% of patients,[14] but its effect decreased over time, and only 50% of patients were still improved after 10 years.[15] Pneumatic dilatation is even less effective for control of chest pain, with a beneficial response noted by one investigator in 16% of patients.[1] In those with persistent pain, a gradual improvement occurred over a 10-year period. Our data show that chest pain resolved in 84% of patients and improved in 11%. This suggests that the improvement is the result of improved esophageal emptying. The operation we performed in patients with chest pain was identical to that for patients without chest pain. Thus it is unnecessary to perform a longer proximal myotomy as would be the case for patients with diffuse esophageal spasm and chest pain.[16]

In summary, results of our study show that laparoscopic Heller myotomy improves chest pain and dysphagia in patients with esophageal achalasia. This is another reason to consider laparoscopic myotomy to be the treatment of choice for this disease.

REFERENCES

1. Eckardt VF, Stauf B, Bernhard G. Chest pain in achalasia: Patient characteristics and clinical course. Gastroenterology 1999;116:1300–1304.
2. Bondi JL, Godwin DH, Garrett JM. "Vigorous" achalasia. Its clinical interpretation and significance. Am J Gastroenterol 1972;58:145–155.
3. Sanderson DR, Ellis FH, Schlegel JF, Olsen AM. Syndrome of vigorous achalasia: Clinical and physiologic observations. Dis Chest 1967;52:508–517.
4. Patti MG, Diener U, Molena D. Esophageal achalasia: Preoperative assessment and postoperative follow-up. J GASTROINTEST SURG 2001;5:11–122.
5. Camacho-Lobato L, Katz PO, Eveland J, Vela M, Castell DO. Vigorous achalasia. Original description requires minor change. J Clin Gastroenterol 2001;33:373–377.
6. Patti MG, Molena D, Fisichella PM, Whang K, Yamada H, Perretta S, Way LW. Laparoscopic Heller myotomy and Dor fundoplication for achalasia: Analysis of successes and failures. Arch Surg 2001;136:870–877.
7. Goldenberg SP, Burrell M, Fette GG, Vos C, Traube M. Classic and vigorous achalasia: A comparison of manometric, radiographic, and clinical findings. Gastroenterology 1991; 101:743–748.
8. Shiino Y, Houghton SG, Filipi CJ, Awad ZT, Tomonaga T, Marsh RE. Manometric and radiographic verification of esophageal body decompensation for patients with achalasia. J Am Coll Surg 1999;189:158–163.
9. Zaninotto G, Costantini M, Molena D, Portale G, Costantino M, Nicoletti L, Ancona E. Minimally invasive surgery for esophageal achalasia. J Laparoendosc Adv Surg Tech 2001; 11:351–359.
10. Ackroyd R, Watson DI, Devitt PG, Jamieson GG. Laparoscopic cardiomyotomy and anterior partial fundoplication for achalasia. Surg Endosc 2001;15:683–686.
11. Finley RJ, Clifton JC, Stewart KC, Graham AJ, Worsley DF. Laparoscopic Heller myotomy improves esophageal emptying and symptoms of achalasia. Arch Surg 2001;136:892–896.
12. Sharp KW, Khaitan L, Scholz S, Holzman MD, Richards WO. 100 consecutive minimally invasive Heller myotomies: Lessons learned. Ann Surg 2002;235:631–639.
13. Pasricha PJ, Rai R, Ravich WJ, Hendrix TR, Kalloo AN. Botulinum toxin for achalasia: Long-term outcome and predictors of response. Gastroenterology 1996;110:1410–1415.
14. Vaezi MF, Richter JE, Wilcox CM, Schroeder PL, Birgisson S, Slaughter RL, Koehler RE, Baker ME. Botulinum toxin versus pneumatic dilatation in the treatment of achalasia: a randomized trial. Gut 1999;44:231–239.
15. West RL, Hirsch DP, Bartelsman JF, de Borst J, Ferwerda G, Tytgat GN, Boeckxstaens GE. Long term results of pneumatic dilation in achalasia followed for more than 5 years. Am J Gastroenterol 2002;97:1346–1351.
16. Parrilla Paricio P, Martinez de Haro LF, Ortiz Escandell A, Morales Cuenca G, Molina Martinez J. Short myotomy for vigorous achalasia. Br J Surg 1993;80:1540–1542.

# Intratracheal Long-Term pH Monitoring: A New Method to Evaluate Episodes of Silent Acid Aspiration in Patients After Esophagectomy and Gastric Pull Up

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Aspiration of gastric contents is considered a leading cause of postoperative pulmonary complications after esophagectomy and gastric pull up but has been difficult to diagnose. We used intratracheal long-term pH monitoring to evaluate the prevalence of aspiration of gastric contents in patients undergoing these operations. Continuous intratracheal pH monitoring was carried out during the first 72 postoperative hours in 16 patients with esophageal carcinoma who had undergone esophagectomy and gastric pull up. A drop in the pH to less than 4 was defined as an episode of acid aspiration. All patients except one tolerated the probe without any difficulties. Episodes of acid aspiration could be detected in 12 (80%) of 15 patients (5 of 8 after transhiatal esophagectomy, 7 of 7 after transthoracic esophagectomy, 2 of 5 with reconstruction in the anterior mediastinum, and 9 of 10 with reconstruction in the posterior mediastinum). The number of aspiration episodes was significantly higher during postoperative day 1 ($P = 0.03$) compared to postoperative days 2 and 3. Two patients developed pneumonia later in the postoperative course. Both of them had several episodes of acid aspiration detected by pH monitoring immediately postoperatively. Intratracheal pH monitoring is a safe, feasible, and well-tolerated method for detecting episodes of acid aspiration after esophagectomy and gastric pull up. Aspiration of gastric contents is a common phenomenon particularly during the first 24 postoperative hours after transthoracic esophagectomy and gastric pull up in the posterior mediastinum and appears to correlate with the development of postoperative pneumonia. (J GASTROINTEST SURG 2003;7:599–602) 

KEY WORDS: Intratracheal pH, monitoring, silent aspiration, esophagectomy

Pulmonary complications are the leading cause of morbidity and mortality after esophagectomy. The incidence of pulmonary complications after esophageal resection varies from 5% to 55%.[1–4] After esophageal resection, anatomic and physiologic alterations affecting pulmonary function occur as a result of intraoperative pulmonary trauma, intrathoracic organ interposition, and postoperative aspiration. Aspiration may cause swallowing impairment due to disturbances of the upper esophageal sphincter.[5,6] Excessive reflux of duodenal juice[7,8] and the ability of the intrathoracic stomach to produce acid despite esophagectomy-associated vagotomy[7,9,10] are potential sources of refluxate.

In the present study we used this continuous production of acid in the intrathoracic stomach to investigate the frequency of aspiration episodes by means of intratracheal pH monitoring in the early postoperative period in patients who had undergone esophagectomy and gastric pull up for esophageal cancer.

## PATIENTS AND METHODS

### Patients

Sixteen patients (13 men and 3 women, median age 59.5 years [range 44 to 69 years]) diagnosed as having esophageal carcinoma (adenocarcinoma in 10, squamous cell carcinoma in 6), who had undergone

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subtotal esophagectomy (transhiatal route in 9, right transthoracic route in 7) and reconstruction with a gastric tube and cervical anastomosis (anterior mediastinum in 6, posterior mediastinum in 10), were included in the study. The study was approved by the local ethics committee, and all patients gave informed consent. A nasogastric tube was placed in all patients to avoid postoperative distention of the interposed stomach, and all patients were given acid suppression medication postoperatively ($H_2$ blocker [Famotidin, 20 mg 3 times/day]). In addition, patients were kept in a semi-upright position with the head elevated throughout the study.

### pH Monitoring

Intratracheal pH monitoring was performed using glass electrodes (Medtronic GmbH, Düsseldorf, Germany). After the patient entered the recovery room and was in stable condition, a pH probe was passed through the nasotracheal tube; the probe was positioned 1 cm below the distal end of the tube where it remained until extubation, generally within 2 to 12 hours postoperatively. After extubation, the pH probe was placed 1 cm distal to the vocal chords under bronchoscopic guidance, and the measurement was continued for up to 72 hours. An episode of acid aspiration was defined as a drop in pH to less than 4, and the data were analyzed manually over 24-hour periods (Fig. 1). In addition, an intragastric pH probe was placed during the first 24 hours in all patients to assess acid production in the interposed stomach.

## RESULTS

With the exception of one patient who requested removal of the tube after 48 hours because of a sore throat and hoarseness, all patients tolerated the intratracheal pH probe very well. The 72-hour postoperative measurement was completed in 15 patients. There were no complications associated with measurement.

Despite acid suppression with an $H_2$ blocker, the median intragastric pH during the monitoring period was 2.9. The intragastric pH was less than 4 over more than 50% of the measuring period in all patients.

Episodes of acid aspiration on intratracheal pH monitoring were detected in 12 (80%) of 15 patients in whom the measurement was completed. A significantly greater number of episodes of acid aspiration occurred during the first 24 postoperative hours compared to the second or third 24-hour period. A greater number of patients had episodes of acid aspiration during the first 24 postoperative hours compared to the second and third 24-hour periods (Table 1).

Periods of acid aspiration were detected in only five of eight patients who had undergone transhiatal esophagectomy but in all seven patients who had a transthoracic esophagectomy. Among patients who underwent reconstruction in the anterior mediastinum, episodes of acid aspiration were detected in two of five patients but in 9 of 10 patients after reconstruction in the posterior mediastinum (Table 2).

In the later postoperative course, two patients developed pneumonia as demonstrated both clinically


**Fig. 1.** Twenty-four-hour intratracheal pH monitoring showing two episodes of acid aspiration (*arrows*).

**Table 1.** Episodes of acid aspiration detected during the postoperative study period in 15 patients who completed the measurement

| Patient | 0–24 hr | 25–48 hr* | 49–72 hr* |
|---|---|---|---|
| B.S.† | 6 | 3 | 0 |
| L.G. | 0 | 0 | 0 |
| M.K. | 0 | 0 | 0 |
| Z.H. | 1 | 0 | 0 |
| Z.G. | 1 | 0 | 0 |
| F.P. | 1 | 1 | 0 |
| G.W. | 1 | 0 | 0 |
| S.D. | 2 | 0 | 0 |
| H.R. | 2 | 0 | 0 |
| S.W.† | 5 | 2 | 0 |
| H.P. | 1 | 1 | 0 |
| Z.L. | 0 | 0 | 0 |
| P.H. | 1 | 0 | 0 |
| W.K. | 1 | 1 | 0 |
| M.A. | 2 | 0 | 0 |

*$P < 0.05$ compared to the first 24-hour postoperative period (Mann-Whitney U test).
†These patients developed pneumonia during the later postoperative course.

and radiographically. Both patients had episodes of acid aspiration detected during the first and second 24-hour periods (B.S. and S.W. in Table 1).

## DISCUSSION

Aspiration is a well-known cause of pulmonary complications in patients after subtotal esophagectomy and reconstruction with a gastric tube, but this has not been investigated sufficiently. We utilized the ability of the intrathoracic stomach to produce acid, which was verified by intragastric pH monitoring, to detect episodes of aspiration by means of intratracheal pH monitoring. A modification of this technique, with introduction of the intratracheal pH probe through the cricothyroid membrane, has been used by others to detect episodes of acid aspiration in patients with gastroesophageal reflux disease.[11,12] In our study only 1 of 16 patients was unable to tolerate the pH tube, and no complications occurred, which is an indication that the technique of intratracheal pH monitoring is safe, feasible, and well tolerated.

**Table 2.** Episodes of acid aspiration detected on intratracheal pH monitoring according to the operative technique used

| Operative technique | Total patients | Patients with episodes of acid aspiration |
|---|---|---|
| Resection | | |
| Transhiatal | 8 | 5 |
| Transthoracic | 7 | 7 |
| Reconstruction | | |
| Anterior mediastinum | 5 | 2 |
| Posterior mediastinum | 10 | 9 |

Others have used video radiographic tests to assess postoperative aspiration, and episodes of aspiration have been documented in 13% to 53% of patients after esophagectomy.[3,13] The present study shows that episodes of acid aspiration can be documented in up to 80% of patients when prolonged intratracheal pH monitoring is used. Aspiration of gastric juice after esophagectomy and gastric pull up is thus much more common than was previously realized.

Despite the fact that all patients were given an $H_2$ blocker three times per day for acid suppression, the interposed stomach still produced sufficient acid to result in a pH $< 4$ for more than 50% of the monitoring period. Similar data have been reported previously.[7,9] This finding indicates that in order to prevent acid reflux into the cervical esophagus and subsequent aspiration, stronger medications such as proton pump inhibitors are needed, particularly during the initial postoperative days. This approach, however, still will not solve the problem of reflux (and possible subsequent aspiration) of nonacid gastric and duodenal juices, which is common in mechanically ventilated patients.[14]

Although there were no significant differences between the operative techniques, there was a tendency for more patients to have reflux episodes detected when they had undergone a transthoracic resection with reconstruction in the posterior mediastinum. This is consistent with findings in other studies demonstrating the superiority of the transhiatal approach with regard to pulmonary complications.[15,16] However, no data are available to confirm that reconstruction in the anterior mediastinum leads to fewer pulmonary complications compared to reconstruction in the posterior mediastinum.[17] One possible factor could be the shorter distance to the cervical region when reconstruction is performed in the posterior mediastinum making regurgitation and subsequent aspiration more likely.[18] A second difference is that when the reconstruction is performed in the anterior mediastinum, the cervical esophagus is pulled anteriorly in order to create the cervical anastomosis. This "kinking" could work like an antireflux valve and prevent acid from flowing over the anastomosis causing episodes of acid aspiration.

Other investigators have performed video radiographic tests to assess aspiration during the late postoperative course when the oral intake was started.[13]

However, no data are available for the early postoperative course. We could show that a significantly greater number of patients had episodes of acid aspiration detected during the first 24 hours compared to the second and third 24-hour periods. In fact, not a single episode of aspiration was detected during the third 24-hour period. It is a well-known fact that tracheal tubes do not prevent leakage of fluid to the lungs.[19,20] This leakage instead takes place down longitudinal folds that are present in the cuff wall. Thus patients are best protected against aspiration when they are extubated as soon as possible. Two of the 15 patients developed pneumonia on postoperative days 5 and 8, respectively. On intratracheal pH monitoring, both patients had several episodes of acid aspiration detected during the first and second 24-hour periods, indicating that there might be a correlation between the number of postoperative aspiration periods and the development of pneumonia. Larger patient populations are required to actually prove that this correlation exists.

## CONCLUSION

The present study shows that intratracheal pH monitoring is a safe, feasible, and well-tolerated technique for detecting episodes of silent aspiration in patients after esophagectomy and gastric pull up. Aspiration of gastric content is a common phenomenon in these patients despite acid suppression with an $H_2$ blocker, especially when the operations are performed transthoracically and reconstructions are in the posterior mediastinum. The occurrence of silent episodes of aspiration seems to correlate with the development of pneumonia in the later postoperative course.

REFERENCES

1. Elman A, Giuli R, Sancho-Garnier H. Risk factors of pulmonary complications following esophagectomy in carcinoma of the oesophagus. Results of the prospective study conducted by the OESO group. In Siewert JR, Hölscher AH, eds. Diseases of the Oesophagus, 1st ed. Berlin: Springer, 1987, pp 224–228.
2. Nishi M, Hiramatsa J, Hioki K, et al. Pulmonary complications after subtotal esophagectomy. Br J Surg 1988;75: 527–530.
3. Bartels H, Siewert JR. [Postoperative lung complications: Special problems exemplified by esophageal surgery.] Langenbecks Arch Chir 1990;(Suppl II):1101–1107.
4. Dumont P, Wihelm JM, Hentz JG, et al. Respiratory complications after surgical treatment of esophageal cancer. A study of 309 patients according to the type of resection. Eur J Cardiothorac Surg 1995;9:539–543.
5. Sasaki A. Swallowing disorders after esophagectomy in thoracic esophageal cancer. Nippon Geka Gakkai Zasshi 1994; 95:359–367.
6. Ekberg O, Lindgren S, Schultze T. Pharyngeal swallowing in patients with paresis of recurrent nerve. Acta Radiol Diagn 1986;27:697–700.
7. Bonavina L, Anselmino M, Ruol A, et al. Functional evaluation of the intrathoracic stomach as an oesophageal substitute. Br J Surg 1992;79:529–532.
8. Mannell A, Hinder RA, San-Garde BA. The thoracic stomach: A study of gastric emptying, bile reflux and mucosal change. Br J Surg 1984;71:438–441.
9. Hashimoto M, Imamura M, Shimada Y, et al. Twenty-four hour monitoring of pH in the gastric tube replacing the resected oesophagus. J Am Coll Surg 1995;180:666–672.
10. Nishikawa M, Murakami T, Tangoku A, et al. Functioning of the intrathoracic stomach after esophagectomy. Arch Surg 1994;129:837–841.
11. Donnelly RJ, Berrisford RG, Jack CIA. Simultaneous tracheal and oesophageal pH monitoring: Investigating reflux-associated asthma. Ann Thorac Surg 1993;56:1029–1034.
12. Jack CIA, Walshaw MJ, Tran J, et al. Twenty-four-hour tracheal pH monitoring—a simple and non-hazardous investigation. Respir Med 1994;88:441–444.
13. Machimura T, Makuuchi H, Sugihara T, et al. Analysis of the swallowing movement for dysphagia after oesophageal cancer operation with video radiography. Nippon Geka Gakkai Zasshi 1989;90:286–290.
14. Wilmer A, Tack J, Frans E, et al. Duodenogastroesophageal reflux and esophageal mucosal injury in mechanically ventilated patients. Gastroenterology 1999;116:1293–1299.
15. Makela J, Laitinen S, Kairaluoma G. A comparison of transthoracic and transhiatal resection for thoracic oesophageal cancer. Observation of 30 years. Ann Chir Gynaecol 1991; 80:340–345.
16. Bolton JS, Sardi A, Bowen JC, et al. Transhiatal and transthoracic esophagectomy: A comparative study. J Surg Onco1 1992;51:249–253.
17. Bartels H, Thorban S, Siewert JR. Anterior versus posterior reconstruction after transhiatal esophagectomy. A randomized controlled trial. Br J Surg 1993;80:1141–1144.
18. Coral RP, Constant-Neto M, Silva IS, et al. The influence of the transposed stomach through the posterior mediastinum on the respiratory forced expiratory volume and forced vital capacity in patients with resected esophageal cancer. Dis Esoph 1998;11:48–50.
19. Young PJ, Rollison M, Downward G, et al. Leakage of fluid past the tracheal tube cuff in a bench top model. Br J Anaesth 1997;78:557–562.
20. Young PJ, Ridley SA, Downward G. Evaluation of a new design of tracheal tube cuff to prevent leakage of fluid to the lungs (Historical Lectures Encke 17/05/02). Br J Anaesth 1998;80:796–799.

# Behavior of Plasma Hemoglobin in an Experimental Model of Occlusive Mesenteric Ischemia

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The difficulties in establishing the diagnosis of mesenteric ischemia are responsible for the high mortality rate that is associated with this clinical condition. We studied the behavior of plasma hemoglobin in an experimental model of occlusive mesenteric ischemia in mice. Our results showed a clear relationship between the duration of ischemia and plasma hemoglobin levels. With regard to the time frames studied (3 hours, 6 hours, 12 hours, and 24 hours), comparison with control groups produced calculated *P* values of less than 0.01 for all time frames with the exception of the 3-hour group. This test may have the potential to aid in the diagnosis of mesenteric ischemia as well as the follow-up of its course after various therapeutic approaches. (J GASTROINTEST SURG 2003;7:603–605) 

KEY WORDS: Mesenteric ischemia, diagnosis, plasma hemoglobin, experimental

Mesenteric ischemia is a condition that still poses major difficulties in its clinical management. Despite technologic advances in the treatment of this disease, its mortality continues to be high. The major reason is the difficulty in establishing the diagnosis. Even the significant advantage provided by angiographic studies is not sufficient to solve this problem. A simple test with good sensitivity and specificity, alone or in combination with other parameters, could greatly contribute toward improving this scenario. This report analyzes the results of an experimental study that was carried out to assess the behavior of plasma hemoglobin in mesenteric ischemia.

## METHODS

The purpose of the study was to examine the behavior of plasma hemoglobin in an experimental model of occlusive mesenteric ischemia. Experiments were performed on anesthetized (ether) adult female mice according to the standards for the use and care of laboratory animals. The study was approved by the local research committee. Ischemia was produced by occlusion of the proximal mesentery (small bowel) using surgical sutures (Polycot 000; Johnson & Johnson–Ethicon, São Paulo, Brazil). After the induction of ischemia, the following four time frames were studied: 3 hours, 6 hours, 12 hours, and 24 hours. A sham procedure (opening and closing the abdominal cavity) was also used for each of the time frames (i.e., 10 mice were used in each group for a total of 80 mice). Just before autopsy, blood samples were collected through cardiac puncture, and the plasma was centrifuged and kept at −8° C. Analyses of plasma hemoglobin were performed using the TMB/$H_2O_2$ reaction (Sigma catalogue number 527-A, Sigma, São Paulo, Brazil). Because different groups of mice were used for each time frame studied (n = 80 mice), statistical analyses were carried out by means of the Mann-Whitney U test.

## RESULTS

Of the 80 mice, four died. All deaths occurred in the 24-hour ischemic group. The biochemical results are presented in Table 1 and Fig. 1. The data show an increase in plasma hemoglobin levels that was proportional to the duration of bowel ischemia. This increase reached statistical significance in the 6-, 12-, and 24-hour groups. Autopsy confirmed the presence of ischemia in all mice in the experimental groups

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**Table 1.** Plasma hemoglobin measurements (mean values)

| Time of ischemia | Control group (mg/dl) | Ischemic group (mg/dl) | *P* value (Mann-Whitney) |
|---|---|---|---|
| 3 h | 61.68 (n = 10) | 663.43 (n = 10) | 0.650 |
| 6 h | 45.47 (n = 10) | 116.66 (n = 10) | 0.007 |
| 12 h | 24.70 (n = 10) | 194.93 (n = 10) | 0.001 |
| 24 h | 81.66 (n = 10) | 353.15 (n = 6) | 0.002 |

(n = 40), as well as normal intestine in all mice in the control groups (n = 40).

## DISCUSSION

The mortality rate for mesenteric ischemia remains high. Mansour,[1] in reviewing a large series, found mortality rates ranging from 60% to 100%. A French study analyzed changes in mortality with regard to different time frames and showed that rates decreased from 77% to 59% between 1980–85 and 1990–95, respectively.[2] According to these numbers, it is easy to see that our improvements were far from satisfactory. The difficulty in diagnosing mesenteric ischemia is the main reason for these results, and this difficulty is primarily due to the scarcity of clinical signs. It is well known that the sudden occurrence of abdominal pain is one of the very few consistent features of mesenteric ischemia. Unfortunately, peritoneal signs do not occur until the bowel becomes necrotic.[3] The clinical assessment of mesenteric ischemia, even when done by experienced physicians, is incorrect in approximately 30% of cases.[4] In 1977, Boley et al.[5] showed that an "aggressive" approach could reduce the mortality rate from 70% to 80% to approximately 40%. Liberal and early use of angiography was the backbone of this "aggressive" approach. Twenty years later, Boley et al.[6] reaffirmed that, despite the improvements over the past two decades, this clinical entity still produces poor results. In addition to angiography, other tests have also been used, among them computed tomography, duplex ultrasonography, nuclear magnetic resonance imaging, measurements of "natural" magnetic fields, radioxenon washout analyses, and tonometry.[7–12] Although all of these represent signigicant contributions, limitations still create important diagnostic dilemmas when considering their clinical application.

The reason why we chose to use plasma hemoglobin levels to diagnose mesenteric ischemia is that ischemic bowel was, in our minds, very likely to produce hemolysis. Our results show a clear correlation between the duration of ischemia and plasma hemoglobin levels, confirming our initial hypothesis. After we had finished analyzing our data, we found a report, published in 1969, demonstrating an increase in hemoglobin levels during experimental ischemia.[13]

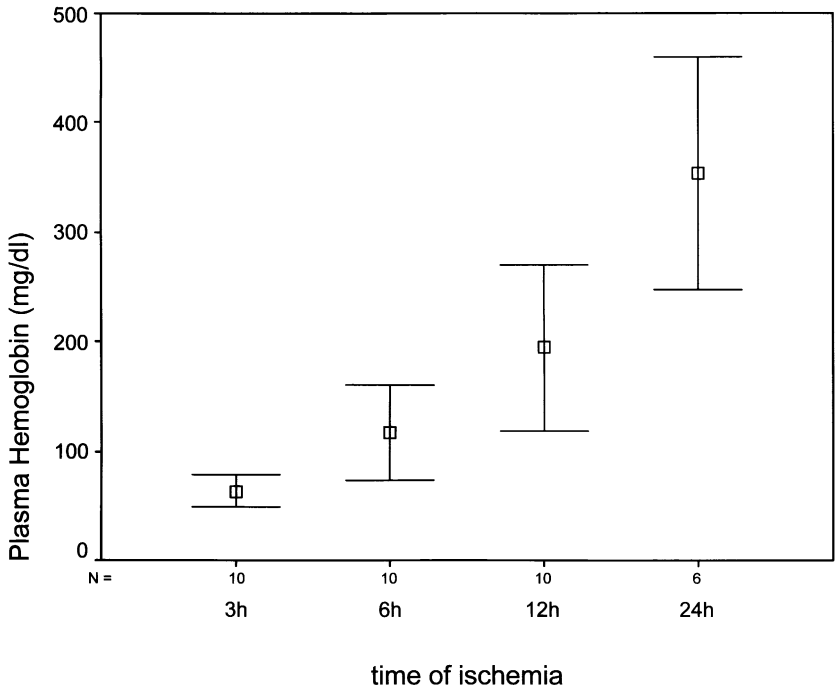


**Fig. 1.** Plasma hemoglobin levels in the ischemic groups (mean values and 95% confidence intervals).

Although this report focused on acid phosphatase and ribonuclease levels, an increase in plasma hemoglobin was seen after 1 hour of ischemia. Even with the convincing data we obtained from our experiments, we do not believe that plasma hemoglobin alone will be useful as a specific test for mesenteric ischemia. Hemolysis is a biological event that is not specific by itself and can occur in a variety of conditions. The amount of necrotic tissue, in addition to the time of ischemia, also probably affects plasma hemoglobin levels. However, the sensitivity and specificity of a test should be evaluated in a setting that is as close as possible to the one in which it is intended for use. It is possible that when the test is performed in patients suspected to have mesenteric ischemia on the basis of other evaluations (e.g., clinical), we may find supporting evidence in determining the presence of an ischemic process. We do not consider plasma hemoglobin levels to be appropriate for use as a screening tool for mesenteric ischemia. We believe its usefulness instead may reside in its ability to confirm a suspicious diagnosis and/or aid in follow-up after various therapeutic approaches. An ideal test would be one that is noninvasive, fast, and easy to perform, with good sensitivity and specificity, that can be used alone or combined with other data. At the present time, we can only say that the measurement of plasma hemoglobin levels is noninvasive, fast and easy to perform, and correlates very well with the time of bowel ischemia in an experimental model. We hope that a better analysis of this and other tools can help to change the scenario that was very well described by Boley et al.[6] when they stated that "the best part of the history of mesenteric ischemia remains to be written."

REFERENCES

1. Mansour MA. Management of acute mesenteric ischemia. Arch Surg 1999;134:328–330; discussion 331.
2. Duron JJ, Peyraud P, Boukhtouche S, et al. [Acute mesenteric ischemia: Changes in 1985–1995. Surgical Research Association]. Chirurgie 1998;123:335–342.
3. Taylor BM, Jamieson WG, Durand D. Preinfarction diagnosis of acute mesenteric ischemia by simple measurement of inorganic phosphate in body fluids. Can J Surg 1979;22:40–45.
4. Montgomery RA, Venbrux AC, Bulkley GB. Mesenteric vascular insufficiency. Curr Probl Surg 1997;34:941–1025.
5. Boley SJ, Sprayregan S, Sammartano RJ, et al. Initial results from an agressive roentgenological and surgical approach to acute mesenteric ischemia. Surgery 1977;82:848–855.
6. Boley SJ, Brandt LJ, Sammartano RJ. History of mesenteric ischemia. The evolution of a diagnosis and management. Surg Clin North Am 1997;77:275–288.
7. Chaikof EL. Developing a discriminant noninvasive test for early mesenteric ischemia: Measuring the basic rhythms of life. J Vasc Surg 1999;30:367–369.
8. Richards WO, Garrard CL, Allos SH, et al. Noninvasive diagnosis of mesenteric ischemia using a SQUID magnetometer. Ann Surg 1995;221:696–704; discussion 704–705.
9. Taourel PG, Deneuville M, Pradel JA, et al. Acute mesenteric ischemia: Diagnosis with contrast-enhanced CT. Radiology 1996;199:632–636.
10. Poole JW, Sammartano RJ, Boley SJ. The use of tonometry in the early diagnosis of mesenteric ischemia. Curr Surg 1987;44:21–24.
11. Horton KM, Fishman EK. Multi-detector row CT of mesenteric ischemia: Can it be done? Radiographics 2001;21: 1463–1473.
12. Williams RA, Wilson SE. Radioxenon washout for the diagnosis of low-flow mesenteric ischemia. J Surg Res 1980;28: 217–222.
13. Bounous G, McArdle AH. Release of intestinal enzymes in acute mesenteric ischemia. J Surg Res 1969;9:339–346.

# Evaluation and Management of Patients With Recurrent Peptic Ulcer Disease After Acid-Reducing Operations: A Systematic Review

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This systematic review examines the evidence for commonly employed strategies of managing patients with recurrent ulcer disease after acid-reducing operations. Particular attention is given to recent evidence relating *Helicobacter pylori* (*H. pylori*) and nonsteroidal anti-inflammatory drugs (NSAIDs) to ulcer recurrence after operative therapy. MEDLINE word searches of the literature from 1966 to 2001 identified 895 articles that cross-reference the terms "peptic ulcer disease (PUD)," "surgery," and "recurrence." Articles were selected for systematic review of evidence relating incomplete vagotomy, NSAIDs, and *H. pylori* to postoperative ulcer recurrence and evidence supporting common medical and surgical strategies. The relationship between incomplete vagotomy and recurrent ulcer disease is suggested by randomized controlled trials and well-designed prospective case series. The evidence that NSAID use is an important pathogenic factor in recurrent ulcer disease includes the relationship between NSAIDs and primary PUD, the occurrence of NSAID-induced ulcers in patients taking proton pump inhibitors, and case series demonstrating virulent ulcer disease in patients taking aspirin despite prior acid-reducing operations. The relationship between *H. pylori* infection and postoperative ulcer recurrence remains uncertain despite multiple controlled trials and well-designed case series that have documented high rates of *H. pylori* infection in postoperative patients. The initial management of patients with recurrent ulcer disease after acid-reducing operations consists of a protein pump inhibitor or a histamine-2 receptor antagonist and antibiotics directed at *H. pylori*, if present. Evidence for this regimen includes prospective randomized trials demonstrating the efficacy of cimetidine in healing ulcers after acid-reducing operations and prospective, randomized studies documenting the efficacy of histamine-2 receptor antagonists and protein pump inhibitors in the management of patients with primary PUD. The critical role that *H. pylori* infection plays in primary PUD and the minimal risks associated with *H. pylori* eradication strongly support the initiation of antibiotic therapy when *H. pylori* is present. The principal indication for operative management of recurrent PUD is the occurrence of ulcer complications that cannot be managed by medical or endoscopic means. The operative management of patients with failed acid-reducing operations is based on ulcer recurrence rates and morbidity and mortality rates in randomized and nonrandomized prospective trials of patients with primary PUD and retrospective case series of patients undergoing remedial operative procedures after various failed acid-reducing operations. (J GASTROINTEST SURG 2003;7:606–626.)


KEY WORDS: Recurrent peptic ulcer disease, peptic ulcer disease, vagotomy, antrectomy, parietal cell vagotomy

Recurrent peptic ulceration is one of the most frequent causes of unsatisfactory long-term results after operations for peptic ulcer disease (PUD). Although the number of patients requiring elective operations for PUD has declined dramatically, large numbers of acid-reducing operations have been performed. Furthermore, operations to manage acute complications of ulcer disease are still commonly performed.

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The availability of potent inhibitors of gastric acid secretion and improved understanding of the pathophysiology of primary PUD, particularly with regard to *Helicobacter pylori* (*H. pylori*) and nonsteroidal anti-inflammatory drugs (NSAIDs), has fundamentally altered the therapeutic approach to patients with ulcer disease. The purpose of this article is to review the evidence for commonly employed strategies for evaluating and managing patients with recurrent ulcer disease after acid-reducing operations. Particular attention is given to recent evidence relating *H. pylori* and NSAIDs to ulcer recurrence after operative therapy.

## METHODS

MEDLINE word searches of the literature published from 1966 to 2001 were conducted using the terms "peptic ulcer disease" and "surgery" in combination with "recurrence." This search yielded 37,283 articles for the term "peptic ulcer disease," 7385 articles for the surgical treatment of PUD, and 895 articles that cross-referenced the terms "peptic ulcer disease," "surgery," and "recurrence." The MEDLINE abstracts (or titles) of these 895 articles were examined by two of us (R.H.T and G.S.) to identify primary and review articles containing information pertinent to this review. A total of 175 articles were chosen for in-depth review based, in part, on the presence of one of the following characteristics: prospective design, large patient cohort, periods of follow-up longer than 10 years, and publication within the past 10 years. The level of evidence for each of the following questions was assigned using the criteria in Table 1:[1,2] (1) What is the role of incomplete vagotomy, NSAIDs, and *H. pylori* in the pathogenesis of recurrent ulcer disease after acid-reducing operations; (2) what is the best medical treatment for patients with recurrent ulcers after acid-reducing operations; and (3) what is the best operative treatment for patients with recurrent PUD after acid-reducing operations?

## INCIDENCE AND TIMING OF RECURRENT DUODENAL ULCER DISEASE

There are many prospective reports documenting the rate of recurrent ulceration after various acid-reducing operations with long periods of follow-up (Table 2). The incidence of ulcer recurrence is lowest for the most extensive procedures such as truncal vagotomy and antrectomy and higher for nonresectional procedures such as truncal vagotomy and pyloroplasty and parietal cell vagotomy.[3–13] The most common sites for ulcer recurrence are peripyloric, duodenal, and peristomal (i.e., within 1 cm of a gastrojejunostomy). The time to ulcer recurrence is related, at least in part, to the particular operation performed. Most patients who develop recurrent ulcerations after a truncal vagotomy and pyloroplasty or truncal vagotomy and antrectomy do so within the first 3 to 5 postoperative years, whereas patients who have undergone a parietal cell vagotomy appear to be at risk for recurrent ulcer disease for at least 13 years[3,4,6,7,14] (Fig. 1). In one early study, 70% of the recurrences after truncal vagotomy and pyloroplasty, truncal vagotomy and antrectomy, and gastric resection occurred within the first 3 postoperative years.[15] These data are similar to those reported by Jordan et al.[7] in a prospective randomized comparison of parietal cell vagotomy and selective vagotomy and antrectomy. Meisner et al.[3] and Jordan et al.[7] noted a progressive increase in ulcer recurrences after parietal cell vagotomy for at least the first 13 years after the procedure. The monthly risk of ulcer recurrence after parietal cell vagotomy was estimated to be between 0.07% and 0.38%,[7,16,17] and the rate after selective gastric vagotomy and antrectomy was estimated to be 0.008%.[7]

## CLINICAL PRESENTATION

Many patients with recurrent ulcer disease after ulcer surgery are asymptomatic.[18] The others present

**Table 1.** Level of evidence rating[1,2]

| Level of evidence | Type of investigation |
|---|---|
| Ia | Evidence obtained from meta-analysis of randomized controlled trials |
| Ib | Evidence obtained from at least one randomized controlled trial |
| IIa | Evidence obtained from at least one well-designed controlled trial without randomization |
| IIb | Evidence obtained from at least one other type of well-designed quasiexperimental study |
| III | Evidence obtained from well-designed nonexperimental studies, such as comparative studies, correlational studies, and case studies |
| IV | Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities |

**Table 2.** Frequency of recurrent peptic ulcer disease after acid-reducing operations

| Reference | Study description | Study design | Level of evidence | Sample size | Average follow-up (yr) or range (yr) | Recurrence rate (%) |
|---|---|---|---|---|---|---|
| Highly selective vagotomy | | | | | | |
| Meisner et al.[3] (1988) | Estimate probability of ulcer recurrence after PCV | Long-term systematic follow-up, case series | III | 339 | 15 | 27* |
| Johnston et al.[4] (1991) | Long-term follow-up of patients undergoing PCV | Long-term systematic follow-up, case series | III | 305 | 10–20 | 15 |
| von Holstein et al.[5] (1987) | Long-term follow-up of patients undergoing PCV | Long-term systematic follow-up, case series | III | 100 | >10 | 18 |
| Koruth et al.[6] (1990) | Comparison of PCV and TV & P | Prospective, randomized | Ib | 57 | 12 | 5 |
| Jordan and Thornby[7] (1994) | Comparison of PCV and SV & A in 200 patients followed over 20 yr | Prospective, randomized | Ib | 102 | 10–20 | 14 |
| Hoffman et al.[8] (1987) | Long-term prospective follow-up of 135 patients undergoing PCV | Long-term systematic follow-up, case series | III | 135 | 14–18 | 30 |
| Hoffman et al.[9] (1989) | Comparison of TV and drainage, selective vagotomy and drainage, and PCV in 197 patients | Prospective, randomized | Ib | 80 | 11–15 | 39* |
| Macintyre et al.[10] (1990) | Long-term follow-up of patients undergoing PCV 5–15 years postop (82% follow-up) | Long-term systematic follow-up, case series | III | 283 | 12 | 19 |
| Herrington et al.[11] (1986) | Long-term prospective follow-up of 131 patients undergoing PCV | Long-term systematic follow-up, case series | III | 131 | 6–13 | 9 |
| Koo et al.[12] (1983) | Comparison of TV & D, TV & A, and PCV in 152 patients | Prospective, randomized | Ib | 50 | 4 | 16 |
| Koruth et al.[6] (1990) | Comparison of PCV and TV & P in 137 patients | Prospective, randomized | Ib | 59 | 12 | 7 |
| Hoffman et al.[9] (1989) | Comparison of TV & D, selective vagotomy and drainage and PCV in 197 patients | Prospective, randomized | Ib | 78 | 11–15 | 28* |
| Koo et al.[12] (1983) | Comparison of TV & D, TV & A, and PCV in 152 patients | Prospective, randomized | Ib | 51 | 4 | 12 |
| Truncal vagotomy and drainage | | | | | | |
| Taylor et al.[13] (1990) | Comparison of anterior lesser curve seromyotomy with posterior truncal vagotomy and TV & P in 146 patients | Prospective, randomized | Ib | 69 | 4.5 | 3 |

*Table 2 continued.*

**Table 2.** *Continued*

| Reference | Study description | Study design | Level of evidence | Sample size | Average follow-up (yr) or range (yr) | Recurrence rate (%) |
|---|---|---|---|---|---|---|
| Vagotomy and antrectomy | | | | | | |
| Jordan and Thornby[7] (1994) | Comparison of PCV and SV & A in 200 patients followed over 20 yr | Prospective, randomized | Ib | 92 | 10–20 | 2 |
| Hoffman et al.[9] (1989) | Comparison of TV & D, SV & D, and PCV in 197 patients | Prospective, randomized | Ib | 90 | 11–15 | 37* |
| Koo et al.[12] (1983) | Comparison of TV & D, TV & A, and PCV in 152 patients | Prospective, randomized | Ib | 51 | 4 | 0 |

PVC = parietal cell vagotomy; SV & A = selective vagotomy and antrectomy; TV & A = truncal vagotomy and antrectomy; TV & D = truncal vagotomy and drainage; TV & P = truncal vagotomy and pyloroplasty.
*Kaplan-Meier estimates after selective vagotomy and antrectomy.

with recurrent abdominal pain and/or one of the following complications of their disease: hemorrhage, perforation, or gastric outlet obstruction.[14,19–24] The relative frequency of the symptomatic clinical scenarios is shown in Table 3. The following three points deserve emphasis: (1) Most patients with epigastric pain after an operation for PUD do not actually have recurrent ulcers.[23–25] Mosiman et al.[25] found that only about one third of patients with postoperative dyspeptic pain had recurrent ulcers. These investigators and others have noted that the pain of a recurrent ulcer is often indistinguishable from that of other postgastrectomy complications such as impaired gastric emptying (gastroparesis), esophagitis, or bile reflux gastritis.[23–25] (2) Free perforation into the peritoneal cavity is a relatively unusual mode of presentation for patients with recurrent ulcer disease in the absence of aspirin (acetylsalicylic acid [ASA]) or NSAID use, and (3) recurrent ulcers due to ASA, and perhaps other NSAIDs, are associated with a high frequency of severe complications including obstruction, bleeding, and even perforation.[21,26]

## ETIOLOGY

The two most common causes of recurrent ulcer disease are incomplete vagotomy and ulcerogenic medications, particularly NSAIDs. The relationship between *H. pylori* and recurrent ulcer disease is unclear. The evidence relating incomplete vagotomy, NSAID use, and *H. pylori* infection to recurrent ulcer disease after acid-reducing operations is reviewed in Table 4. Less common causes include hypersecretory states, such as gastrinoma, and retained excluded gastric antrum. At the present time, there is little evidence to suggest that hypercalcemia (in the absence of gastrinoma) and gastric stasis cause recurrent ulcer disease, G-cell hyperplasia, or the presence of a long afferent limb.

### Role of Incomplete Vagotomy in the Pathogenesis of Recurrent Ulcer Disease

There is substantial evidence relating incomplete vagotomy to recurrent ulcer disease after acid-reducing operations.[7,10,27–30] All forms of vagotomy reduce basal acid output and stimulate gastric acid output by 50% to 80%.[7,27–29,31] Gastric resection, with or without vagotomy, reduces acid secretion by as much as 90%.[7,31] This degree of inhibition of acid secretion persists for as long as 10 to 20 years postoperatively.[7,29,31]

The relationship between incomplete vagotomy, persistent acid production, and recurrent ulcer disease is suggested by studies demonstrating greater levels of acid production in patients with ulcer recurrence than in patients without recurrence. For example, a prospective study of 280 patients undergoing parietal cell vagotomy found that 72% of patients with a post–parietal cell vagotomy basal acid output greater than 1.4 mmol/hr developed recurrent ulcer disease compared with only 8% of patients whose basal acid output was less than 1.4 mmol/hr[27] (Fig. 2). Similarly, 18% of the patients in that study with a postoperative peak acid output greater than 12 mmol/hr developed recurrent ulcer disease, whereas only 3% of those with stimulated acid output less than 12 mmol/hr developed a recurrence.[27]

Using another assay of vagal integrity, Feldman et al.[30] found that the ratio of acid output after sham feeding to peak acid output (SAO/PAO) was significantly greater in patients whose ulcers recurred post-

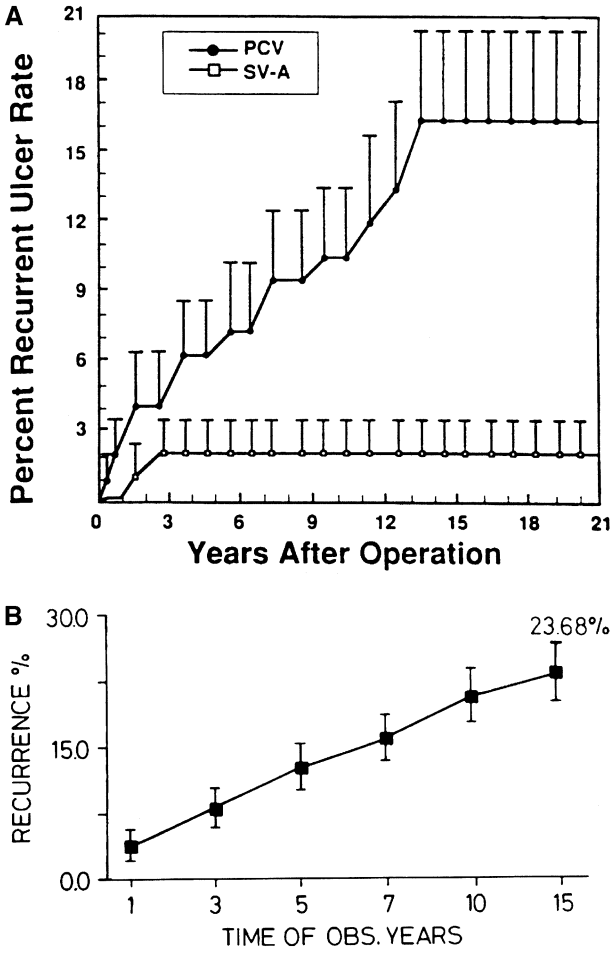


**Fig. 1. A,** Frequency and timing of ulcer recurrence after parietal cell vagotomy (*PCV*) or selective vagotomy and antrectomy (*SV-A*). Jordan and Thornby[7] reported the results of a prospective, randomized comparison between parietal cell vagotomy (n = 100) and selective vagotomy and antrectomy (n = 100). Each curve represents the expected probability plus 1 standard error for ulcer recurrence. The monthly average recurrence rate was 0.069% for parietal cell vagotomy and 0.0083% for vagotomy and antrectomy. (From Jordan PH Jr, Thornby J. Twenty years after parietal cell vagotomy or selective vagotomy antrectomy for treatment of duodenal ulcer: Final report. Ann Surg 1994;220:283–296.) **B**, Frequency and timing of ulcer recurrence after parietal cell vagotomy using Kaplan-Meier plots ± 1 standard deviation. Meisner et al.[3] reported these data based on observations in 339 patients undergoing parietal cell vagotomy followed for a median period of 108 months (range 1 to 197 months). Ulcers recurred in 62 (18.3%) of the 339 patients. (From Meisner S, Jorgensen LN, Sensen HE. The Kaplan and Meier and the Nelson estimate for the probability of ulcer recurrence 10 and 15 years after parietal cell vagotomy. Ann Surg 1988;207:1–3.)

operatively than in those without a recurrence. More important, of the five patients with ulcer recurrence and a high SAO/PAO, repeat vagotomy dramatically reduced acid production and prevented ulcer recurrence. Stenquist et al.[28] reported that a high postoperative SAO/PAO predicted early (within 5 years postoperatively) but not late (>5 years) ulcer recurrence, suggesting the importance of other factors such as NSAID use in late ulcer recurrence. The latter observation is consistent with studies demonstrating the recurrence of ulcers in patients with complete vagotomies and the lack of a difference in the average (or median) gastric acid output between patients who have a recurrence of ulcers and those who do not.[7,21,31–33]

## Role of NSAIDs in the Pathogenesis of Recurrent Peptic Ulcer Disease

Evidence relating NSAID use to recurrent ulcer disease after acid-reducing operations includes the following: (1) the well-known association between NSAIDs and complicated primary PUD;[34–36] (2) the suggestion that overt or surreptitious NSAID use is responsible for recurrent ulcers after the effective eradication of *H. pylori*;[37] (3) the observation that NSAID-induced ulcers occur in patients in whom gastric acid secretion is significantly suppressed by the administration of high-dose proton pump inhibitors (PPIs);[38,39] and (4) two observational studies documenting the occurrence of virulent recurrent ulcer disease in patients taking ASA despite prior operations that profoundly reduced gastric acid secretion.[21,26] Hirschowitz and Lanas[21] reported 30 patients who chronically used ASA and developed recurrent ulcer disease after various acid-reducing operations. The rate of ulcer recurrence was 80% to 90% despite the fact that patients undergoing remedial procedures of increasing complexity had progressively greater reductions in gastric acid production. In this study the ulcerations were multiple, deep, and caused stenosis of the gastric outlet. Most important, the only patients who had healing of their ulcers were those who stopped taking ASA. These observations are consistent with those reported by Perrault et al.[26] in a case series.

The quantity of ASA required to produce recurrent ulceration, particularly in the hypochlorhydric stomach, is unknown. In the study by Hirschowitz and Lanas,[21] the patients took 1 to 3.5 gm per day (serum salicylate levels of 3 to 30.4 mg/100 ml), suggesting that the virulent ulcer disease reported in their study was induced by large doses of ASA. In a recent study by Cryer and Feldman,[40] in normal volunteers with an intact stomach, they found that even very low doses of ASA (10 mg/day) reduce gastric mucosal prostaglandin levels by 60% and cause gastroduodenal mucosal injury. These data are consistent with epidemiologic and autopsy studies suggest-

**Table 3.** Symptoms associated with recurrent ulcers after acid-reducing operations

| Reference | Sample size | Pain (%) | Bleeding (%) | Obstruction (%) | Perforation (%) | Notes |
|---|---|---|---|---|---|---|
| Schirmer et al.[14] (1982) | 166 | 45 | 41 | 12 | 1 | One patient presented with diarrhea |
| Kinney et al.[19] (1988) | 42 | 55 | 40 | 5 | 0 | — |
| Lee et al.[20] (1998) | 93 | 58 | 42 | — | — | — |
| Hirschowitz[21] (1998)* | 30 | — | 23 | 43 | 23 | Other symptoms (e.g. pain) are not described in 11% of patients. |
| Heppell et al.[22] (1983) | 120 | 43 | 27 | 19 | 7 | Other symptoms of recurrent ulcer disease are not described in 4% of patients |

*Aspirin-associated ulcers.

ing that ASA dosages as low as 75 to 325 mg/day (or even 325 mg every other day) may cause gastrointestinal ulcers and bleeding.[41,42] Whether patients with ulcers who undergo prior acid-reducing operations are more vulnerable (or protected) against ASA-induced ulcers is uncertain.

## Role of *H. pylori* in the Pathogenesis of Recurrent Peptic Ulcer Disease

In contrast to the well-known pathogenic role that *H. pylori* plays in primary PUD,[43–45] the relationship between *H. pylori* infection and recurrent ulcer disease after acid-reducing operations is unclear. The prevalence of *H. pylori* infection after vagotomy without gastric resection is 65% to 98% up to 14 years postoperatively, and the prevalence of infection after gastric resection ranges from 18% to 49% up to 20 years postoperatively.[20,46–52] There are surprisingly few data relating persistent colonization to recurrent ulcer disease. Several studies have found that the prevalence of *H. pylori* infection in patients with recurrent ulcer disease is similar to that in patients without recurrent disease.[20,46–52] These studies are summarized in Table 4.

Even in the presence of an incomplete vagotomy, it remains unclear whether *H. pylori* significantly increases the risk of ulcer recurrence. In one study of 122 patients undergoing vagotomy, who were followed for up to 14 years, the only patients who developed ulcer recurrence were those with incomplete vagotomy, irrespective of the status of the *H. pylori*. Only one in four patients with both persistent *H. pylori* infection and an incomplete vagotomy developed recurrent ulcer disease.[48] These data suggest that acid-reducing operations, per se, do not affect gastric *H. pylori* infection and that patients who were infected preoperatively remain infected after their ulcer operations. Despite these data, the relationship between *H. pylori* and the recurrence of ulcers postoperatively remains of concern, particularly given recent data suggesting that patients with *H. pylori* infections are more susceptible to NSAID-induced gastric mucosal injury than are patients without *H. pylori* infection.[53]

## Unusual Causes of Recurrent Ulcer Disease After Acid-Reducing Operations

***Retained Gastric Antrum.*** Gastric antrum retained within the duodenal stump after gastric resection and Billroth II gastrojejunostomy is a very rare but important cause of recurrent ulcer disease. In these instances, the excluded antral mucosa is constantly bathed by alkaline duodenal and pancreatic fluid, resulting in the continuous secretion of gastrin and hence gastrin-mediated acid hypersecretion. The diagnosis should be suspected in patients with recurrent ulcer disease and hypergastrinemia after gastric resection and a Billroth II gastrojejunostomy. A sodium 99m-technetium pertechnetate scan demonstrating retained antral tissue within the end of the afferent loop confirms the diagnosis. The diagnosis may also be made endoscopically by histologically documenting pyloric or gastric mucosa at the end of the afferent loop. Excision of the retained antral tissue is curative. This complication can be avoided by frozen-section evaluation of the duodenal margin at the time of the initial resection. Identification of Brunner's glands at the distal resection margin confirms complete excision of the antrum.

***Gastrinoma.*** Although gastrinoma is a rare cause of primary PUD, it assumes much greater importance in patients with recurrent ulceration, particularly after gastric resection. Multiple or jejunal ulcerations, rugal hypertrophy, and a history of diarrhea are important diagnostic clues. About one fourth of

**Table 4.** Evidence that incomplete vagotomy, nonsteroidal anti-inflammatory drugs, and *Heliocobacter pylori* are important factors in the pathogenesis of recurrent ulcer disease after acid-reducing operations

| Reference | Study description | Study design | Level of evidence |
|---|---|---|---|
| Incomplete vagotomy | | | |
| Jordan and Thornby[7] (1994) | Comparison of PCV and SV & A in 200 patients followed over 20 yr; ulcer recurrence and acid secretion higher in PCV group | Prospective, randomized | Ib |
| Macintyre et al.[10] (1990) | Long-term follow-up of patients undergoing PCV 5–15 years postop (82% follow-up); higher recurrence rate with incomplete vagotomy | Long-term systematic follow up, case series | III |
| Cohen et al.[27] (1993) | Quantitation of gastric acid release both pre- and postop in patients undergoing PCV with correlation between acid secretion and ulcer recurrence (N = 280 patients) | Case series with acid studies | IIb |
| Stenquist et al.[28] (1994) | Quantitation of postop sham acid ouput in 98 patients after PCV recurrence rate with complete vagotomy = 8%; with incomplete vagotomy = 23%. | Case series with acid studies | IIb |
| Braghetto et al.[29] (1988) | Comparison of PCV and extended PCV in 80 patients with duodenal ulcers; all patients had postop acid studies; low recurrence rate; acid studies similar in both groups | Prospective, randomized | Ib |
| Feldman et al.[30] (1980) | Quantitation of sham feeding to peak acid output in 50 nonvagotomized subjects and 15 vagotomized patients with duodenal ulcers; all 5 patients with acid studies diagnostic of incomplete vagotomy underwent repeat vagotomy with significant reduction in acid secretion and cure of their ulcer disease | Case series with acid studies | IIb |
| NSAID use | | | |
| Hirschowitz and Lanas[21] (1998) | Series of 30 patients with recurrenct ulcer disease after acid-reducing operations; with continued NSAID use ulcer recurrence is the rule despite complete vagotomy | Case series with salicylate levels | III |
| Perrualt et al.[26] (1988) | Case report of 5 patients with recurrent ulcer after acid-reducing operations; All had surreptitious use of NSAIDs | Case series with salicylate levels | III |
| *Helicobacter pylori* | | | |
| Lee et al.[20] (1998) | No clear correlation between *H. pylori* and ulcer recurrence after acid-reducing operations | Prospective series with *H. pylori* studies | IIb |
| Peetsalu et al.[46] (1991) | Determination of *H. pylori* infection in patients with ulcers after ulcer operations; no correlation between *H. pylori* and recurrent ulcers | Case series | IIb |
| Leivonen et al.[47] (1997) | No clear correlation between *H. pylori* and ulcer recurrence after acid-reducing operations in 155 patients | Case series | III |
| Peetsalu et al.[48] (1998) | 14-year follow-up of 122 patients after PCV; *H. pylori* status and endoscopic Congo red studies performed; no correlation between *H. pylori* status and recurrent ulcers | Case series | IIb |
| Leivonen et al.[49] (1998) | 90 patients followed 5+ years after gastrectomy for ulcer disease; negative correlation between *H. pylori* and recurrent ulcers | Case series | III |
| Schilling et al.[50] (1999) | Patients undergoing gastroscopy for ulcer symptoms; 50 with prior ulcer surgery, 50 controls; *H. pylori* found in 37% with ulcer recurrence, 73% with primary ulcers | Case-control study | IIa |
| Csendes et al.[51] (1996) | 31 patients with PCV, 133 with primary ulcers; 81% of primary ulcers *H. pylori* +, 71% of PCV patients *H. pylori* + despite no ulcer recurrence | Case series | IIb |

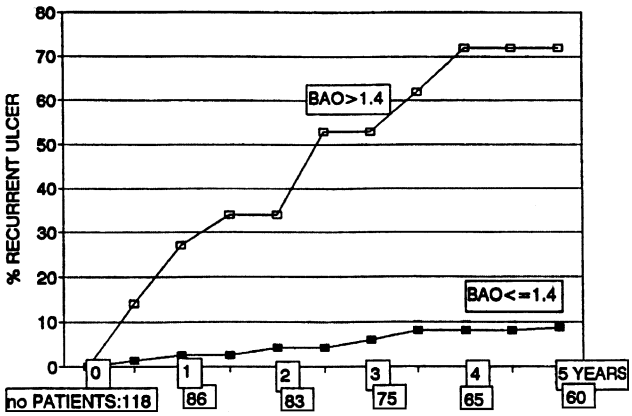


**Fig. 2.** Relationship between elevated basal acid output (*BAO*) and recurrence of PUD after parietal cell vagotomy. These data show the actuarial recurrent ulceration rate in 118 patients undergoing parietal cell vagotomy. Those patients with a BAO greater than 1.4 mmol/hr had a significantly higher rate of ulcer recurrence than did those with a BAO less than 1.4 mmol/hr. (From Cohen F, Valleur P, Serra J, Brisset D, Chiche L, Hautefeuille P. Relationship between gastric acid secretion and the rate of recurrent ulcer after parietal cell vagotomy. Ann Surg 1993;217:253–259.)

patients with gastrinomas have multiple endocrine neoplasia-1 (MEN-1) and 40% to 60% of patients with MEN-1 will have a gastrinoma. Thus the presence of hypercalcemia and hyperparathyroidism in a patient with recurrent ulcer disease strongly suggests the diagnosis of gastrinoma and MEN-1.

***Hypercalcemia and Hyperparathyroidism.*** With the exception of patients with MEN-1, there are few published data to suggest that patients with hypercalcemia and hyperparathyroidism have an increased risk of PUD. Although experimentally induced hypercalcemia may stimulate gastrin release and gastric acid secretion,[53] basal and stimulated gastric acid secretion and serum gastrin levels are not significantly elevated in patients with chronic hypercalcemia associated with hyperparathyroidism.[54] Furthermore, in the absence of MEN-1 syndrome, there are few epidemiologic data to support a relationship between hyperparathyroidism and PUD.[55]

***Impaired Gastric Emptying.*** An association between impaired gastric emptying, gastroparesis, and recurrent ulcer disease (especially gastric ulcers) has been suggested since the early days of gastric surgery. It is postulated that gastric distention and retained food increase gastrin release and thus acid secretion.[56,57] Although at one time it was thought to be responsible for as many as 12% of cases of recurrent ulceration,[15] at present the relationship between delayed gastric emptying and recurrent PUD is unclear. The principal evidence against the notion that impaired gastric emptying causes recurrent gastric ulcers is the high rate of ulcer recurrence in patients with gastric outlet obstruction treated only by revision of the anastomosis.[23,58] It is likely that in most patients with gastric outlet obstruction and recurrent ulcer disease, outlet obstruction is the consequence, and not the cause, of ulcer recurrence.

***Long Afferent Loop After Billroth II Gastrectomy.*** The presence of a long afferent loop in a Billroth II reconstruction has often been mentioned as cause of recurrent ulceration. The long afferent loop is proposed to cause deficient buffering of the acidic gastric juice in the jejunal limb resulting in ulceration. Although there is elegant experimental evidence in dogs from the 1950s supporting this mechanism,[59,60] only a few cases reported in the literature in humans are attributed to this cause.[61] In these reports, the definition of long afferent limb is imprecise. Based on the paucity of solid evidence in humans, we do not consider a long afferent limb to be an important cause of recurrent postoperative peptic ulcers.

***Antral G-Cell Hyperplasia (Pseudo–Zollinger-Ellison Syndrome).*** This syndrome is described in patients with excessive gastrin release and therefore exaggerated acid production. It is believed to result from an excessive number of antral G-cells without an extragastric source of gastrin. The hallmarks of the syndrome are excessive acid and gastrin production in response to meals, a negative secretin stimulation test for gastrinoma, a virulent course of ulcer disease, and resolution of the syndrome with antrectomy. The existence of this entity remains controversial. Despite a number of articles published on the topic, only two case series clearly rule out gastrinoma by provocative testing,[62,63] and only one of these includes postoperative recurrent ulcers.[63] Further complicating the use of this diagnosis is the fact that both series predate the recognition of *H. pylori* as an important etiologic agent in PUD, and hence do not include data on *H. pylori* status. Of note, *H. pylori* infection has been shown to increase the gastrin and acid response to food,[64,65] raising the possibility that G-cell antral hyperplasia may, in fact, represent *H. pylori* infection. Based on the paucity of published evidence, we believe that G-cell antral hyperplasia cannot be regarded as a significant cause of recurrent postoperative ulcers.

## INITIAL DIAGNOSTIC EVALUATION

A detailed history and physical examination will identify symptoms of ulcer disease or evidence of complications, for example, hematemesis and melena, anemia, vomiting, or weight loss. A thorough medical history may also provide insight into the cause of

the ulcer recurrence, for example, the use of ulcerogenic medications or Zollinger-Ellison syndrome. In the absence of symptoms and signs of perforation and peritonitis, the diagnosis of ulcer recurrence is best made by esophagogastroduodenoscopy (EGD). In addition to documenting the presence and location of the ulcer, this study may provide valuable information regarding ulcer etiology and the presence of *H. pylori*. Multiple ulcers and those in atypical locations strongly suggest the presence of a hypersecretory syndrome or the use of NSAIDs. Retained food, a gastric bezoar, or a stenotic anastomosis suggests associated impairment of gastric emptying. Endoscopic biopsy of gastric ulcers is of particular importance in detecting cancer. Last, EGD is invaluable in the evaluation and treatment of patients bleeding from ulcer disease.

Upper gastrointestinal barium contrast studies are of limited value in diagnosing recurrent ulcer disease after acid-reducing operations. Various investigators have documented that this study has a sensitivity and specificity of less than 50% in detecting ulcers in the postoperative setting. The impaired accuracy of this test is due principally to the difficulty in detecting ulcerations in the presence of postoperative deformities of the stomach and duodenum. Contrast radiographs may, however, provide important information in the evaluation of patients with suspected gastric outlet obstruction and in those whose postoperative anatomy is uncertain.

A fasting serum gastrin level should be obtained in all patients with recurrent ulcer disease to identify patients with gastrin-mediated hypersecretory syndromes. With rare exceptions,[66] a normal fasting serum gastrin concentration excludes the possibility of Zollinger-Ellison syndrome, whereas a serum gastrin level greater than 1000 pg/ml, combined with a fasting gastric pH below 2.5,[67] is virtually diagnostic. Of note, achlorhydria alone may be associated with markedly elevated serum gastrin levels, and hence it is important to quantify gastric pH in patients with markedly elevated serum gastrin concentrations. Patients with lesser degrees of hypergastrinemia will require provocative testing with a secretin stimulation test to confirm the diagnosis of gastrinoma. Patients with retained gastric antrum typically have fasting serum gastrin concentrations two to four times the normal range; in these instances, a secretin stimulation test will be negative.

## INITIAL MANAGEMENT

In the usual scenario in which a patient presents with recurrence of upper abdominal pain and endoscopy demonstrates recurrent ulcer disease, medical therapy consists of a PPI or histamine-2 receptor antagonist (H2-RA) and antibiotics directed at *H. pylori*, if present. The use of a PPI or H2-RA for managing patients with recurrent PUD after acid-reducing operations is based on the following evidence: (1) early prospective randomized clinical trials demonstrating the efficacy of acid suppression with H2-RAs in healing ulcers after acid-reducing operations[68–70] and (2) clinical trials documenting the efficacy of H2-RAs and PPIs in the management of patients with primary ulcer disease[71–75] and ulcers associated with the use of NSAIDs.[38,39,76] These studies are reviewed in Table 5. To our knowledge, no studies have directly examined the use of PPIs in the management of patients with recurrent ulcer disease after acid-reducing operations. The optimal duration of treatment with a PPI or H2-RA is unknown. In one early prospective randomized clinical trial, cessation of cimetidine after 1 year of treatment was associated with a 71% rate of ulcer recurrence.[70] This study supports the use of long-term maintenance PPI or H2-RA therapy in patients with ulcer disease after acid-reducing operations; however, these data were generated before the importance of *H. pylori* and NSAIDs was recognized in the pathogenesis of ulcer disease.

Although no data directly support the eradication of *H. pylori* in patients with postoperative ulcer recurrence, the critical role that this infection plays in primary PUD,[37,43–45] the possibility that *H. pylori* promotes NSAID-induced mucosal injury,[53] and the minimal risks associated with *H. pylori* eradication strongly support the use of antibiotic therapy, for example, the addition of amoxicillin and clarithyromycin to the PPI for 14 days in the presence of *H. pylori*. The presence of *H. pylori* may be documented by histologic evaluation of gastric biopsies or, alternatively, by serologic, breath, or fecal tests.

A thorough review of the patient's medication use (both prescription and nonprescription) must be performed to identify ulcerogenic medications. Patients and their families should be carefully counseled regarding the various over-the-counter preparations containing NSAIDs, the important relationship between NSAID use and ulcer disease, and the necessity of discontinuing these medications. Serum salicylate levels may be useful in identifying patients with surreptitious ASA use as a pathogenic factor in ulcer recurrence, but this test is of no value in identifying nonaspirin NSAIDs or in detecting the use of low-dose ASA regimens. Hirschowitz and Lanas[21] report that serum salicylate testing of patients from the Southeastern United States with recurrent ulcers found at least as many patients who were sur-

**Table 5.** Evidence supporting various medical treatments for recurrent ulcer disease after acid-reducing operations

| Treatments | Evidence | Reference | Study description | Study design | Level of evidence |
|---|---|---|---|---|---|
| Acid suppression with H2-RAs or PPIs | Prospective studies demonstrating healing of postop ulcers with H2-RAs | Gugler et al.[68] (1979) | Randomized, double-blind multicenter trial in which 15 patients with postop recurrent ulcers were treated with cimetidine (1 g/day for 8 wk) or placebo; ulcers healed in 7 of 8 cimetidine-treated patients and only 1 of 8 placebo-treated patients | Prospective, randomized, double-blind multicenter | Ib |
| | | Stage et al.[69] (1983) | Randomized, double-blind trial in which 23 of 24 patients with postop recurrent ulcers who had their ulcers healed with ranitidine (150 mg bid for 6 wk) were randomized to ranitidine (q hs) or placebo; Ulcers re-recurred in 9 patients within 4 months and recurrences were significantly more frequent in placebo-treated patients than in those receiving ranitidine ($P = 0.01$) | Prospective, randomized, double-blind | Ib |
| | | Koo et al.[70] (1982) | Prospective, nonrandomized comparison of 46 patients with postop recurrent ulcers who received cimetidine (1 g/day for 6–12 wk, then 400 mg q hs as maintenance therapy) (N = 23) or underwent repeat operation (N = 23); discontinuation of cimetidine after 1 yr was associated with ulcer recurrence in 71.4% of patients | Prospective, nonrandomized | IIb |
| | Prospective studies demonstrating healing of primary PUD with H2-RAs | Binder et al.[71] (1978) | Multicenter, prospective, randomized, double-blind, placebo-controlled trial comparing cimetidine and placebo in the healing of duodenal ulcers in 308 patients; after 2 wk of therapy, 56% of cimetidine-treated patients and 37% of patients receiving placebo had healing of their ulcers ($P < 0.05$) | Prospective, nonrandomized double-blind | Ib |

*Table 5 continued.*

**Table 5.** *Continued*

| Treatments | Evidence | Reference | Study description | Study design | Level of evidence |
|---|---|---|---|---|---|
| | | Legerton[72] (1984) | Review of prospective studies demonstrating the efficacy of H2-RA in the healing of duodenal and gastric ulcers | Review of prospective clinical trials | IV |
| | | Gitlin et al.[73] (1987) | Multicenter, prospective, randomized, double-blind, placebo-controlled trial comparing famotidine vs. placebo in the healing of duodenal ulcers; 8 wk of treatment with famotidine resulted in the healing of 82% of ulcers vs. 45% for placebo | Prospective, randomized, double-blind trial | Ib |
| | Prospective studies demonstrating healing of primary PUD and NSAID-induced ulcers with PPIs | Hawkey et al.[38] (1998) | Double-blind comparison of omeprazole (40 mg q d) or misoprostol (200 μg qid) in healing NSAID-induced ulcers in 935 patients; at 8 wk of therapy, the overall healing rates were similar between the omeprazole and misoprostol groups (75% and 71%, respectively); maintenance therapy with omeprazole was associated with fewer ulcer recurrences than misoprostol (39% vs. 52%, respectively; $P = 0.001$) | Prospective, randomized, double-blind trial | Ib |
| | | Dekkers et al.[74] (1999) | Prospective randomized, double-blind, multicenter trial comparing rabeprazole and omeprazole in 205 patients with duodenal ulcers; the ulcer healing rates after 4 wk of treatment for rabeprazole and omeprazole were 98% and 93%, respectively | European, multi-center, randomized, double-blind trial | Ib |
| | | Poynard et al.[75] (1995) | Meta-analysis of five randomized double-blind clinical trials comparing lansoprazole with ranitidine or famotidine in the treatment of acute duodenal ulcers; The 4 wk healing rate of lansoprazole was 85% compared with 75% healing rate for H2-RA ($P < 0.01$; odds ratio = 2.27, 95% confidence interval 1.5–3.2) | Meta-analysis of five randomized double-blinded trials | Ia |

*Table 5 continued.*

**Table 5.** *Continued*

| Treatments | Evidence | Reference | Study description | Study design | Level of evidence |
|---|---|---|---|---|---|
| Eradication of *H. pylori* | Prospective studies demonstrating healing of primary PUD by eradication of *H. pylori* | Hentschell et al.[44] (1993) | Prospective, randomized comparison of ranitidine, amoxicillin, and metronidazole vs. ranitidine and placebo in 104 patients with *H. pylori* infection and duodenal ulcers; after 6 wk of treatment, the ulcers were healed in 92% of patients receiving antibiotics + ranitidine and 75% of patients receiving ranitidine alone ($P = 0.01$); over the next 12 months ulcer recurrence was significantly more frequent in those patients with persistent *H. pylori* infection when compared with those without *H. pylori* (85 vs. 2%, respectively; $p < 0.001$). | Prospective, randomized, double-blind trial | Ib |
| | | Van der Hulst et al.[37] (1997) | Prospective follow-up of 247 patients with PUD and *H. pylori* infection; none of the 141 patients in whom *H. pylori* was eradicated developed recurrent ulcer disease over 2.5 yr follow-up | Prospective, case series | IIb |
| | | Graham et al.[45] (1992) | Prospective, randomized comparison of ranitidine + triple therapy (bismuth subsalicylate, tetracycline, metronidazole) vs. ranitidine alone in 109 *H. pylori*–infected patients; the probability of ulcer recurrence for patients receiving triple therapy was significantly less than that for patients receiving ranitidine alone (12% vs. 95% for duodenal ulcers; 13% vs. 74% for gastric ulcers); 50% of patients receiving ranitidine alone had ulcer recurrence within 12 weeks of healing, whereas ulcer recurrence in the triple-therapy group could be related to failure to eradicate *H. pylori* infection or NSAID use | Prospective, randomized trial | Ib |

reptitiously using ASA as patients who admitted to ASA use.

NSAID use, including low-dose ASA, should ideally be discontinued during the period of ulcer healing, if feasible. Once ulcer healing has been documented endoscopically, non-NSAID analgesic agents, such as acetaminophen or tramadol, should be substituted for the NSAIDs. If these are ineffective, then nonacetylated NSAIDs, such as salsalate, nabumetone, etodoloac, or a cyclooxygenase (COX)-2–specific NSAID, such as celecoxib or rofecoxib, should be considered because they are associated with a lower rate of ulcer disease compared to traditional (non–COX-2 selective) NSAIDs. If a traditional NSAID is required, a rare event nowadays, then prophylactic combination therapy with either misoprostol or a PPI should be administered.[38] Consideration should be given to substituting clopidogrel for low-dose aspirin for cardiovascular prophylaxis. Because of the potential for even low doses of ASA to contribute to peptic ulceration[41,42] and the recognition that prior ulcer disease is an important risk factor for NSAID-induced gastrointestinal complications,[77] patients continued on low-dose ASA and not switched to clopidogrel should receive ulcer prophylaxis with misoprostol or a PPI.

## INDICATIONS FOR OPERATIVE MANAGEMENT AND PREOPERATIVE EVALUATION

### Indications for Operative Management

Historically, the indications for operative management of recurrent PUD are the failure of medical therapy or the occurrence of complications that cannot be managed nonoperatively. Literature from the late 1970s and early 1980s suggested that approximately 20% of patients with recurrent ulcer disease require operative management.[23,68–70] Although more recent figures are lacking, we believe the frequency of operative management of recurrent ulcer disease is much lower today, especially for patients with nonhealing ulcers in the absence of complications. Clearly, the adequacy of prior medical management and the elimination of risk factors for ulcer recurrence (e.g., NSAID use) are important considerations in determining whether a patient is an appropriate candidate for operative therapy—that is, recalcitrant ulcer disease must be refractory to an appropriate course of medical treatment. Based on recent experiences, the predominant indication for remedial surgery is severe ulcer-related complications such as bleeding and gastric outlet obstruction, with medically refractory ulcer disease being less common than in previous decades.[21,26,78]

### Preoperative Considerations

In general, the management of patients with recurrent ulcer disease entails the use of the operative procedure with the lowest risk of recurrence that the patient is medically able to tolerate. Various options are available to allow the surgeon to tailor the remedial procedure to the specific needs of the patient. The preoperative evaluation should provide insight into the etiology of the patient's recurrent ulcer disease, the nature of his or her previous operative procedure, the presence of complications of the ulcer, and an understanding of the patient's overall medical conditions that affect his or her ability to tolerate the surgical procedure.

### Etiology of Recurrent Ulcer Disease

The initial assessment of patients with recurrent ulcer disease may provide information that is useful in determining the cause of the ulcer, such as NSAID use, gastrinoma, or retained antrum, however, it will not document the adequacy of the prior vagotomy. Because most patients with recurrent ulcer disease are managed successfully with medication, including many with an incomplete vagotomy, assessment of the vagotomy by quantitating gastric acid secretion becomes important only when surgical treatment is contemplated. Historically, the most commonly used methods of assessing the completeness of vagotomy are the measurement of basal and stimulated acid secretion with or without sham feeding. The current unavailability of pentagastrin severely limits the capability of measuring stimulated or peak acid output and perhaps the widespread applicability of these tests.

***Basal and Stimulated Gastric Acid Secretion Without Sham Feeding.*** Gastric secretory analysis is performed by fluoroscopically positioning a nasogastric (or orogastric) tube so that the tip of the tube is in the gastric antrum or in the distal gastric remnant in the case of an antrectomy. Basal acid secretion (BAO) is determined by measuring the volume and pH of gastric juice for 1 hour, usually in 15-minute aliquots. With the use of a standardized table, pH is converted to millimoles of hydrogen ions per liter of gastric juice and BAO is expressed as millimoles of hydrogen ions per hour. After measurement of the BAO, PAO is determined by measuring gastric acid secretion for 1 hour after the subcutaneous administration of 6 to 10 $\mu$g/kg of pentagastrin. PAO is calculated as the sum of the two greatest consecutive 15-minute acid outputs multiplied by two (to express the results in millimoles per hour). BAO greater than 2 mmol/hr and/or a PAO greater than 12 mmol/hr suggests persistent vagal innervation of the stomach.[27]

***Basal and Stimulated Acid Secretion With Sham Feeding.*** Sham feeding stimulates gastric acid secretion solely via vagal pathways, and thus measurement of gastric acid secretion after sham feeding is a sensitive and reliable physiologic test of the completeness of vagotomy.[28,30] This test is performed by measuring BAO for 1 hour, after which a steak meal and 300 ml of water are presented to the patient who then chews but does not swallow the food. This sham feeding is carried out for 30 minutes during which time GAO (sham acid output [SAO]) is measured every 15 minutes for 1 hour (30 minutes during and 30 minutes after sham feeding). PAO is then determined by measuring acid secretion for 1 hour after the subcutaneous injection of 12 $\mu$g/kg pentagastrin, if available. Feldman et al.[79] found that the SAO/PAO ratio of 50 unoperated normal subjects had a normal distribution with a mean of 0.39, a standard deviation of $\pm$ 0.11, and a range of 0.11 to 0.83. From these measurements it was predicted that 95% of subjects with normal vagal innervation of the stomach would have SAO/PAO ratios greater than 0.10. Thus patients with SAO/PAO ratios less than 0.10 are considered to have complete vagotomies, whereas individuals with ratios greater than 0.10 have incomplete vagotomies. Interpretation of the sham feeding test assumes a normal or near-normal fasting serum gastrin concentration. Patients with Zollinger-Ellison syndrome or retained gastric antrum may have SAO/PAO ratios greater than 0.1, even after complete vagotomy.[23]

### Nature of the Previous Operative Procedure

It is critical that the surgeon understand the exact nature of the previous operative procedure before the remedial operation is performed. This information may be gleaned by carefully reviewing the previous operative note and pathology report. The endoscopic findings and a barium contrast study may also provide useful information regarding the extent of the prior resection and the particular postoperative anatomy.

### Presence of Complications of Ulcer Disease

The presence of complications of the recurrent ulcer disease strongly influences the appropriateness of various remedial operative procedures. For example, a bleeding peptic ulcer that cannot be controlled endoscopically necessitates an abdominal approach for ligation of the bleeding vessel and often a more extensive acid-reducing procedure. Ulcer recurrence causing gastric outlet obstruction necessitates both revision of the anastomosis and a more extensive acid-reducing procedure. In those patients presenting with ulcer perforation, the degree of contamination and the hemodynamic stability of the patient clearly influence the appropriateness of a particular remedial procedure. For example, hemodynamic instability and/or marked contamination of the upper abdomen favors simple closure of the gastrointestinal perforation without attempt at resection and reanastomosis.

### Presence of Medical Comorbidity

The accurate assessment of the operative risk-benefit ratio is crucial to the successful management of patients with postoperative recurrent PUD. The presence of chronic medical diseases may significantly increase the risk of perioperative morbidity and mortality. This risk, in turn, influences the specific procedure chosen. For example, an elderly frail patient with an incomplete truncal vagotomy and adequate gastric drainage would tolerate a thoracoscopic truncal vagotomy better than a truncal vagotomy and antrectomy. In this setting, the surgeon would do well to accept the slightly higher risk of recurrent ulcer disease associated with repeat vagotomy alone for the less "risky" thoracoscopic procedure.

## OPERATIVE MANAGEMENT

The choice of a particular operation for a patient with recurrent ulcer disease is based on the following tenets: (1) the remedial procedure should be that with the lowest recurrence risk that the patient is medically able to tolerate; (2) the procedure should be tailored to the particular needs of the patient based on the adequancy of the prior vagotomy and drainage procedure, medical comorbidity, presence of complications of the ulcer, and the extent of the prior resection; and (3) non–acid-reducing procedures such as local ulcer excision, revision of drainage procedures alone, and closure of perforations are associated with high failure rates.[23,24,58]

Commonly recommended operative procedures for various failed initial acid-reducing operations are described in Table 6. These operative options are based on the following evidence: (1) ulcer recurrence rates and mortality rates for particular operative procedures in prospective randomized and nonrandomized clinical trials of patients treated for primary PUD (Table 2) and (2) retrospective studies documenting the incidence of ulcer recurrence, early and late complications, and mortality rates associated with various remedial operative procedures (Table 6).

Patients with an incomplete vagotomy and recurrent ulcer disease after truncal vagotomy and pyloroplasty or parietal cell vagotomy may be treated by

**Table 6.** Evidence supporting specific remedial operations for patients with recurrent peptic ulcer disease

| Remedial operation | Study description | Level of evidence | Sample size | Operative mortality | Recurrence rate (%) | Visick grade (I or II; excellent or good) | Visick grade (III or IV; fair or poor) |
|---|---|---|---|---|---|---|---|
| Truncal vagotomy alone | | | | | | | |
| Schirmer et al.[14] (1982) | Retrospective case series of 166 patients undergoing reoperation between 1951 and 1980 at Duke University Hospital for ulcer recurrence after various acid-reducing operations; average follow-up 12.3 yr | III | 59 | 0 (0.0%) | 10 (16.9) | — | — |
| Heppell et al.[22] (1983) | Retrospective case series of 120 patients undergoing reoperation between 1970 and 1975 at Mayo Clinic for ulcer recurrence after various acid-reducing operations. >5 yr follow-up available for only 27 patients (22.5%) | III | 62 | 2 (3.2%) | 6 (10%) | 37 (60%) | 14 (23%) |
| Stabile and Passaro[58] (1976) | Detailed literature review from 1950 to 1974 cataloguing the results of more than 3400 surgically treated cases of recurrent ulcers after various operations | IV | 888 | 10 (1.1%) | 135 (15.2%) | 571 (64.3%) | 90 (10.1%) |
| Ingvar et al.[80] (1986) | Retrospective case series of 40 consecutive patients undergoing reoperation between 1971 and 1980 at University Hospital, Lund, Sweden, for ulcer recurrence after PCV | III | 16 | 0 (0.0%) | 1 (6.25%) | 14 (87.5%) | 2 (12.5%)* |
| Truncal vagotomy + antrectomy | | | | | | | |
| Schirmer et al.[14] (1982) | Retrospective case series of 166 patients undergoing reoperation between 1951 and 1980 at Duke University Hospital for ulcer recurrence after various acid-reducing operations; average follow-up was 12.3 yr | III | 31 | 1 (3.2%) | 6 (19.4%) | — | — |

*Table 6 continued.*

**Table 6.** *Continued*

| Remedial operation | Study description | Level of evidence | Sample size | Operative mortality | Recurrence rate (%) | Visick grade (I or II; excellent or good) | Visick grade (III or IV; fair or poor) |
|---|---|---|---|---|---|---|---|
| Heppell et al.[22] (1983) | Retrospective case series of 120 patients undergoing reoperation between 1970 and 1975 at Mayo Clinic for ulcer recurrence after various acid-reducing operations; >5 yr follow-up available for only 27 patients (22.5%) | III | 35 | 0 (0.0%) | 1 (2.9%) | 20 (57%) | 7 (20%) |
| Stabile and Passaro[58] (1976) | Detailed literature review from 1950 to 1974 cataloguing the results in more than 3400 surgically treated cases of recurrent ulcer following various operations. | IV | 76 | 6 (7.9%) | 6 (7.9%) | 48 (63.2%) | 6 (7.9%) |
| Resection or re-resection only | | | | | | | |
| Schirmer et al.[14] (1982) | Retrospective case series of 166 patients undergoing reoperation between 1951 and 1980 at Duke University Hospital for ulcer recurrence after various acid-reducing operations; average follow-up was 12.3 yrs | III | 25 | 0 (0.0%) | 3 (12.0%) | — | — |
| Heppell et al.[22] (1983) | Retrospective case series of 120 patients undergoing reoperation between 1970 and 1975 at Mayo Clinic for ulcer recurrence after various acid-reducing operations; >5 yr follow-up available for only 27 patients (22.5%) | III | 23 | 2 (8.7%) | 2 (8.7%) | 8 (35%) | 9 (39%) |
| Stabile and Passaro[58] (1976) | Detailed literature review from 1950 to 1974 cataloguing the results in more than 3400 surgically treated cases of recurrent ulcer following various operations. | IV | 1344 | 53 (3.9%) | 191 (14.2%) | 894 (66.5%) | 99 (7.4%) |

*Table 6 continued.*

**Table 6.** *Continued*

| Remedial operation | Study description | Level of evidence | Sample size | Operative mortality | Recurrence rate (%) | Visick grade (I or II; excellent or good) | Visick grade (III or IV; fair or poor) |
|---|---|---|---|---|---|---|---|
| Browder et al.[78] (1997) | Retrospective case series of 20 patients with recurrent ulcers after gastric resection more than 10 years previously (average time to recurrence 21 yr) | III | 20 | 0 (0.0%) | 0 (0.0%) | 16 (80%) | 4 (20%) |
| Ingvar et al.[80] (1986) | Retrospective case series of 40 consecutive patients undergoing reoperation between 1971 and 1980 at University Hospital, Lund, Sweden for ulcer recurrence after PCV | III | 17 | 0 | 1 (6%) | 14 (82%) | 3 (18%)† |
| Hoffman et al.[84] (1986) | Retrospective case series of 60 patients with recurrent ulcers after vagotomy (PCV = 23; TV or SV & D = 37) treated with partial gastrectomy; average follow-up was 8 yr | III | 51 | 1 (1.67%) | 4 (7.8%) | 30 (59%) | 21 (41%) |

*Five patients required remedial operations to treat ulcer recurrence (n = 1) or severe postgastrectomy symptoms/complications (n = 4).
†Four patients required remedial operations to treat gastric outlet obstruction.

antrectomy with or without truncal vagotomy. These procedures have a relatively low incidence of ulcer recurrence and a modest risk of morbidity and mortality.[14,22,23,58,80,81] For patients with a failed truncal vagotomy and pyloroplasty with adequate gastric drainage and an incomplete vagotomy, transthoracic or thoracoscopic vagotomy represent very good surgical options, particularly in relatively high-risk patients.[23,82,83] Thoracoscopy is generally well tolerated and avoids the potential morbidity of repeat dissection within the esophageal hiatus and upper abdomen necessitated by an abdominal approach. Operative revision after parietal cell vagotomy is thought to be associated with lower morbidity risk than other initial acid-reducing procedures.[11]

Historically, the operative approach in patients with ulcer recurrence after a truncal vagotomy and antrectomy or a distal gastrectomy is partial gastric resection. Recurrent PUD after truncal vagotomy and antrectomy or partial gastrectomy strongly suggests the presence of confounding factors such as NSAID use or a hypersecretory state. Recent studies have documented the importance of ASA abuse in the etiology of such virulent ulcer disease and very high rates of ulcer recurrence after even very aggressive operative intervention.[21,26] In the past, this situation has been managed operatively by further gastric resection that may necessitate subtotal or even total gastrectomy. Unfortunately, severe postgastrectomy symptoms after these extensive procedures occur in as many as 20% to 40% patients.[14,22,58,78,80,84] Patients with recurrent ulcer disease and an incomplete vagotomy may benefit from a thoracoscopic truncal vagotomy so long as NSAID use has been eliminated and there is no evidence of gastric stasis or gastric outlet obstruction. Again, this thoracic approach avoids a difficult dissection in the upper abdomen and eliminates a likely cause of ulcer recurrence. In those instances where ulcer recurrence is accompanied by gastric outlet obstruction, vagotomy and revision of the anastomosis (with further gastric resection) are necessary to relieve the mechanical obstruction and further reduce gastric acid secretion.

Ulcer recurrence after adequate resection for gastric ulcer disease strongly suggests the use of NSAIDs or the presence of a hypersecretory state such as that associated with a gastrinoma or retained excluded

gastric antrum. Also, patients who have undergone resection for gastric ulcers appear to have a threefold increase in the risk of gastric adenocarcinoma when followed for more than 25 years after a Billroth II reconstruction.[85] Clearly, an aggressive diagnostic approach, including endoscopic biopsy, is necessary in patients with gastric ulcers. In general, the operative approach in patients with recurrent benign gastric ulcers has been further gastric resection. However, the postgastrectomy complications associated with extended gastric resection and the relative high frequency of NSAID use in these patients (with its attendant negative effect on surgical outcomes) should relegate extended gastric resection for recurrent gastric ulcer disease to a very small cohort of patients.

## RESULTS OF REMEDIAL OPERATIONS

Numerous retrospective studies have evaluated the results of remedial ulcer operations performed between 1950 and 1985.* The results of the largest studies are reviewed in Table 6. Unfortunately, there are very few recent data on the results of operations for recurrent PUD and no prospective data.

### Ulcer Recurrence

Overall the frequency of ulcer recurrence varies from 8% to 22%. The likelihood of ulcer recurrence is dependent on the remedial procedure performed with the highest rates associated with repeat vagotomy alone and lower rates associated with repeat vagotomy and antrectomy or distal gastrectomy. Revision of a gastroenterostomy alone or any other non–acid-reducing operation is associated with a high rate of ulcer recurrence.[23,58] Patients who continue to take ASA (and probably other NSAIDs) after the operative management of their ulcer disease appear to be at particularly high risk for recurrence (80% to 90%) regardless of the operative procedure performed. The virulence of the ulcer disease is suggested by the high rate of gastric outlet obstruction, perforation, and death in these patients.[21,26]

### Operative Mortality

Early studies reported that the overall mortality rate of operations for recurrent ulcer disease was 2% to 4%. In the collected review by Stabile and Passaro,[58] the operative mortality rate for truncal vagotomy and antrectomy, partial gastric resection, and vagotomy and drainage was between 2.2% and 3.7% depending on the procedure.[58] Similar results are reported in more recent smaller studies.[19,78] Browder et al.[78] had no deaths among 20 patients with recurrent ulcers who underwent gastric resection with or without vagotomy. The presence of a complication of ulcer disease mandating an emergency operation significantly increases the risk of operative mortality and likely has a greater effect on mortality than the magnitude of the operative procedure.[14,22] For example, in a study by Heppell et al.,[22] among 120 patients there was one death after 107 elective procedures and three deaths after 13 emergency operations. In contrast, a more recent study by Kinney et al.[19] reported no deaths among 20 patients who were undergoing either elective or emergency treatment of recurrent ulcer disease.

### Quality of Life

The chronic postoperative complications of both primary and remedial acid-reducing operations include diarrhea, dumping, chronic abdominal pain syndromes, impaired gastric emptying, osteoporosis, and anemia. Most investigators report that 60% to 80% of patients who undergo remedial operations for recurrent PUD will have either no symptoms or only occasional mild symptoms (Visick grades I and II), whereas 20% to 40% will have severe or incapacitating symptoms including ulcer recurrence (Visick grades III and IV). Excluding ulcer recurrence, approximately 10% to 20% of patients undergoing remedial operative procedures will have chronic symptoms that have a significant impact on the patients' life (Visick grades III and IV—without ulcer recurrence).*

## SUMMARY

Patients with symptoms suggestive of recurrent PUD after acid-reducing operations should undergo a careful medical history and physical examination with particular attention to identifying evidence of complications of ulcer disease. Given the frequent use of NSAIDs and the importance of these agents in the pathogenesis of recurrent PUD, patients must be carefully questioned regarding their use and treatment with less ulcerogenic analgesics and anti-inflammatory agents instituted. EGD is performed to docu-

*References 14,15,19–22,58,78,80–84.

*References 14,15,19–22,58,78,80–84.

ment the presence of an ulcer and determine the presence or absence of *H. pylori.* Serum is obtained for a fasting gastrin determination to identify unusual but treatable causes of recurrent ulceration. In the absence of achlorhydria, fasting serum gastrin concentrations greater than 1000 pg/ml are virtually diagnostic of a hypersecretory syndrome. For those patients with recurrent PUD, treatment is initiated with a PPI or H2-RA and, if *H. pylori* infection is documented, antibiotic therapy is used. Repeat EGD is usually performed 6 to 8 weeks later to document ulcer healing. If the ulcer is healed, the patient is treated with long-term maintenance acid suppression with a PPI or H2-RA. Operative management is considered for those patients with nonhealing symptomatic ulcers or those who develop a complication of their ulcer disease that cannot be managed nonoperatively. The most appropriate surgical procedure depends on the exact nature of the previous operation, the adequacy of the previous vagotomy, the presence of gastric stasis or outlet obstruction, and the presence of significant medical comorbidity. In general, the preferred operative approach will be that with the lowest rate of ulcer recurrence which the patient is able to tolerate. In most good-risk patients with an incomplete vagotomy, this will be a repeat vagotomy and antrectomy. In those patients with significant medical illnesses and ulcer disease related to an incomplete vagotomy, a thoracoscopic truncal vagotomy may be preferable, provided that the patient has had a previous and still functional emptying procedure such as pyloroplasty or gastrojejunostomy. Patients who develop ulcer recurrence after more extensive procedures, such as truncal vagotomy and antrectomy or truncal vagotomy and partial gastric resection, must be strongly suspected of using either NSAIDs or ASA or having a hypersecretory state such as a gastrinoma or a retained gastric antrum.

REFERENCES

1. Antes G, Galandi D, Bouillon B. What is evidence-based medicine. Langenbecks Arch Surg 1999;384:409–416.
2. AHCPR (1992) Acute pain management: Operative or medical procedures and trauma. Clinical practice guideline No. 1. AHCPR Publication No. 92-003.
3. Meisner S, Jorgensen LN, Jensen HE. The Kaplan and Meier and the Nelson estimate for the probability of ulcer recurrence 10 and 15 years after parietal cell vagotomy. Ann Surg 1988;207:1–3.
4. Johnston GW, Spencer EFA, Wilkinson AJ, Kennedy TL. Proximal gastric vagotomy: Follow-up at 10-20 years. Br J Surg 1991;78:20–23.
5. von Holstein C, Graffner H, Oscarson J. One hundred patients ten years after parietal cell vagotomy. Br J Surg 1987;74:101–103.
6. Koruth NM, Dua KS, Brunt PW, Matheson NA. Comparison of highly selective vagotomy with truncal vagotomy and pyloroplasty: Results at 8-15 years. Br J Surg 1990;77:70–72.
7. Jordan PH Jr, Thornby J. Twenty years after parietal cell vagotomy or selective vagotomy antrectomy for treatment of duodenal ulcer: Final report. Ann Surg 1994;220:283–296.
8. Hoffman J, Olesen A, Jensen HE. Prospective 14- to 18-year follow-up study after parietal cell vagotomy. Br J Surg 1987;74:1056–1059.
9. Hoffman J, Jensen H-E, Christiansen J, Olesen A, Loud FB, Hauch O. Prospective controlled vagotomy trial for duodenal ulcer: Results after 11-15 years. Ann Surg 1989; 209:40–45.
10. Macintyre IMC, Millar A, Smith AN, Small WP. Highly selective vagotomy 5-15 years on. Br J Surg 1990; 77:65–69.
11. Herrington JL, Davidson J, Shumway SJ. Proximal gastric vagotomy: Follow-up of 109 patients for 6-13 years. Ann Surg 1986;204:108–113.
12. Koo J, Lam SK, Chan P, Lee NW, Lam P, Wong J, Ong GB. Proximal gastric vagotomy, truncal vagotomy with drainage, and truncal vagotomy with antrectomy for chronic duodenal ulcer: A prospective, randomized controlled trial. Ann Surg 1983;197:263–271.
13. Taylor TV, Lythgoe JP, McFarland JB, Gilmore IT, Thomas PE, Ferguson GH. Anterior lesser curve seromyotomy and posterior truncal vagotomy versus truncal vagotomy and pyloroplasty in the treatment of chronic duodenal ulcer. Br J Surg 1990;77:1007–1009.
14. Schirmer BD, Meyers WC, Hanks JB, Kortz WJ, Jones RS, Postlethwait RW. Marginal ulcer: A difficult problem. Ann Surg 1982;195:653–661.
15. Bambach CP, Coupland GAE, Cumberland VH, Lorang ME. Surgery for recurrent peptic ulceration. Aust NZ J Surg 1978;48:141–147.
16. Jensen HE, Kjaergaard J, Meisner S. Ulcer recurrence two to twelve years after parietal cell vagotomy for duodenal ulcer. Surgery 1983;94:802–806.
17. Andersen D, Hostrup H, Amdrup E. The Aarhus county vagotomy trial. II. An interim report on reduction in acid secretion and ulcer recurrence rate following parietal cell vagotomy and selective gastric vagotomy. World J Surg 1978;2:91–100.
18. Johnston D, Blackett RL. Recurrent peptic ulcers. World J Surg 1987;11:274–282.
19. Kinney E, Goderwis D, Mullins RJ, Larson GM. Management of recurrent duodenal ulcer disease. Am Surg 1988; 54:15–18.
20. Lee YT, Sung JJY, Choi CL, Chan FKL, Ng EKW, Ching JYL, Leung WK, Chung SCS. Ulcer recurrence after gastric surgery: Is Helicobacter pylori the culprit? Am J Gastroenterol 1998;93:928–931.
21. Hirschowitz BI, Lanas A. Intractable upper gastrointestinal ulceration due to aspirin in patients who have undergone surgery for peptic ulcer. Gastroenterology 1998;114:883–892.
22. Heppell J, Bess MA, McIlrath DC, Dozois RR. Surgical treatment of recurrent peptic ulcer disease. Ann Surg 1983; 198:1–4.
23. Thirlby RC. Postoperative recurrent ulcer. Gastroenterol Clin North Am 1994;23:295–311.
24. McFadden DW, Zinner MJ. Reoperation for recurrent peptic ulcer disease. Surg Clin North Am 1991;71:77–92.
25. Mosiman F, Donovan IA, Alexander-Williams J. Pitfalls in the diagnosis of recurrent ulceration after surgery for peptic ulcer disease. J Clin Gastroenterol 1985;7:133–136.
26. Perrault J, Fleming CR, Dozois RR. Surreptitious use of salicylates: A cause of chronic recurrent gastroduodenal ulcers. Mayo Clin Proc 1988;63:337–342.

27. Cohen F, Valleur P, Serra J, Brisset D, Chiche L, Hautefeuille P. Relationship between gastric acid secretion and the rate of recurrent ulcer after parietal cell vagotomy. Ann Surg 1993;217:253–259.
28. Stenquist B, Forssell H, Olbe L, Lundell L. Role of acid secretory response to sham feeding in predicting recurrent ulceration after proximal gastric vagotomy. Br J Surg 1994;81:1002–1006.
29. Braghetto I, Csendes A, Lazo M, Rebolledo P, Diaz A, Bardavid A, Bahamonde A, Thomet G. A prospective, randomized study comparing highly selective vagotomy and extended highly selective vagotomy in patients with duodenal ulcer. Am J Surg 1988;155:443–446.
30. Feldman M, Richardson CT, Fordtran JS. Experience with sham feeding as a test for vagotomy. Gastroenterology 1980;79:796–800.
31. Emas S, Grupcev G, Ericksson B. Ten-year follow-up of a prospective, randomized trial of selective proximal vagotomy with ulcer excision and partial gastrectomy with gastroduodenostomy for treating corporeal gastric ulcer. Am J Surg 1994;167:596–600.
32. Stoddard CJ, Johnson AG, Duthie HL. The four to eight year results of the Sheffield trial of elective duodenal ulcer surgery—Highly selective or truncal vagotomy. Br J Surg 1984;71:779–782.
33. Kjaergaard J, Jensen H-E, Allermand H. Inadequately reduced acid secretion after vagotomy for duodenal ulcer: A follow-up study three to nine years after surgery. Ann Surg 1980;192:711–715.
34. Lanas A, Sekar C, Hirschowitz BI. Objective evidence of aspirin use in both ulcer and non-ulcer upper and lower gastrointestinal bleeding. Gastroenterology 1992;103:862–869.
35. Lanas A, Serrano P, Bajador E, Esteva F, Benito R, Sainz R. Evidence of aspirin use in both upper and lower gastrointestinal perforation. Gastroenterology 1997;112:683–689.
36. Weaver GA, Harper RL, Storey JA, Jenkins PL, Merrell NB. Nonsteroidal anti-inflammatory drugs are associated with gastric outlet obstruction. J Clin Gastroenterol 1997;20:196–198.
37. Van der Hulst R, Rauws EAJ, Koycu B, Keller JJ, Bruno MJ, Tijssen JGP, Tytgat GNJ. Prevention of ulcer recurrence after eradication of Helicobacter pylori: A prospective long-term follow-up study. Gastroenterology 1997;113: 1082–1086.
38. Hawkey CJ, Karrasch JA, Szczepanski L, Walker DG, Barkun A, Swannell AJ, Yeomans ND. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal anti-inflammatory drugs: the OMNIUM study. N Engl J Med 1998;338:727–734.
39. Hawkey CJ. Progress in prophylaxis against nonsteroidal anti-inflammatory drug-associated ulcers and erosions. Am J Med 1998;104:67S–74S.
40. Cryer B, Feldman M. Effects of very low dose daily, long-term aspirin therapy on gastric, duodenal, and rectal prostaglandin levels and on mucosal injury in healthy humans. Gastroenterology 1999;117:17–25.
41. The SALT Collaborative Group. Swedish aspirin low-dose trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischaemic events. Lancet 1991;338:1345–1349.
42. Allison MC, Howatson AG, Torrance CJ, Lee FD, Russell RI. Gastrointestinal damage associated with the use of nonsteroidal anti-inflammatory drugs. N Engl J Med 1992;327: 749–754.
43. NIH Consensus Conference. Helicobacter pylori in peptic ulcer disease. JAMA 1994;272:65–69.
44. Hentschell E, Brandstatter G, Dragosics B, Hirschl AM, Nemec H, Schutze K, Taufer M, Wurzer H. Effect of ranitidine and amoxicillin plus metronidazole on the eradication of Helicobacter pylori and the recurrence of duodenal ulcer. N Engl J Med 1993;328:308–312.
45. Graham DY, Lew GM, Klein PD, Evans DG, Evans DJ, Saeed ZA, Malaty HM. Effect of treatment of Helicobacter pylori infection on the long-term recurrence of gastric or duodenal ulcer: A randomized, controlled study. Ann Intern Med 1992;116:705–708.
46. Peetsalu A, Maaroos HI, Sipponen P, Peetsalu M. Long-term effect of vagotomy on gastric mucosa and Helicobacter pylori in duodenal ulcer patients. Scand J Gastroenterol 1991;26(Suppl 186):77–83.
47. Leivonen MK, Haglund CH, Nordling SF. Helicobacter pylori infection after partial gastrectomy for peptic ulcer and its role in relapsing disease. Eur J Gastroenterol Hepatol 1997;9:371–374.
48. Peetsalu M, Maaroos HI, Peetsalu A. Completeness of vagotomy, Helicobacter pylori colonization and recurrent ulcer 9 and 14 years after operation in duodenal ulcer patients. Eur J Gastroenterol Hepatol 1998;10:305–311.
49. Leivonen MK, Nordling SF, Haglund CH. The course of Helicobacter pylori infection after partial gastrectomy for peptic ulcer disease. Hepatogastroenterology 1998;45:587–591.
50. Schilling D, Adamek HE, Wilke J, Schauwecker P, Martin WR, Arnold JC, Benz C, Labenz J, Riemann JE. Prevalence and clinical importance of Helicobacter pylori infection in patients after partial gastric resection for peptic ulcer disease. A prospective evaluation of Helicobacter infection on 50 resected patients compared with matched nonresected controls. Z Gastroenterol 1999;37:127–132.
51. Csendes A, Smok G, Coronel M, Avendano R, Zenteno G, Cordova H. The presence of Helicobacter pylori in nonoperated duodenal ulcer patients compared to patients late after highly selective vagotomy. Dig Dis Sci 1996;41:2366–2368.
52. Sito E, Konturek PC, Konturek SJ, Bielanski W, Stachura J. Helicobacter pylori infection after gastrectomy and vagotomy in duodenal ulcer patients. J Physiol Pharmacol 1996; 47:229–237.
53. Reeder DD, Jackson BM, Ban J, Clendinnen BG, Davidson WD, Thompson JC. Influence of hypercalcemia on gastric secretion and serum gastrin concentrations in man. Ann Surg 1970;172:540–546.
54. Wilson SD, Singh RB, Kalkhoff RK. Does hyperparathyroidism cause hypergastrinemia? Surgery 1976;80:231–237.
55. Linos DA, van Heerden JA, Abboud CF, Edis AJ. Primary hyperparathyroidism and peptic ulcer disease. Arch Surg 1978;113:384–386.
56. Hangen D, Maltz GS, Anderson JE, Knauer CM. Marked hypergastrinemia in gastric outlet obstruction. J Clin Gastroenterol 1989;11:442–444.
57. Amdrup E, Brandsborg M, Brandsborg O, Lovgreen NA. Interrelationship between serum gastrin concentration, gastric acid secretion, and gastric emptying rate in recurrent peptic ulcer. World J Surg 1979;3:235–240.
58. Stabile BE, Passaro E Jr. Recurrent peptic ulcer. Gastroenterology 1976;70:124–135.
59. Kirulik LB, Merendino KA. An experimental study of the buffering capacity of the contents of the upper small bowel. Surgery 1954;35:532–537.
60. Kirulik LB, Merendino KA. An elucidation of the intestinal sensitivity factor and the distance factors in the incidence of stomal ulcer in the Bilroth II type of gastroenterostomy. Surgery 1954;35:538–546.
61. Nuboer JF. Recurrent ulceration after surgical treatment of gastroduodenal peptic ulcer. Ann R Coll Surg Engl 1961; 28:303–320.

62. Lewin JL, Yang K, Ulrich T Elashoff JD, Walsh J. Primary gastrin cell hyperplasia: Report of five cases and a review of the literature. Am J Surg Pathol 1987;8:821–832.
63. Friesen SR, Tomita T. Further experience with pseudo-Zollinger-Ellison syndrome: Its place in the management of neuroendocrine duodenal ulceration. World J Surg 1984;8: 552–560.
64. Graham DY, Opekun A, Lew GM, Evans DJ Jr, Klein PD, Evans DG. Ablation of exaggerated meal-stimulated gastrin release in duodenal ulcer patients after clearance of Helicobacter (Campylobacter) pylori infection. Am J Gastroenterol 1990;85:394–398.
65. Levi S, Beardshall K, Swift I, Foulkes W, Playford R, Ghosh P, Calam J. Antral Helicobacter pylori, hypergastrinaemia, and duodenal ulcers: Effect of eradicating the organism. BMJ 1989; 299:1504–1505.
66. Wolfe MM, Jain DK, Edgerton JR. Zollinger-Ellison syndrome associated with persistently normal fasting serum gastrin concentrations. Ann Intern Med 1985;103:215–217.
67. Weber HC, Orbuch M, Jensen RT. Diagnosis and management of Zollinger-Ellison syndrome. Semin Gastrointest Dis 1995;6:79–89.
68. Gugler R, Lindstaedt H, Miederer S, Mockel W, Rohner HG, Schmitz H, Szekessy T. Cimetidine for anastomotic ulcers after partial gastrectomy: A randomized controlled trial. N Engl J Med 1979;301:1077–1080.
69. Stage JG, Friis J, Nielsen OV. Ranitidine treatment of patients with postoperative recurrent ulcers [abstr]. Scand J Gastroenterol 1983;86(Suppl):80.
70. Koo J, Lam SK, Ong GB. Cimetidine versus surgery for recurrent ulcer after gastric surgery. Ann Surg 1982;195:406–412.
71. Binder HJ, Cocco A, Crossley RJ, Finkelstein W, Font R, Friedman G, Groarke J, Hughes W, Johnson AF, McGuigan JE, Summers R, Vlahcevic R, Wilson EC, Winship DH. Cimetidine in the treatment of duodenal ulcer: A multicenter double blind study. Gastroenterology 1978;74:380–388.
72. Legerton CW. Duodenal and gastric ulcer healing rates: a review. Am J Med 1984;77(Suppl 5B):2–7.
73. Gitlin N, McCullough AJ, Smith JL, Mantell G, Berman R. A multicenter, double-blind, randomized, placebo-controlled comparison of nocturnal and twice-a-day famotidine in the treatment of active duodenal ulcer disease. Gastroenterology 1987;92:48–53.
74. Dekkers CPM, Beker JA, Thjodleifsson B, Gabryelewicz A, Bell NE, Humphries TJ, et al. Comparison of rabeprazole 20 mg versus omeprazole 20 mg in the treatment of active duodenal ulcer: A European multicentre study. Aliment Pharmacol Thera 1999;13:179–186.
75. Poynard T, Lemaire M, Agostini H. Meta-analysis of randomized clinical trials comparing lansoprazole with ranitidine or famotidine in the treatment of acute duodenal ulcers. Eur J Gastroenterol Hepatol 1995;7:661–665.
76. Yeomans ND, Tulassay Z, Juhasz L, Racz I, Howard JM, van Rensburg CJ, Swannell AJ, Hawkey CJ. A comparison of omeprazole with randitidine for ulcers associated with nonsteroidal anti-inflammatory drugs: The ASTRONAUT study group. N Engl J Med 1998;338:719–726.
77. Gabriel SE, Jaakkimainen L, Bombardier C. Risks for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. Ann Intern Med 1991;115:787–796.
78. Browder W, Thompson J, Youngberg G, Walters D. Delayed ulcer recurrence after gastric resection: A new postgastrectomy syndrome. Am Surg 1997;63:1091–1096.
79. Feldman M, Richardson CT, Fordtran JS. Effects of sham feeding on gastric acid secretion in healthy subjects and duodenal ulcer patients: Evidence for increased basal vagal tone in some ulcer patients. Gastroenterology 1980;79:796–800.
80. Ingvar C, Adami HO, Enander LK, Enskog L, Rydberg B. Clinical results of reoperation after failed highly selective vagotomy. Am J Surg 1986;152:308–312.
81. Hoffman J, Meisner S, Jensen HE. Antrectomy for recurrent ulcer after parietal cell vagotomy. Br J Surg 1983;70: 120–121.
82. Thirlby RC, Feldman M. Transthoracid vagotomy for postoperative peptic ulcer: Effects on basal, sham feeding- and pentagastrin-stimulated acid secretion and on clinical outcome. Ann Surg 1985; 201:648–655.
83. Laws HL, Naughton MJ, McKernan JB. Thoracoscopic vagectomy for recurrent peptic ulcer disease. Surgical Laparosc Endosc 1992;2:24–28.
84. Hoffman J, Shokouh-Amiri MH, Klarskov P, Madsen OG, Jensen HE. Gastrectomy for recurrent ulcer after vagotomy: Five- to nineteen-year follow-up. Surgery 1986;99: 517–522.77.
85. Toftgaard C. Gastric cancer after peptic ulcer surgery. A historic prospective cohort investigation. Ann Surg 1989; 210:159–164.

# Solitary Necrotic Nodule of the Liver: A Riddle That Is Difficult to Answer

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Solitary necrotic nodule of the liver is an unusual lesion that is often an incidental finding on abdominal imaging, intraoperative examination, or post mortem. Most reported cases of solitary necrotic nodule have been in males, and over three quarters of these lesions have occurred in the right lobe of the liver. Pathologically, solitary necrotic nodule is a benign lesion characterized by a completely necrotic core that is often partly calcified, surrounded by a dense hyalinized fibrous capsule containing elastin fibres. The ultrasound appearance of solitary necrotic nodule is usually of a "target" lesion with a hyperechoic center, while on CT scan they appear as non-enhancing hypodense lesions that are typical of metastatic adenocarcinoma or peripheral cholangiocarcinoma. The impression of malignancy is further enforced with the finding of necrotic cellular material on biopsy and the macroscopically hard and "gritty" nature of the nodules. Currently, permanent histopathology of solitary necrotic nodules is the only accurate method of diagnosis. However, solitary necrotic nodules are usually of a bilobed or lobulated shape that is unusual for malignant liver lesions, and they often lie in close proximity to hepatic inflow structures. Solitary necrotic nodule should be suspected in liver lesions with this configuration, location, and on a biopsy showing a large amount of necrosis. (J GASTROINTEST SURG 2003;7:627–630.) 

KEY WORDS: Hepatic neoplasm, solitary necrotic nodule

As the safety of hepatic resection has improved and its benefits for patients with primary and secondary tumors of the liver have become clearer, a more aggressive approach of the management of liver lesions has been adopted. This in turn has led to the definition of new pathologies and new lesions.[1] Solitary necrotic nodule of the liver was first reported in 1983 by Shepherd and Lee,[2] who described four lesions, two of which were post mortem findings, with a characteristic histological appearance. Solitary necrotic nodule is a benign lesion and can be pathologically distinguished from other benign liver lesions. However, because of the presence of necrosis, biopsies of these lesions are frequently misinterpreted as metastases or primary liver tumors.

The purpose of this report is to highlight this condition. While fewer than 50 cases have been reported in the literature, as more patients with liver lesions are referred for hepatic resection, solitary necrotic nodule will need to be considered as a differential, particularly in those patients with a biopsy suggestive of necrotic adenocarcinoma.

## CASE REPORT

A 40-year-old Caucasian female presented with a single, self-limited episode of vaginal bleeding. Her past history was unremarkable apart from a brief hospitalization for observation after blunt abdominal trauma 8 months prior. Physical examination, including pelvic examination, was within normal limits. An abdominal ultrasound was undertaken. Both uterus and ovaries were not enlarged. However views of the liver showed a soft tissue mass in the right lobe (Figure 1*A*). A malignant lesion was suspected and ultrasound-guided needle biopsy showed necrotic material suspicious for, but not diagnostic of, metastatic carcinoma (Figures 2*A* and *B*). The patient's

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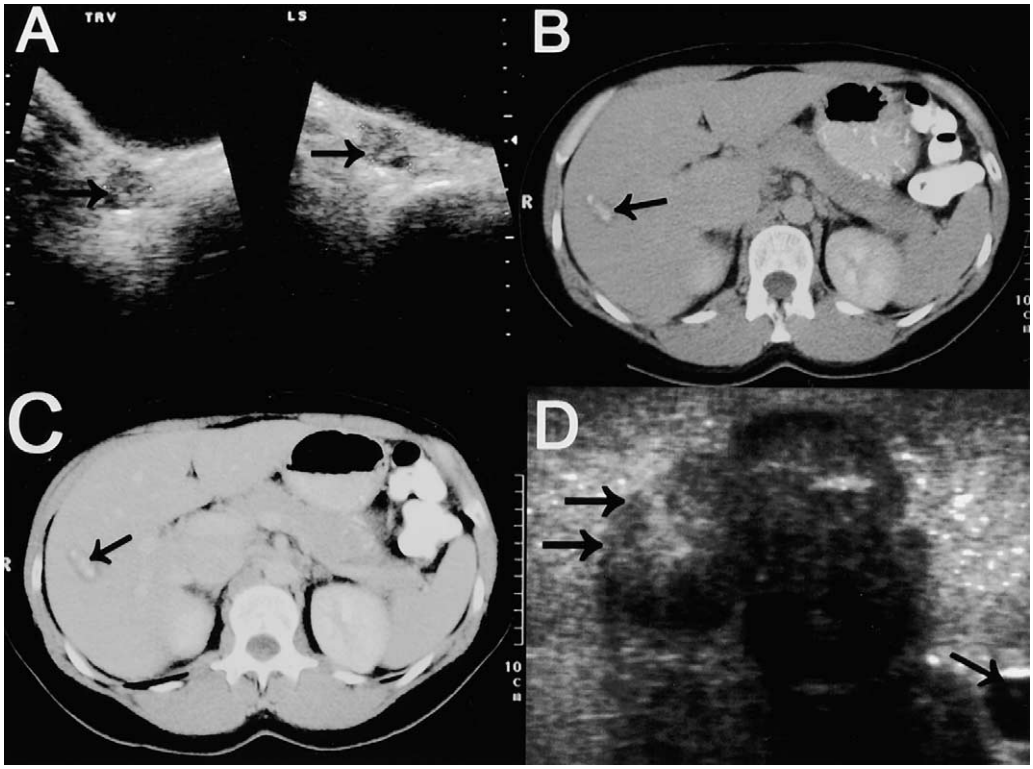


**Fig. 1.** (**A**) Transcutaneous ultrasound of the liver demonstrating a lesion in the right lobe with central hyperechoic area surrounded by a hypoechoic rim (*arrow*). (**B**) Non contrast CT scan showing a partly calcified bilobed lesion in segment V. (**C**) CT scan post contrast showing the non-enhancing lesion in segment V. (**D**) Intraoperative ultrasound demonstrating the bilobed hyperechoic lesion in segment V.

full blood count, liver function tests, and electrolytes were in the normal range, while serology for hepatitis *A*, *B*, and *C* was negative. The tumor markers Ca 15-3, Ca 19-9, Ca 125, carcinoembryonic antigen (CEA), and alpha fetoprotein (αFP) were not elevated. The patient then underwent a full diagnostic work-up for a possible primary tumor site. Mammography and breast examination were normal, as were upper and lower gastrointestinal endoscopy, skin examination, and cervical cytology. Further investigation with CT scan of the chest and abdomen showed no other metastatic lesions and a solitary, partly calcified lesion in segment V (Figures 1*B* and *C*). A bone scan showed increased isotopic uptake in the area of the right costal margin suggesting osteolytic metastases; however plain X-rays of this area showed two healing rib fractures related to previous trauma. The patient was then referred for liver resection with a clinical diagnosis of either a small peripheral cholangiocarcinoma or a metastasis from a tumor of unknown primary. Intraoperative ultrasound showed a bilobed, hypoechoic mass 3 cm in diameter closely related to the segment V inflow (Figure 1*D*). A right hepatic lobectomy was performed without complication. Sectioning of the resected specimen showed a lobulated 30 × 30 × 25 mm mass lying 40 mm from the capsule. The lesion was firm and "gritty" in consistency with a well defined margin. Permanent histology is shown in Figures 2*C* and *D*.

Postoperatively the patient did well, leaving the hospital on day 6 postresection. She remains well 2 years following her initial presentation.

## DISCUSSION

Solitary necrotic nodule of the liver is an unusual lesion with just 40 cases reported in the world literature.[2–13] The current case was taken from 500 referrals with liver masses presenting over a 2-year period. Other investigators have also documented a similar incidence of solitary necrotic nodule with Berry defining 2 lesions in 1000 post mortems[9] and Tsui et al. documenting 7 lesions in 4000 patients.[11] The majority of solitary necrotic nodules have presented in the seventh and eighth decades of life.[2,6,7,9,11,12] However, the lesions have also been reported in patients as young as 27 years of age[11] and a number of cases, including this one, have been found in patients

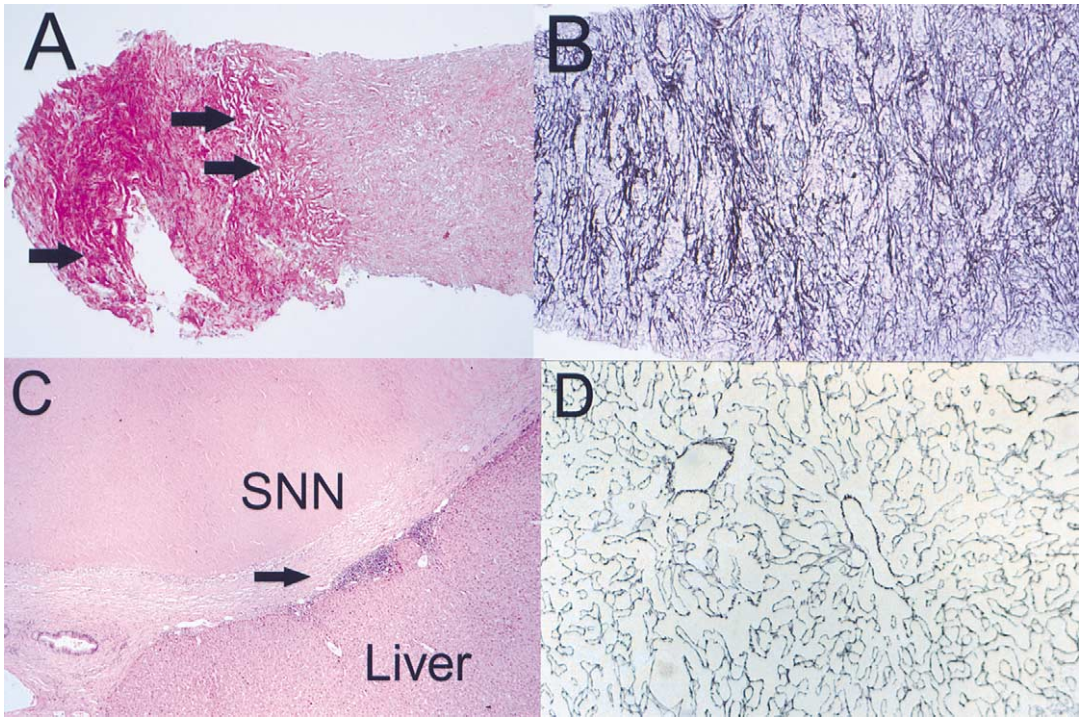


**Fig. 2.** (**A**) Core needle biopsy of the solitary necrotic nodule showing a large amount of necrotic cellular material suggestive of adenocarcinoma (*arrow*) separated from adjacent normal liver tissue by a fibrous capsule (*double arrow*; Van Geisen; magnification ×100). (**B**) Reticulin staining (magnification ×100) of the core needle biopsy showing a collapsed reticulin framework and pattern suggestive of vascular spaces. (**C**) Permanent section from the solitary necrotic nodule (SNN) showing a well circumscribed lesion containing necrotic tissue surrounded by a fibrous capsule (*arrow*). Normal hepatic tissue is adjacent (Liver: hematoxylin and eosin, magnification ×50). (**D**) Reticulin staining (magnification ×100) demonstrating a well preserved reticulin framework within the nodule.

in their thirties and forties.[11,12] Of the 19 cases reported in which the gender of the patient is specified, 13 are male suggesting a male preponderance.[2,7,9,11,12]

Solitary necrotic nodules are not symptomatic and all reported cases have been incidental findings at postmortem, operation, or radiological investigation. In the initial description of Shepherd and Lee[2] all solitary necrotic nodules were noted to be on the surface of the liver and most on the right side. This may simply reflect the ease with which the surface of the right lobe of the liver may be examined but also raises the possibility that trauma may be involved in the pathogenesis of these lesions. Subsequent reports, including this one, have documented the presence of solitary necrotic nodules within the hepatic parenchyma with cross-sectional imaging[3] and these lesions may be more commonly seen as a more aggressive approach to the investigation and management of focal liver lesions is adopted. Interestingly, only four of the reported solitary necrotic nodules have been found in the left lobe.[2,11]

The riddle of solitary necrotic nodule for surgeons is in the making of a preoperative diagnosis. As in this case, they are usually an incidental finding in an otherwise well patient, although the presence of a previous cancer with metastatic potential has been documented in up to 50% of patients[4] making past medical history of questionable use. Also, tumor markers are never elevated, as in this case. Radiological imaging is not specific and may be deceiving. Solitary necrotic nodules present with a hyperechoic center on ultrasound examination suggesting a "target" lesion (Figure 1*A*).[3] The lesions are hypodense masses on computed tomographic scans having a similar appearance to metastatic adenocarcinoma or peripheral cholangiocarcinoma. As in the current case, fine-needle aspiration biopsy yields necrotic cellular material that is often interpreted as suspicious for carcinoma (Figure 2*A*).[4] We have recently highlighted the dangers of tumor dissemination with percutaneous biopsy of metastatic colorectal tumors[14] and the confusing results of biopsy in solitary necrotic nodule also emphasize that, like other inves-

tigations, biopsy has a finite reliability. The impression of malignancy in solitary necrotic nodule may be further reinforced by the presence of multiple lesions[10] and the macroscopic appearance of a firm white nodule that is of "gritty" consistency. However, solitary necrotic nodules are often of a bilobed or lobulated shape that is unusual for primary or metastatic liver lesions,[4] and they often lie in close proximity to hepatic inflow structures (Figure 1*D*).[11] Solitary necrotic nodule should be suspected in liver lesions with this configuration, location, and in which biopsy shows a large amount of necrosis.

Currently the only reliable way to make the diagnosis of solitary necrotic nodule is permanent histology of the entire lesion. Characteristically, this shows a completely necrotic core with a dense hyalinized fibrous capsule containing elastin fibers. Calcification has also been documented.[2] Characteristically Ziehl-Neelsen, Gram, and PAS stains do not reveal bacteria or fungi. Several investigators have documented the presence of protozoa or helminthic larvae with solitary necrotic nodules[7,11] and it has been suggested that solitary necrotic nodules represent fibrous nodules caused by visceral larva migrans, sclerosing hemangiomata, necrotic metastases, or organized intrahepatic thrombi.[2] However, Berry[9] has provided evidence that solitary necrotic nodules are derived from vascular lesions and may represent infarcted or thrombosed hemangiomas. Feeder vessels have been identified and the pattern of reticulin within the lesions suggests a collapsing vascular field (Figure 2*B*).[10] Sundaresan *et al.*[12] have compared solitary necrotic nodules, necrotic metastases, and hemangiomas and concluded that solitary necrotic nodules compare closely to hemangiomas in that both lesions are commonly found at the anterior border of the liver, they often lie close to portal tracts (as in this case), they often have a bilobed configuration,[4] and residual hemangioma-like structures are often found with detailed microscopic inspection. Thus, it appears that solitary fibrous nodules represent a degenerate hemangioma although these histological appearances may also occur at the end stage of a variety of benign liver lesions.[15]

The natural history of solitary fibrous nodule is unclear. Most cases have been diagnosed following resection or at postmortem. De Luca *et al.*[4] have reported a patient followed for 24 months in whom the nodule decreased in size and, given that the lesions are not neoplastic, it seems reasonable to expect that they would pursue a resolving course. However, given the uncertainty over the optimum method of definitive preoperative diagnosis and the often misleading results of cross sectional imaging and biopsy, it seems likely that most solitary fibrous nodules will be managed with resection in order to obtain a diagnosis. Most patients are unwilling to watch lesions that appear malignant in an era of safe hepatic resection.

REFERENCES

1. Nakamura Y. Non-neoplastic lesions in the liver. Pathology Int 1995;45:703–714.
2. Shepherd NA, Lee G. Solitary necrotic nodules of the liver simulating hepatic metastases. J Clin Pathol 1983;36:1181–1183.
3. Yoon KH, Yun KJ, Lee JM, Kim CG. Solitary necrotic nodules of the liver mimicking hepatic metastases: Report of two cases. Korean J Radiol 2000;1:165–168.
4. De Luca M, Luigi B, Formisano C, Formato A, De Werra C, Cappuccio M, Loffredo A, Forestieri P. Solitary necrotic nodule of the liver misinterpreted as malignant lesion: Considerations on two cases. J Surg Oncol 2000;74(Suppl):219–222.
5. Alfieri S, Carriero C, Doglietto GB, Pacelli F, Crucitti F. Solitary necrotic nodule of the liver: Diagnosis and treatment. Hepato-Gastroenterology 1997;44:1210–1211.
6. Carella R, Fortunato C, Gubinelli M, D'Errico A, Mancini AM. Solitary necrotic nodule of the liver simulating a metastasis. Pathologica 1993;85:573–577.
7. Clouston AD, Walker NI, Prociv P. Parasitic origin of a solitary necrotic nodule of the liver. J Clin Pathol 1993; 46:578.
8. Berry CL. Solitary necrotic nodule of liver; a non-existent lesion. J Pathol 1985;146:263A.
9. Berry CL. Solitary "necrotic nodule" of the liver: A probable pathogenesis. J Clin Pathol 1985;198:1278–1280.
10. Shepherd NA. solitary necrotic nodule. J Clin Pathol 1990;43:348–349.
11. Tsui WM, Yuen RW, Chow LT, Tse CC. Solitary necrotic nodule of the liver: parasitic origin? J Clin Pathol 1992;45: 975–978.
12. Sundaresan M, Lyons B, Akosa AB. "Solitary" necrotic nodules of the liver: An aetiology reaffirmed. Gut 1991;32: 1378–1380.
13. Desai S, Prabhu SR, Shrividya S. Fibrosing necrotic nodule of the liver. Indian J Gastroenterol 1995;14:23–24.
14. Rodgers MS, Collinson R, Desai S, Stubbs RS, McCall JL. The risk of dissemination with biopsy of colorectal liver metastases. Dis Colon Rectom 2002 (in press).
15. Berry CL, Shepherd NA. Solitary necrotic nodule of the liver. J Clin Pathol 1990;43:348–349.

# Small Cell Carcinoma of the Cystic Duct: A Case Report

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Small cell carcinoma usually involves the lung and rarely affects the biliary tract, especially the cystic duct. In this article we report a case of small cell carcinoma of the cystic duct in a 46-year-old Japanese man. The patient presented with abdominal pain and jaundice. Imaging showed a small nodule in the cystic duct invading the common bile duct with dilatation of the proximal biliary tree. The hepatic artery and portal vein were free from invasion. Extended right hepatic lobectomy, cholecystectomy, and resection of the extrahepatic proximal bile ducts were performed together with lymph node dissection under the tentative diagnosis of carcinoma of the cystic duct. Histopathologic examination of the resected specimen revealed small cell carcinoma arising in the cystic duct and extending into the common bile duct. The postoperative clinical course was uneventful, and the patient is doing well without any signs of recurrence 1 year after the operation. To our knowledge this is the first documented case of a small cell carcinoma arising in the cystic duct. (J GASTROINTEST SURG 2003;7:631–634.) 

KEY WORDS: Small cell carcinoma, cystic duct carcinoma, gallbladder carcinoma

Small cell carcinoma is usually seen in the lung and rarely involves the gastrointestinal tract including the biliary tree. Small cell carcinoma of organs other than the lung has been termed extrapulmonary small cell carcinoma (EPSCC) and has been recognized as a distinct clinicopathologic entity from carcinoma of the lung since the initial description by Duguid and Kennedy[1] in 1930. In general, small cell carcinoma exhibits aggressive proliferation, and its clinical course is dismal even after resection.[2,3] Seventy cases of small cell carcinoma in the gallbladder have been reported,[4–23] but none in the cystic duct. We report herein a patient with small cell carcinoma of the cystic duct that was resectable because of the early development of acute cholecytitis and obstructive jaundice, which was due to invasion of the bile duct. We review the reports of 70 patients with small cell carcinoma of the gallbladder in the English literature and emphasize that this is the first documentation of a small cell carcinoma of the cystic duct.

## CASE REPORT

A 46-year-old Japanese man was hospitalized on January 12, 2000, because of upper abdominal pain and jaundice. On physical examination, jaundice was noted and tenderness was recognized in the right upper quadrant, but no mass or organomegaly was observed. Pertinent laboratory data included the following: total bilirubin, 6.7 mg/dl; direct bilirubin, 4.7 mg/dl; glutamic oxaloacetic transaminase, 79 IU/L; glutamic pyruvic transaminase, 219 IU/L; alkaline phosphatase, 427 IU/L; and γ-glutamyltranspeptitase, 130 IU/L. These data indicated obstructive jaundice. Tumor markers, including carcinoembryonic antigen, 19-9 carbohydrate antigenic determinant, and Duke pancreas-II were all within normal limits. Computed tomography (Fig. 1) and ultrasonography of the abdomen showed a mass at the cystic duct and dilatation of the proximal biliary tree. Abdominal angiography showed an encasement of the cystic artery in the arterial phase, and a tumor stain at the cystic duct in the venous

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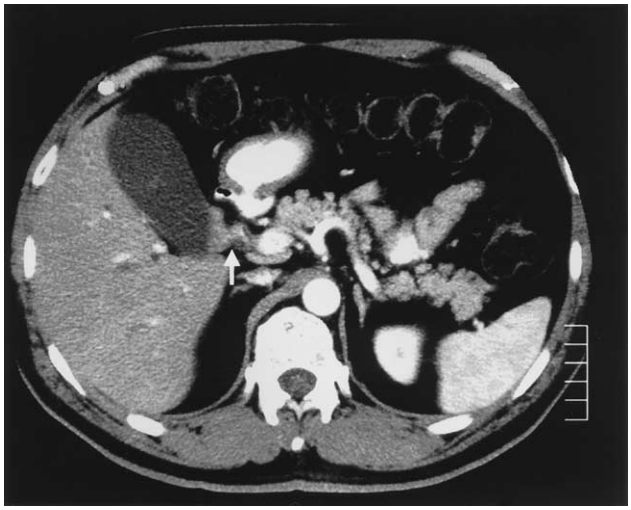

**Fig. 1.** Abdominal CT scan showing an irregular mass in the cystic duct (*arrow*).

phase. As the level of serum bilirubin rose rapidly up to 9.3 mg/dl, percutaneous transhepatic biliary drainage was performed on January 18, 2001. Percutaneous transhepatic gallbladder drainage was performed for persistent dilatation of the gallbladder on January 25, 2001. Tube cholangiography revealed filling defects in the cystic duct and common bile duct (Fig. 2). Endoscopic retrograde cholangiopancreatography showed complete obstruction of the middle common bile duct. Cytologic examination of the drained bile was negative for malignant cells.

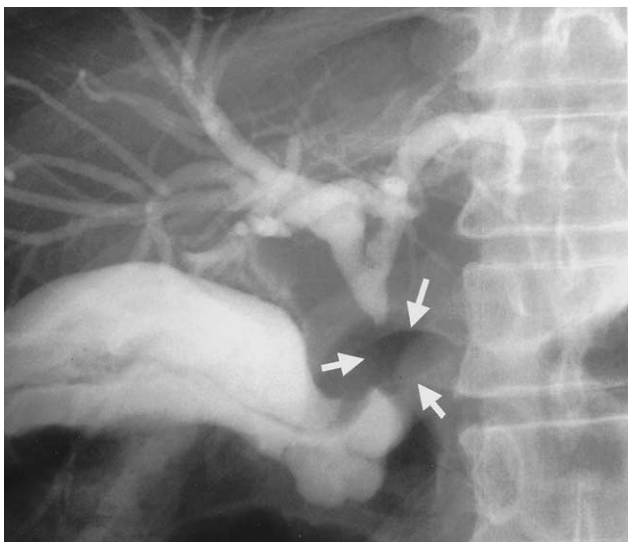

**Fig. 2.** Percutaneous transhepatic cholangiogram showing a filling defect in the cystic duct and the common bile duct (*arrows*).

On the basis of these findings, the patient was diagnosed as having carcinoma of the cystic duct involving the common bile duct, and laparotomy was performed on March 12, 2001. When the abdomen was opened, neither peritoneal dissemination nor liver metastasis was noted. A hard mass, measuring 2 × 3 cm, was palpated at the cystic duct. This mass invaded the common bile duct. Some regional lymph nodes in the hepatoduodenal ligament were swollen and considered to contain metastatic cancer. Extended right hepatic lobectomy, cholecystectomy, and resection of the extrahepatic bile duct were carried out with radical lymph node dissection. Macroscopic examination of the resected specimen revealed a white oval irregular-shaped mass at the cystic duct, measuring 3 cm in diameter. The mass had invaded the adjacent common bile duct (Fig. 3). Microscopically, the tumor was composed of abundant malignant cells with round nuclei and scanty cytoplasm in a trabecular or pseudorosette pattern (Fig. 4, A). Immunohistochemically, the cancer cells were positive for chromogranin A (Fig. 4, B), neuron-specific enolase, and synaptophysin but negative for epithelial membrane antigen and carcinoembryonic antigen. The histopathologic diagnosis was, thus, small cell carcinoma of the cystic duct invading the bile duct. One regional lymph node in the hepatoduodenal ligament contained metastatic carcinoma cells. The patient had an uneventful postoperative recovery. He is alive and well 1 year after operation without any signs of recurrence.

## DISCUSSION

Small cell carcinoma is usually seen in the lung and exhibits very aggressive growth. The clinical course is

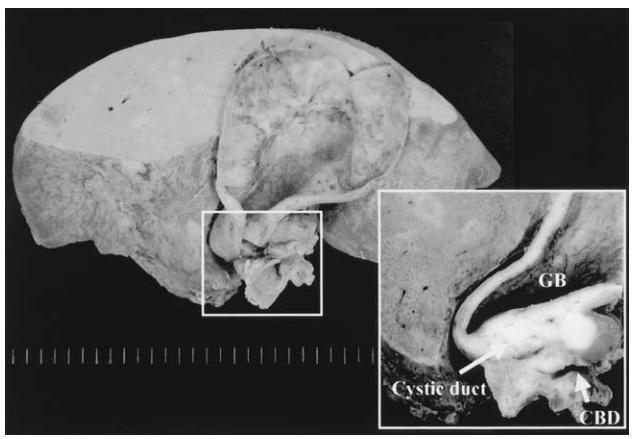


**Fig. 3.** Macroscopic findings of the tumor. A white oval irregular tumor, measuring 3 cm, is located in the cystic duct and invades the common bile duct (*CBD*). GB = gallbladder.

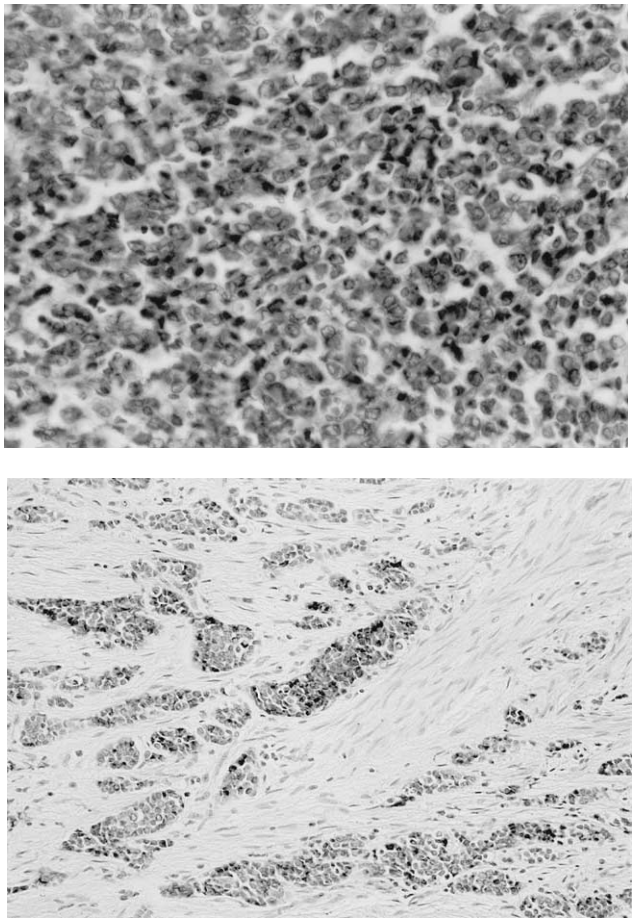

**Fig. 4.** Microscopic findings of the tumor. **A**, The tumor is composed of abundant malignant cells with round nuclei and scanty cytoplasm. **B**, The tumor cells are positive for chromogranin A.

dismal even after surgical resection. EPSCC has been reported in various organs including the larynx, skin, salivary glands, and the entire gastrointestinal tract.[2] EPSCC is often detected at an advanced stage, similar to small cell carcinoma of the lung, and a complete resection can be rarely performed. The prognosis for EPSCC is as unfavorable as that of small cell carcinoma of the lung, the 5-year survival rate being 13%.[3]

Regarding the biliary tract, only 70 patients with small cell carcinoma of the gallbladder have been reported in the English literature.[4–23] Albores-Saavedra et al.[4] reported an incidence of 4.2% (19 small cell carcinomas) in a series of 448 gallbladder carcinomas. Fujii et al.[23] reviewed 54 cases of small cell carcinoma of the gallbladder: 19 found at autopsy and 35 removed at operation. Thirty-six of the 54 patients were women and 18 were men; the mean age was 64.1 years. Distant metastases were evident in 28 (90.3%) of 31 patients whose operative findings were available. Only three patients (9.7%) were stage I, and 16 (51.6%) were stage IV, as shown by metastasis. The median survival time for the 33 patients who had a resection was 25.8 months, and 1- and 5-year survival rates were 47.3% and 11.5%, respectively. Thus the clinical course of patients with small cell carcinoma of the gallbladder is extremely poor.

Primary carcinoma of the cystic duct is a rare neoplasm, the prevalence being 1.5% of gallbladder cancers.[24] The diagnosis of carcinoma of the cystic duct is sometimes difficult because the tumors easily invade the surrounding organs and determination of the site of origin is difficult. Farrar[25] proposed the criteria for the diagnosis of carcinoma of the cystic duct as follows: (1) growth restricted to the cystic duct; (2) no neoplastic process present in the gallbladder, hepatic ducts, and common bile duct; and (3) histologic confirmation of the presence of carcinoma cells in the mass. In our patient the tumor was located mainly in the cystic duct but involved the common bile duct. Thus this tumor does not strictly fulfill the criteria of Farrar et al.[25] However, the tumor was mainly located in the cystic duct, and we made the diagnosis of primary carcinoma of the cystic duct from the topological location of the tumor.

Carcinoma of the cystic duct is generally classified as a part of carcinoma of the gallbladder. However, the prognosis for cystic duct carcinoma is better than that for gallbladder carcinoma.[26] Gallbladder carcinoma is usually detected at an advanced stage because of the paucity of specific symptoms and curative resection can be carried out in a limited number of the patients. Henson et al.[27] reported that 39.8% of patients with gallbladder carcinoma are classified as having stage IV lesions when diagnosed. On the other hand, all 23 patients with cystic duct carcinoma reviewed by Shito et al.[28] had adenocarcinoma without lymph node metastasis when diagnosed, and their prognosis was favorable. Yamaguchi et al.[26] speculated that this may be due not only to the early development of symptoms caused by obstruction of the narrow lumen of the cystic duct, but also to slow growth and late metastasis. The patient reported here was diagnosed as having carcinoma of the cystic duct at a relatively early stage because of the development of acute cholecystitis and obstructive jaundice, enabling us to perform a potentially curative resection in spite of the aggressive nature of small cell carcinoma. The patient has been doing well without any signs of recurrence for 1 year after the operation.

To the best of our knowledge, this is the first report of primary small cell carcinoma of the cystic duct. The favorable outcome can be obtained by surgical resection because of the relatively early occurrence of the clinical symptoms, although small cell carcinoma is notorious for its aggressive nature.

REFERENCES

1. Duguid JB, Kennedy AM. Oat cell carcinoma of mediastinal glands. J Pathol Bacteriol 1930;33:93–99.
2. Remick SC, Hafez GR, Carbone PP. Extrapulmonary small-cell carcinoma. A review of the literature with emphasis on therapy and outcome. Medicine 1987;66:451–471.
3. Galanis E, Frytak S, Lloyd RV. Extrapulmonary small cell carcinoma. Cancer 1997;79:1729–1736.
4. Albores-Saavedra J, Cruz-Ortiz H, Alcantara-Vazques A, Henson DE. Unusual types of gallbladder carcinoma. A report of 16 cases. Arch Pathol Lab Med 1981;105:287–293.
5. Albores-Saavedra J, Soriano J, Larraza-Hernandez O, Aguirre J, Henson DE. Oat cell carcinoma of the gallbladder. Hum Pathol 1984;15:639–646.
6. Guo KJ, Yamaguchi K, Enjoji M. Undifferenciated carcinoma of the gallbladder. A clinicopathologic, histochemical, and immunohistochemical study of 21 patients with a poor prognosis. Cancer 1988;61:1872–1979.
7. Friedman MD, Wheeler WE. Cancer of the gallbladder. South Med J 1990;83:485–486.
8. Duan HJ, Ishigame H, Ishii Z, Itoh N, Shigematsu H. Small-cell carcinoma of the gallbladder combined with adenocarcinoma. Acta Pathol Jpn 1991;41:841–846.
9. Iida Y, Tsutumi Y. Small cell (endocrine cell) carcinoma of the gallbladder with squamous and adenocarcinomatous components. Acta Pathol Jpn 1992;42:119–125.
10. Ron IG, Wigler N, Ilie B, Chaitchik S. Small cell carcinoma of the gallbladder: Clinical course and response to chemotherapy. Tumori 1992;78:207–210.
11. Johnstone AK, Zuch RH, Anders KH. Oat cell carcinoma of the gallbladder. A rare and highly lethal neoplasm. Arch Pathol Lab Med 1993;117:1009–1012.
12. Nishihara K, Tsuneyoshi M. Small cell carcinoma of the gallbladder: A clinicopathological, immunohistochemical and flow cytometrical study of 15 cases. Int J Oncol 1993;3:901–908.
13. Nishihara K, Nagai E, Tsuneyoshi M, Nagashima M. Small-cell carcinoma combined with adenocarcinoma of the gallbladder. A case report with immunohistochemical and flow cytometric studies. Arch Pathol Lab Med 1994;118:177–181.
14. Muraina OI, Tank R, Dhingra C, Vuletin JC, Colella F, Abdelsayed G, Pachter BR, Honikman L. Small cell carcinoma of the gallbladder. Report of two cases. Am J Gastroenterol 1996;91:792–794.
15. Debois JM, De Vriendt P, Charels K. Small cell carcinoma of the gallbladder. Acta Chir Belg 1998;98:110–112.
16. Kuwabara H, Uda H. Small cell carcinoma of the gallbladder with intestinal metaplastic epithelium. Pathol Int 1998;48: 303–306.
17. Chaung SS, Lin CN, Chu CH, Chen FF. Small cell carcinoma of the gallbladder: Report of two cases. Pathol Oncol Res 1999;5:235–238.
18. Moskal TL, Zhang PJ, Nava HR. Small cell carcinoma of the gallbladder. J Surg Oncol 1999;70:54–59.
19. Matsuo S, Shinozaki T, Yamaguchi S, Matsuzaki S, Takami Y, Hayashi T, Kanematsu T. Small-cell carcinoma of the gallbladder: Report of a case. Surg Today 2000;30:89–93.
20. Mithal U, Heroor A, Khan K, Dudhat S, Jagannath P, Soman CS, Desouza LJ. Small cell carcinoma of gall bladder. Indian J Gastroenterol 2000;19:33.
21. Maitra A, Tascilar M, Hruban RH, Offerhaus GJ, Albores-Saavedra J. Small cell carcinoma of the gallbladder. A clinicopathologic, immunohistochemical, and molecular pathology study of 12 cases. Am J Surg Pathol 2001;25:595–601.
22. Pavitharn K, Doval DC, Vaid AK, Verma RN. Small cell carcinoma of the gall bladder: Case report and review of literature. Trop Gastroenterol 2001;3:170–171.
23. Fujii H, Aotake T, Horiuchi T, Chiba Y, Imamura Y, Kuniyoshi T. Small cell carcinoma of the gallbladder: A case report and review of 53 cases in the literature. Hepatogastroenterology 2001;48:1588–1593.
24. Vaittinen E. Carcinoma of the gallbladder. A study of 390 cases diagnosed in Finland 1953-1967. Ann Chir Gynaecol Fenn Suppl 1970;168:1–81.
25. Farrar DAT. Carcinoma of the cystic duct. Br J Surg 1951;30:183–185.
26. Yamaguchi K, Nishihara K, Tsuneyoshi M. Carcinoma of the cystic duct. J Surg Oncol 1991;48:282–286.
27. Henson DE, Albores-Saavedra J, Corle D. Carcinoma of the gallbladder. Histologic type, stage of disease, grade, and survival rates. Cancer 1992;70:1493–1497.
28. Shito M, Shintoku J, Miyazaki H. Primary carcinoma of the cystic duct associated with sarcoid reactions: Report of a case. Surg Today 1997;27:1177–1181.

# Spontaneous and Traumatic Intra-Peritoneal Perforations of Hepatic Hydatid Cysts: A Case Series

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Little is known about the presentation, management, outcome, and recurrence of hydatid cyst perforations. We reviewed the charts of all patients admitted to our emergency service for 7 years to identify patients who were surgically treated for intra-peritoneal hydatid cyst perforations. Twelve hydatid cysts were identified in 7 patients (5 males; median age 22 yr; range 8–67). The perforations occurred spontaneously in 5 patients, and were the result of mild trauma in 2 patients. Diagnostic tools included ultrasound (US, n = 4), computed tomography (CT, n = 3), and diagnostic peritoneal lavage (DPL, n = 1). The cysts were treated with radical (n = 3) or conservative (n = 9) operative techniques. Intra-cavitary and intra-abdominal spaces were washed in 6 and 5 patients, respectively. The median follow-up time was 41 months (range 3–58). Indirect hemagglutination test was positive in 3 patients, but CT confirmed cyst recurrence in only 2 of these patients. Both had had large cysts and had undergone conservative therapy (endocystectomy and external drainage). An intra-abdominal recurrence was observed in a patient whose abdomen had not been washed during surgery. In conclusion, patients with hydatid cyst perforations in our study generally presented with severe abdominal findings. US, CT, and DPL may be helpful for the diagnosis. Recurrence may be related to operative technique, location of the cyst, and abdominal wash during the surgery. (J GASTROINTEST SURG 2003;7:635–641.) 

KEY WORDS: Hydatid cyst, perforation, trauma, spontaneous, recurrence

Hydatid disease is a parasitic infection that is usually caused by *Echinococcus granulosus*.[1] It is endemic in the Middle East, South America, and the Mediterranean.[2–4] The liver is the most common location for hydatid disease.

Patients with hydatid disease are mostly asymptomatic until it is incidentally diagnosed or complications occur.[2] Complications are observed in one-third of all patients with hepatic hydatid cysts.[1] Perforation is the most common complication and may have important allergic, obstructive, and infective sequelae. The perforation may open into the biliary tract, into a hollow organ (mostly the colon), or directly into the abdominal cavity.[5] Intra-abdominal rupture occurs in approximately 3.2% of all patients with hepatic hydatid disease.[6] The perforation may be caused by a trauma or it may occur spontaneously due to increased intra-cystic pressure. Emergency surgery is the main treatment for intra-peritoneal rupture of hydatid cysts.[1,6]

Although the diagnosis and treatment of hydatid cyst have been discussed in numerous studies, perforations of the cysts have been rarely reported.[1,6–12] More important, most of these are case reports that did not evaluate the management and outcome of the different surgical techniques. In this paper, we present 7 patients with intra-peritoneal perforation of hepatic hydatid disease and discuss the presentation, diagnosis, management, and recurrence of their disease.

## MATERIALS AND METHODS

The charts of all patients admitted to the Kartal Dr. Lutfi Kirdar Education and Research Hospital

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Emergency Service between January 1, 1995 and December 31, 2001 were reviewed to identify those who required surgical intervention for a perforated hepatic hydatid cyst. We also identified the patients who underwent elective surgery for uncomplicated hepatic hydatid cysts.

The charts of the eligible patients were reviewed for demographic information, admission symptoms, laboratory findings, preoperative evaluation techniques, the duration between admission and surgery, surgical technique, postoperative complications, length of hospital stay, and postoperative use of anti-hydatid drugs. The preoperative evaluation and operative management depended on the surgeons' preferences. All patients were instructed to take albendazole (10 mg/kg) (Andazol, 200 mg, tab; Bilim Ilac, Istanbul) for 3 or 6 months after surgery.

We asked all patients who we found during our review to return to the hospital for the tests to evaluate disease recurrence. These tests consisted of the indirect hemagglutination test (IHA) (Cellognost Echinococcus, Dade Behring Inc., Newark, NJ) and abdominal computed tomography (CT). An echinococcus antibody titer of 1/256 or more was considered positive for disease. The duration between the patients' surgery and follow-up tests were recorded.

## RESULTS

Seven patients (5 men, 2 women) with hepatic hydatid cysts perforations were identified from our hospital records (Table 1). Their mean age at the time of surgery was 22 years (range 8–67). We also identified 92 patients who received elective surgical treatment for uncomplicated hepatic hydatid cysts during the study period. The incidence of hepatic hydatid cyst perforation was 7% in our series.

Two of 7 patients with perforated cysts reported mild abdominal trauma from a fall, which may have caused the hydatid cysts to rupture. The cysts in the remaining 5 patients were considered to have occurred spontaneously. Abdominal pain, nausea, and vomiting were the most common complaints. All patients had abdominal irritation and exhibited signs of defense, rebound, and tenderness. Three patients had leukocytosis. None of the patients had developed any symptoms related to the hydatid cysts before the perforation or had known anything about their disease before the onset of their symptoms (Table 1).

During the preoperative evaluation, 4 patients underwent ultrasound (US) (Fig. 1), which diagnosed the perforation (intra-abdominal fluid) and localization of the cyst in 3 patients and revealed only intra-abdominal fluid in one (patient 1). Because patient 1 had a history of trauma, and because of her abdominal signs and US findings, a diagnostic peritoneal lavage was performed to rule out intra-abdominal hemorrhage. But the lavage revealed abundant clear liquid, which showed cyst hydatid perforation and indicated the need for surgery. Computed tomography was used in 3 patients (Fig. 2), and it was able to show the localizations and perforations of the hydatid cysts (intra-abdominal fluid) in all 3 patients. Neither US nor CT was performed in one patient because her abdominal examination indicated the need for immediate surgical intervention. The ruptured hydatid cyst was diagnosed during laparotomy in this patient.

The median duration between hospital admission and surgical intervention was 9 hours (range 6–36) (Table 2). A midline incision was used for all patients. No other pathologic findings were observed in the 2 trauma patients. All cysts, even if they had not ruptured, were identified and treated.

Twelve hydatid cysts were found in the 7 patients, and the median size of the cysts was 7 cm (range 3–15) (Table 2). Nine cysts were treated with conservative techniques (endocystectomy alone [n = 3] or en-

**Table 1.** The demographics, symptoms, examination and laboratory findings of 7 patients with hepatic hydatid cyst perforation during the admission, and the cause of the perforation

| Patient | Age (yr) | Gender | Symptoms/Findings | Cause | WBC ($mm^3$) | Diagnosis |
|---|---|---|---|---|---|---|
| 1 | 8 | F | Abdominal pain, urticaria | Fall | 17,100 | US, DPL |
| 2 | 22 | F | Abdominal pain, nausea/vomiting | Spontaneous | 22,000 | — |
| 3 | 15 | M | Abdominal pain | Spontaneous | 22,000 | US |
| 4 | 47 | M | Abdominal pain, nausea/vomiting | Spontaneous | 6,800 | CT |
| 5 | 14 | M | Abdominal pain | Fall | 9,000 | CT |
| 6 | 67 | M | Abdominal pain | Spontaneous | 9,800 | CT, US |
| 7 | 36 | M | Abdominal pain | Spontaneous | 7,000 | US |

CT = computerized tomography; US = ultrasound; DP = diagnostic peritoneal lavage.

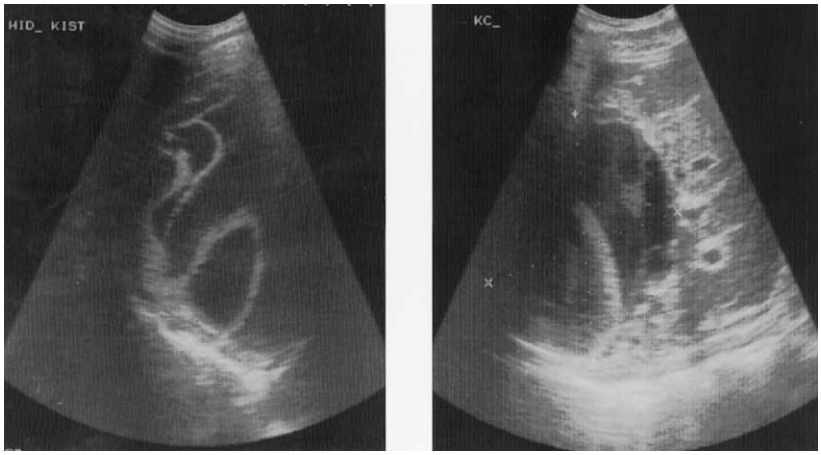


**Fig. 1.** Preoperative ultrasound confirmed hydatid cyst perforation by revealing the location of the perforated cyst (*left*) and intra-abdominal fluid (*right*) (patient 3).

docystectomy combined with external drainage [n = 3], or introflexion [n = 3]). Pericystectomy, which is a radical technique, was used to treat the remaining 3 cysts (Table 2).

During surgery, the intra-cavitary and intra-abdominal spaces were washed with hypertonic solution or povidone iodine and saline (Table 2). None of these cysts was connected to the biliary tract. The median postoperative hospitalization period was 7 days (range 4–13). No complications or mortality occurred postoperatively.

Although all patients were instructed to use Albendazole for 3 to 6 months, 2 patients did not comply with the drug regimen. The patients who used Albendazole did not experience any adverse effects.

All patients returned to the hospital for recurrence evaluation. The median follow-up was 41 months (range 3–64) (Table 3). Three patients had abnormal IHA levels, and CT revealed recurrences in two of these patients. The recurrence developed in the intracavitary space in one patient (Fig. 3) and in both the intra-cavitary and intra-abdominal spaces in the other patient (Fig. 4, Table 3.). Both patients were men. The intracavitary recurrences were treated with endocystectomy and external drainage. The intra-abdominal space was not washed out during the original surgery in the patient with the intra-abdominal recurrence.

Our series was not large enough to analyze the data statistically.

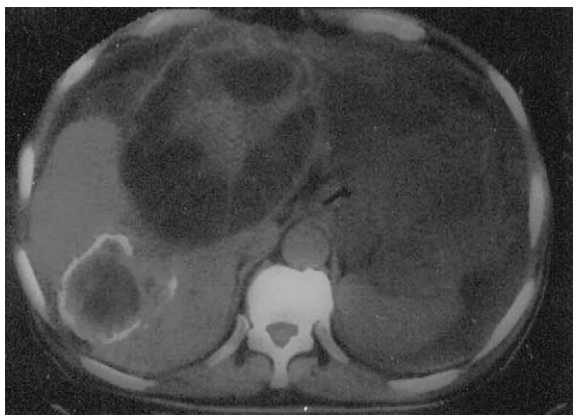

**Fig. 2.** Abdominal computed tomography helped determine the location of the perforated cyst (patient 6).

## DISCUSSION

Intra-abdominal perforation of cyst hydatid is a rare problem, even in endemic regions. In a retrospective review of 471 patients who were surgically treated for hydatid disease over a 20-year period, free cyst rupture into the peritoneal cavity was observed in only 15 of the patients.[6] In another study, Gunay et al. presented 16 patients who were surgically treated for intraperitoneal hydatid cyst perforations over a 12-year period.[1] Our study consisted of 7 patients over a 7-year period.

The intra-cystic pressure may reach as high as 50 cm $H_2O$, and this may cause the cyst to perforate spontaneously or increase the risk of perforation during trauma.[7,8] Even mild traumas like sport injuries can cause cysts to perforate.[9] In our study, 5 of 7 patients reported no trauma, whereas the remaining 2 patients suffered mild trauma from a fall.

**Table 2.** Perioperative data for 7 patients with hepatic hydatid cyst perforation

| Patient | Preoperative duration* (hr) | Localization (segments in cm) | Surgical techniques | Perioperative lavage | | Postoperative hospitalization (days) |
|---|---|---|---|---|---|---|
| | | | | Intra-cavitary | Intra-abdominal | |
| 1 | 8 | Seg 4 (7) | EC + IF | P + S | P + S | 11 |
| 2 | 22 | Seg 1-2 (13) | PeC | P + S | P + S | 11 |
| | | Seg 8 (5) | EC + ED | | | |
| 3 | 18 | Seg 7-8 (10) | EC + IF | P + S | P + S | 7 |
| 4 | 36 | Seg 1-2 (5) | EC + IF | (−) | (−) | 4 |
| | | Seg 5-6 (10) | PeC | | | |
| | | Seg 7 (3) | EC | | | |
| 5 | 7 | Seg 1-2 (4) | EC | HS | HS | 6 |
| 6 | 9 | Seg 1-2 (15) | PeC | HS | HS | 13 |
| | | Seg 6 (7) | EC +ED | | | |
| 7 | 6 | Seg 3 (4) | EC | HS | — | 6 |
| | | Seg 8 (15) | EC + ED | | | |

EC = endocystectomy; IF = introflexion; P = povidon iodine; S = saline (0.9% NaCl); PeC = pericystectomy; ED = external drainage; HS = hypertonic (20% NaCl) solution.
*The duration between the admission and operation.

Abdominal pain, jaundice, nausea, vomiting, and urticaria are the most common symptoms, and all acute abdominal signs such as defense, rebound, and tenderness are generally present.[1,6] Jaundice is related to perforation into the biliary tract, and urticaria and rash are allergic signs. Anaphylaxis or sudden death has also been reported in patients with ruptured hepatic hydatid cysts.[6,10] In our study, abdominal pain, nausea, and vomiting were the most frequent complaints, and all 7 patients had acute abdomen findings. One patient had urticaria and was treated with antihistaminic agents for 5 days beginning with the patient's admission to the hospital. Three patients had elevated white blood cell counts.

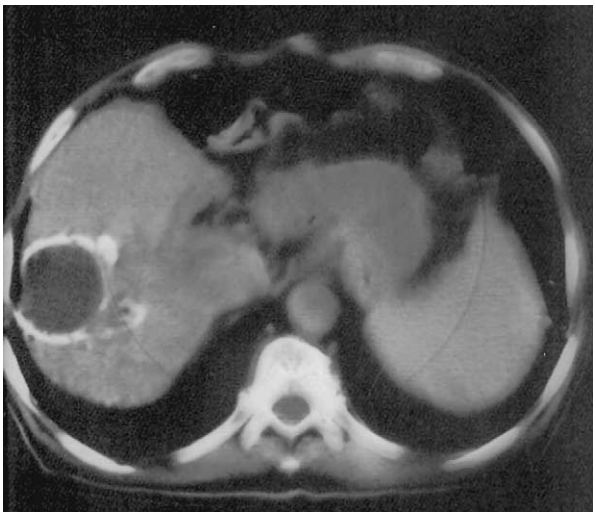

**Fig. 3.** Recurrence of a hydatid cyst in liver segment 6. A pericystectomy was performed only 3 months before computed tomography examination; segments 1 and 2 cannot be seen in this screen (patient 6).

The severe presentation and the infrequency of hydatid cyst perforation may lead the surgeon to misdiagnose the disease. Leviav and Weissberg reported a ruptured hepatic hydatid cyst in a patient who underwent surgery for acute appendicitis through a McBurney incision.[9] In our study, all 7 patients were correctly diagnosed, but in some cases the duration between the admission and operation was long (even 36 hours in a case) because of the difficulty in making the diagnosis.

Ultrasound is a non-invasive, sensitive, cost-effective imaging technique that is available at most institutions, and it has a specificity of 90% in the diagnosis of hydatid cysts.[2] It may be helpful for defining the number and locations of the cysts and the presence of intra-abdominal fluid in patients with perforated hydatid cysts. In our study, US showed both the number of cysts and their locations as well as identified the cyst hydatid rupture in 3 of 4 patients who underwent this exam (Fig. 1). This failure may have been related to the relatively small size of the cyst or to the radiologist who specifically focused on and looked for the ultrasound findings of an abdominal trauma, not a hepatic hydatid cyst. This patient underwent DPL; abundant clear liquid was aspirated from the abdominal cavity, which indicated exploratory laparotomy. In our opinion, DPL is a helpful diagnostic technique because the aspiration material is unique and highly specific to hydatid cyst perforation. Although the specificity of US is approximately 90% in uncomplicated hepatic hydatid cyst patients,

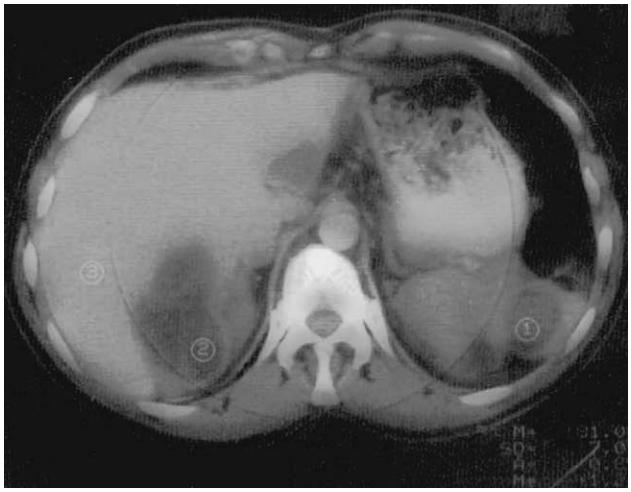

**Fig. 4.** Both intra-abdominal (1) and intra-cavitary cysts (2) (in segment 8) can be seen in this screen (patient 7).

CT may provide better information than US about the location and depth of the cysts in the liver.[2,11] In our study, CT was used in 3 patients and defined both the location of the hepatic cysts and the presence of intra-abdominal fluid in all of the patients. In patient 2, none of these diagnostic techniques was used, and an exploratory laparotomy was performed because of severe abdominal findings. The hydatid cyst perforation was diagnosed during laparotomy.

Surgery is still the main treatment modality for both perforated and uncomplicated hepatic hydatid cysts.[1,2,6,12] The surgical approach in patients with perforated hydatid cyst is more complex than with uncomplicated disease. Because the abdominal spillage of scolices exists during the emergent operations for perforated cysts, the surgeon should not only focus on the disease in the liver but also aim to remove intra-abdominal scolices. In our practice, the surgeon first attempts to eliminate the source of the disease. Thus, immediately after the laparotomy, the perforated cyst is identified and fixed with a clamp. Then the hydatid fluid within the intra-abdominal organs is removed. After the surrounding area of the cyst is protected with sponges in order to prevent further spillage, the intra-cavitary hydatid fluid is aspirated to decrease intra-cystic pressure, and scolicidal agents (hypertonic saline or povidone iodine and saline) are flushed into the cavity. After 3 to 5 minutes, the solution in the cavitary space is aspirated, and the intra-cavitary space is searched for residual scolices. As soon as the scolides are eradicated in the intra-cavitary space, the abdomen is washed with scolicidal agents. In our series, the intra-abdominal lavage was omitted in two patients who had limited abdominal contamination with scolices (Table 2). In our opinion, the remaining part of the surgery is quite similar in both emergent operations for perforated cysts and elective procedures for non-complicated hydatid disease. Whether a radical approach (pericystectomy or segmental resection of liver) is more effective and beneficial than a conservative approach (external drainage, endocystectomy, introflexion, capitonnage, cystojejunostomy) in patients with uncomplicated hydatid cysts is still debatable.[2,13–16] No study has discussed the most efficient surgical approach in intra-peritoneal perforation of hepatic hydatid cyst. Recurrence is less likely in patients who have been treated with pericystectomy, but because it may increase the operative complications such as operative bleeding and postoperative morbidity and mortality, this technique is reserved for peripherally located or pedunculated cysts.[2] In our practice, pericystectomy was generally preferred for larger cysts and in segments that can be easily reached (segments 1-2 in two cases, and segments 5-6 in one case). The remaining 9 cysts were treated with conservative techniques, the aim of which is to drain the intra-cavitary contents and obliterate the cavity. Approximation of the cyst wall with introflexion was performed for the treatment of 3 cysts in our study. External drainage is recommended for the treatment of the cysts that are lo-

**Table 3.** Follow-up and surveillance data for 7 patients with hepatic hydatid cyst perforation

| Patient | Postoperative follow-up (mo) | Postoperative Albendazole (mo) | Recurrence (CT) | | Laboratory (IHA) |
|---|---|---|---|---|---|
| | | | Intra-cavitary | Intra-abdominal | |
| 1 | 56 | 3 | — | — | 1/64 |
| 2 | 58 | — | — | | 1/128 |
| 3 | 41 | — | — | | 1/64 |
| 4 | 10 | 6 | — | | 1/256 |
| 5 | 4 | 3 | — | | 1/512 |
| 6 | 3 | 3 | Seg 6 | | 1/2048 |
| 7 | 64 | 6 | Seg 3, Seg 8 | Splenic hilus | 1/512 |

IHA = indirect hemagglutination test.

cated in the dome of the liver or when the omentum is not available for the obliteration.[2] In our series, we used this technique for the treatment of 3 cysts, 2 of which were located in segment 8.

Since the recurrence is the main concern for the surgeon, the aims of both elective and emergency surgery are to treat the current disease, and prevent the reappearance of the illness. Although Gunay et al. reported no recurrence during the follow-up of 9 patients after intra-abdominal hydatid cyst perforations, in our opinion, recurrence is not uncommon and may be related to factors such as operative technique, the location of the cyst, and intra-cavitary and intra-abdominal lavage during surgery.[1] Because the number of the patients was limited in our study, it was impossible to definitively identify the factors that affected disease recurrence. It is nonetheless interesting to note that none of the patients treated with a radical approach experienced disease recurrence, which is consistent with the literature.[2] The intra-cavitary recurrences observed in 2 patients might have been related to the location of the cysts; because they were difficult to reach, daughter cysts may have been left behind in the intracavitary space. The sizes of these cysts were 7 cm and 15 cm in diameter. We do not know whether there is a relationship between the recurrence and the sizes of the cysts. However, in our opinion, to reduce the chance of intracavitary recurrence, surgeons should either use a radical surgical approach or be extremely cautious not to leave any viable daughter cysts in the cavity. Intra-cavitary lavage is recommended to reduce the recurrence.[1,2]

In our study, two patients who had had intra-cavitary lavage during their initial operations experienced disease recurrence in the cyst cavity. The relationship between the intra-abdominal lavage with scolicidal agents and the recurrence of the disease has never been studied in an emergent surgery setting in the literature. In our series, the abdominal cavity was washed with either hypertonic saline or povidone iodine and saline in 5 patients but was omitted in 2 patients because of the limited spillage of the scolides. However, we observed intra-abdominal recurrence in one of these two patients. We believe that both intra-cavitary and intra-abdominal lavages with scolicidal agents are mandatory in patients who have perforated hydatid disease, even if the observed abdominal spillage of the scolides is limited.

The bile leak is a troublesome problem after hydatid cyst operations. Fortunately, this complication can be prevented if the connection between the cyst and biliary tract is recognized and treated. Thus, surgeons should always search for such a connection during the initial operation. The intra-cavitary spaces should be examined under direct vision, if it is possible, for a potential connection to the biliary tract. If it is impossible to visualize the whole surface of the cyst wall, a sponge may be packed into the cavity, and removed a few minutes later. A green-yellow stain on the sponge proves the connection between the biliary tract and the cyst cavity. Although the incidence of such a complication ranges from 5% to 31% of the cases, interestingly no connection was observed in any of our patients.[1] In our opinion, this is an incidental finding and has no relationship with the hydatid cyst perforations.

We think that patients with perforated hydatid cysts who undergo surgical intervention should be followed closely and undergo tests such as IHA, CT, and abdominal US even if they do not have any complaints related to recurrence of the disease. In our series, no patient had any complaints during follow-up even though 2 of them experienced disease recurrence.

Preoperative use of albendazole is recommended because it cures about 20% to 30% of patients with hydatid cysts (defined as shrinkage or disappearance of the cyst), but its effectiveness in reducing recurrences has not been proven.[17] In our series, all 7 patients were instructed to use Albendazole, but only 5 of them used it. Interestingly, the disease recurred in the patients who had taken Albendazole. In our opinion, this is an area that requires further study to establish the efficacy of postoperative Albendazole in preventing recurrence of the disease.

IHA may be a helpful screening test for the presence of hydatid cyst but the results must be confirmed by a second test because the sensitivity of IHA is only 60%.[18] In our study, the 3 instances of recurrence were detected in 2 patients with IHA and confirmed with abdominal CT examinations. The IHA was also positive in a third patient (a second IHA was also positive in this patient) whose CT findings did not suggest disease recurrence. We do not know if this patient had no recurrence and false positive IHA results or experienced a recurrence that could not be seen with CT. An abdominal US revealed no pathologic findings of cyst hydatid recurrence, and this patient is still being closely followed.

## CONCLUSION

In conclusion, abdominal pain, nausea, and vomiting are the main complaints in patients with hydatid cyst perforations. Acute abdomen findings of defense, rebound, and tenderness are often present. US, CT, and DPL may help the clinician diagnose this rare condition. During surgery, if a radical procedure is not performed, the surgeon should take care not to leave any daughter cysts in the intra-cavitary space.

Intra-cavitary and intra-abdominal washes should be performed to reduce the risk of the recurrence. These patients should be closely followed with tests such as US, IHA, and CT.

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REFERENCES

1. Gunay K, Taviloglu K, Berber E, Ertekin C. Traumatic rupture of hydatid cysts: A 12-year experience from an endemic region. J Trauma 1999;46:164–167.
2. Sayek I, Onat D. Diagnosis and treatment of uncomplicated hydatid cyst of the liver. World J Surg 2001;25:21–27.
3. Utkan NZ, Cantork NA, Gonullo N, Tildirir C, Dulgen M. Surgical experience of hydatid disease of the liver. Omentoplasty or capitonnage versus tube drainage. Hepatogastroenterology 2001;48:203–207.
4. Dogan R, Yuksel M, Cetin G, Suzer K, Alp M, Kaya S. Surgical treatment of hydatid cysts of the lung: Report of 1055 patients. Thorax 1989;44:192–199.
5. Lewall DB, McCorkell SJ. Rupture of echinoccoccal cysts: Diagnosis, classification and clinical implications. AJR 1986; 146:391–394.
6. Placer C, Martin R, Sanches E, Soleto E. Rupture of abdominal hydatid cysts. Br J Surg 1988;75:157–161.
7. Yalin R, Aktan AO, Yegen C, Dosluoglu HH. Significance of intracystic pressure in abdominal hydatid disease. Br J Surg 1992;79:1182–1183.
8. Shapira O, Simon D, Rothstein H, Pfefferman R. Rupture of hepatic echinoccoccal cyst by minimal blunt abdominal trauma. (In Hebrew with English abstract.) Harefuah 1992; 122:80–83.
9. Leviav S, Weissberg D. Traumatic rupture of hydatid cysts. Can J Surg 1996;39:293–296.
10. Kok AN, Yurtman T, Aydin NE. Sudden death due to ruptured hydatid cyst of the liver. J Forensic Sci 1993;38:978–980.
11. Marti-Bonmati L, Serrano FM. complications of hepatic hydatid cysts: Ultrasound, computed tomography, and magnetic resonance diagnosis. Gastrointest Radiol 1990;15: 119–125.
12. Becker K, Frieling T, Saleh A, Haussinger D. Resolution of hydatid cyst by spontaneous rupture into the biliary tract. J Hepatol 1997;26:1408–1412.
13. Ariogul O, Emre A, Alper A, Uras A. Introflexion as a method of surgical treatment for hydatid disease. Surg Gynecol Obstet 1989;169:356–358.
14. Demirci S, Erarslan S, Aadol E, Bozatli L. Comparison of the results of different techniques in the management of hydatid cysts of the liver. World J Surg 1989;13:88–91.
15. Papadimitriou J, Mandrekas A. The surgical treatment of hydatid disease of the liver. Br J Surg 1970;57:431–433.
16. Dintman M, Chaimoff C, Woloch Y, Lubin E, Tikva P. Surgical treatment of hydatid cyst of the liver. Arch Surg 1971;103:76–78.
17. Saimot AG. Medical treatment of liver hydatidosis. World J Surg 2001;25:15–20.
18. Biava MF, Dao A, Fortier A. Laboratory diagnosis of cystic hydatic disease. World J Surg 2001;25:10–14.

# Management of Acute Cholecystitis in the Laparoscopic Era: Results of a Prospective, Randomized Clinical Trial

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The aim of this prospective, randomized study was to determine whether laparoscopic cholecystectomy should be performed as an early or a delayed operation in patients with acute cholecystitis. After diagnostic workup, patients were randomized to one of two groups: (1) early laparoscopic cholecystectomy (i.e., within 7 days after onset of symptoms) or (2) initial conservative treatment followed by delayed laparoscopic cholecystectomy 6 to 8 weeks later. Seventy-four patients were placed in the early-operation group, and 71 patients were assigned to the delayed-operation strategy. There was no significant difference in conversion rates (early 31% vs. delayed 29%), operating times (early 98 [range 30 to 355] minutes vs. delayed 100 [45 to 280] minutes), or complications. Failure with the conservative treatment strategy was noted in 26% of these patients. The total hospital stay was significantly shorter in the early group (5 [range 3 to 63] days) vs. the delayed group (8 [range 4 to 50] days; $P < 0.05$). Despite a high conversion rate, early laparoscopic cholecystectomy offered significant advantages in the management of acute cholecystitis compared to a conservative strategy. The greatest advantage was a reduced total hospital stay.
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KEY WORDS: Gallstone disease, cholecystitis, cholecystectomy, laparoscopy

Management principles for the surgical treatment of acute cholecystitis used to be firmly established. The benefits of open cholecystectomy have been substantiated in a number of prospective, randomized clinical trials, showing that the early-operation strategy was associated with a shorter hospital stay without added morbidity[1,2] compared to delayed elective cholecystectomy. With the introduction of laparoscopy for the surgical approach to gallstone disease, acute cholecystitis was initially considered to pose certain technical challenges for the surgeon and potential risks to the patient, and was therefore considered contraindicated.[3–5] Originally, high complication rates were reported, which were mainly the result of distorted anatomy caused by the acute inflammation. However, with growing experience and greater technical skills, surgeons realized that these obstacles could be managed. Consequently an expanding number of reports became available demonstrating the feasibility of the laparoscopic approach for acute cholecystitis with an acceptable morbidity but still at the expense of a high conversion rate.[6–9] In the Western world, where this disease is so prevalent, we still require more solid data on the pros and cons of a minimally invasive emergency operative approach. The question is: to what should it be compared? Open cholecystectomy is one alternative, but the traditional "gold standard" is initial conservative treatment with referral of the patient for an elective operation after the inflammatory reaction has subsided.[1,2] The aim of the present study was to investigate whether early laparoscopic cholecystectomy is a more cost-effective strategy for managing acute cholecystitis than a conservative strategy in terms of reduced total hospital stay. A more detailed cost analysis will be addressed in a separate report. In addition, we attempted to determine whether acute laparoscopic cholecystectomy was associated with more complications than an elective procedure after initial nonoperative treatment.

## MATERIAL AND METHODS

The study was carried out between December 1998 and December 2000, and included 145 patients. All

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patients were admitted on an emergency basis with a diagnosis of acute cholecystitis; this diagnosis was based on the finding of (1) acute right upper quadrant tenderness and ultrasound evidence of acute cholecystitis (presence of gallstones with a thickened and edematous gallbladder wall, positive Murphy's sign on ultrasound examination, and pericholecystic fluid collections); or (2) acute right upper quadrant tenderness, an ultrasound image showing presence of gallstones, and one or more of the following: temperature above 38° C and/or leukocytosis greater than $10 \times 10$/L, and/or C-reactive protein level greater than 10 mg/L. Patients were excluded from randomization (1) if they had bilirubin greater than 3.5 mg/dl or (2) symptoms for more than 1 week, (3) if they were incapable of understanding information regarding the study, or (4) if they were elderly (>90 years).

Written informed consent was obtained from all patients prior to their enrollment in the trial. The study protocol was approved by the Ethics Committee, Medical Faculty, University of Gothenburg. Patients were randomized into two groups. One group was managed with the early-intervention strategy, where a laparoscopic cholecystectomy was performed within 48 hours after randomization but not later than 7 days after the onset of symptoms. The other group of patients was treated conservatively (i.e., with antibiotics, anti-inflammatory drugs, and intravenous fluids when required); these patients were discharged when symptoms abated and they were readmitted for elective surgery 6 to 8 weeks later. Patients in the delayed-treatment group were admitted 1 day before the planned operation. That day was included in the total hospital stay of this conservative treatment strategy group. Patients in the delayed group who had worsening clinical signs or a recurrence of acute cholecystitis before the planned delayed cholecystectomy were treated with emergency laparoscopic cholecystectomy and subsequently classified as treatment failures.

Data were collected prospectively and included patient demographics, medical history, laboratory results, operative findings, results of operative cholangiography, conversion to open cholecystectomy, operating time, length of hospital stay, change of strategy for patients with a scheduled delayed operation, and any postoperative complications. The data generated from these patients were included in the final results of the conservatively treated patients under the "intention-to-treat" analysis. The demographic data, medical history, laboratory results, and results of ultrasound examination on admission were comparable in the two groups.

### Surgical Procedure

Consultants performed the operations. Fellow residents also participated in the study and operated under supervision. The minimum requirement for a surgeon to participate was a previous record of having performed 25 elective laparoscopic cholecystectomies.

Pneumoperitoneum was created by Veress needle. Dissection was carried out by means of electrocautery, and the cystic duct and artery were secured with titanium clips. Operative cholangiography was performed routinely. At the completion of the operation, subhepatic drains were inserted in selected cases. Resected gallbladders were sent for pathologic examination. All patients received antibiotic prophylaxis (sulfonamide/trimetoprime or cefotaxime/metronidazole) as well as prophylaxis against thrombosis (low molecular heparin, 2500 IU).

### Statistical Analysis

The randomization procedure was carried out by means of a computer-based program after stratification for age and sex. All data are medians (range) unless otherwise stated. For statistical analysis, the Mann-Whitney U test or Spearman rank correlation test was used. Statistical significance was defined as $P < 0.05$.

## RESULTS

Of the 145 patients included in the study, two in the delayed-treatment group refused surgery and were excluded. Seventy-four patients were randomized to the early-treatment group and 71 to the delayed-treatment group. Total hospital stay was 5 (3 to 63) days in the early group and 8 (4 to 50) days in the delayed group ($P < 0.05$). Conservative treatment failure was noted in 14 patients in the delayed group. An additional four patients in the delayed-treatment group had a recurrent attack of acute cholecystitis before the scheduled delayed cholecystectomy. All of these 18 patients (26%) were treated by emergency laparoscopic cholecystectomy and thus were classified as failures of the conservative strategy. This subgroup of patients had a total hospital stay of 10 (5 to 21) days, which was longer than the stay for the successfully treated patients in the delayed-treatment group, but the difference was not statistically significant. There was no difference in complication rates. Ten (55%) of these 18 patients had to be converted to an open procedure.

Twenty-three patients (31%) in the early-treatment group and 20 (29%) in the delayed-treatment

group required conversion to open surgery. The main reason for conversion was difficulty in exposing the gallbladder and Calot's triangle due to severe adhesions. No independent prognostic factors for conversion could be identified.

The operating time was 98 (range 30 to 355) minutes and 100 (range 45 to 280) minutes in the early and delayed groups, respectively. Intraoperative cholangiography was attempted in all patients and was successful in 54 patients (73%) in the early group and 50 patients (72%) in the delayed group. Common bile duct stones were demonstrated in five patients (7%) in the early group and three patients (4%) in the delayed group. Perioperative bleeding of more than 500 ml was recorded. This occurred in six patients (8%) in the early group and one patient (1%) in the delayed group (Table 2).

After each operation, the surgeon was asked if it was considered a technically difficult procedure. The answer was "yes" for 57% of the patients in the early group and 74% of those in the delayed group. The difference was not statistically significant ($P = 0.08$).

In two patients, histopathologic examination unexpectedly revealed the presence of an adenocarcinoma; these patients were subsequently treated by an extended resection.

None of the patients died as a result of the operation, and the overall complication rate was 19%. There was one major bile duct injury, which occurred in the delayed group. We recorded bile duct leaks in six patients (8%) in the early group but none in the delayed group. All of these leaks were successfully treated: four with endoscopic retrograde cholangiopancreatography (ERCP) plus stent, one with ERCP plus sphincterotomy, and one with percutaneous drainage (Table 3). There was no significant difference in complication rates between the two groups.

**Table 1.** Clinical data and laboratory results on admission

| | Treatment group | |
|---|---|---|
| | **Early (n = 74)** | **Delayed (n = 71)** |
| Age (yr) | 58 (22–88) | 55 (20–81) |
| Sex (%female) | 63 | 57 |
| Body weight (kg) | 75 (50–116) | 76 (52–115) |
| Duration of symptoms (hr) | 60 (11–144) | 58 (12–168) |
| Temperature (C) | 37.8 (36.1–40.0) | 37.8 (36.4–39.4) |
| C-reactive protein (mg/L) | 65 (5–350) | 81 (5–380) |

Ranges are in parentheses.

**Table 2.** Operative findings and hospital stay

| | Treatment group | |
|---|---|---|
| | **Early (n = 74)** | **Delayed (n = 69)** |
| Conversion to open surgery | 23 (31%) | 20 (29%) |
| Operating time (min) | 98 (range 30–355) | 100 (range 45–280) |
| Bleeding >500 ml | 6 (8%) | 1 (1%) |
| Intraoperative cholangiography | 54 (73%) | 50 (72%) |
| Common bile duct stones | 5 (7%) | 3 (4%) |
| Total hospital stay (days) | 5 (range 3–63) | 8 (range 4–50) |

## DISCUSSION

The objective of this randomized, clinical study was to assess the efficacy of an early laparoscopic intervention strategy in the management of acute cholecystitis, as reflected by the length of total hospital stay. The outcome clearly favored this strategy over the conservative treatment, which incorporated an elective laparoscopic cholecystectomy 6 to 8 weeks after the initial admission. These results correlate well with those documented during the era of open surgery, showing similar benefits with open cholecystectomy in the acute phase with no additional morbidity and mortality.[1,2] We know from the literature that conversion rates vary considerably among series, ranging from 6% to 35%.[7,10–12] We noted a high conversion rate in the early laparoscopic group (31%). This finding could be interpreted in various ways. One is that the standard of surgery and the level of expertise were suboptimal. The surgeons participating in the study presented a wide range of experience in laparoscopic surgery (although each had previously performed a minimum of 25 laparoscopic

**Table 3.** Postoperative complications

| | Treatment group | |
|---|---|---|
| **Complication** | **Early (n = 74)** | **Delayed (n = 69)** |
| Major bile duct injury | 0 | 1 (1%) |
| Bile duct leak | 6 (8%) | 0 |
| Intra abdominal infection | 2 (3%) | 3 (4%) |
| Other infection | 5 (7%) | 3 (4%) |

cholecystectomies). In our opinion, that is a more accurate reflection of the reality of treating acute cholecystitis than having a small group of dedicated laparoscopic surgeons performing all of the operations.[11] A further dimension to the complexity of performing an acute laparoscopic cholecystectomy was our finding that even at the time of elective cholecystectomy, after 6 to 8 weeks of conservative therapy, we still encountered a similar magnitude of conversion. Such outcome data have been reported in the literature,[11,13] and emphasize the many difficulties faced by surgeons when attempting to remove a gallbladder affected by severe chronic inflammation. It does not appear that allowing the inflammation to subside leads to a technically less demanding operation. We found no significant differences in complication rates between the two strategies, and our figures for complications centered around 19%, which compares well with what is reported in most corresponding series.[10,11,14] It can therefore be concluded that these surgical procedures are not only complex but are also followed by significant morbidity when performed under elective conditions. Examples of this are reflected by a 1% incidence of bile duct injury [15,16] and an 8% incidence of bile leakage. Despite the fact that the latter were managed by conservative endoscopic interventions, these figures emphasize that these patients should preferably be treated in units where upper gastrointestinal surgical and endoscopic expertise is available. It has been argued that the use of intraoperative cholangiography is pivotal to prevent bile duct injuries,[17] but this issue remains controversial. We used intraoperative cholangiography as a routine part of the operative procedure regardless of whether the operation was carried out on an emergency basis. The type of treatment offered to patients randomized to a conservative strategy included antibiotics, analgesics, and parenteral nutrition, as long as their conditions warranted this treatment. More interesting was the fact that 26% of these patients could not be managed according to plan but instead required an emergency operation because of recurrent problems or progressive disease. Similar figures have been presented previously.[2,11] This high rate of failure among patients with acute cholecystitits managed conservatively presents a strong argument for an aggressive immediate surgical approach. Furthermore, valid data are lacking regarding outcomes in the remaining 74% of these patients while they were waiting for the operation in terms of how many had subclinical problems that adversely affected their quality of life.

In conclusion, acute laparoscopic cholecystectomy offers advantages over a conservative management strategy in terms of reduced in-hospital resource consumption with no additional treatment-specific morbidity. The high conversion rate raises the question of whether a shift toward primary open cholecystectomy would offer more cost-effective treatment than is presently applied.

REFERENCES

1. Van der Linden W, Edlund G. Early versus delayed cholecystectomy: The effect of a change in management. Br J Surg 1981;68:753–757.
2. Norrby S, Herlin P, Holmin T, et al. Early or delayed cholecystectomy in acute cholecystitis? A clinical trial. Br J Surg 1983;70:163–165.
3. Cuschieri A, Dubois F, Mouiel J, et al. The European experience with laparoscopic cholecystectomy. Am J Surg 1991; 161:385–387.
4. Schirmer BD, Edge SB, Dix J, et al. Laparoscopic cholecystectomy: Treatment of choice for symptomatic cholelithiasis. Ann Surg 1991;213:665–676.
5. Flowers JL, Bailey RW, Scovill WA, Zucker KA. The Baltimore experience with laparoscopic management of acute cholecystitis. Am J Surg 1991;161:388–392.
6. Kum CK, Goh PM, Isaac JR, et al. Laparoscopic cholecystectomy for acute cholecystitis. Br J Surg 1994;81:1651–1654.
7. Wilson RG, MacIntyre IM, Nixon SJ, et al. Laparoscopic cholecystectomy as a safe and effective treatment for severe acute cholecystitis. Br Med J 1992;305:394–396.
8. Graves HA, Ballinger JF, Anderson WJ. Appraisal of laparoscopic cholecystectomy. Ann Surg 1991;213:655–661.
9. Kiviluoto T, Siren J, Luukkonen P, Kivilaakso E. Randomised trial of laparoscopic versus open cholecystectomy for acute and gangrenous cholecystitis. Lancet 1998;351:321–325.
10. Lo CM, Liu CL, Lai EC, et al. Early versus delayed laparoscopic cholecystectomy for treatment of acute cholecystitis. Ann Surg 1996;223:37–42.
11. Lai PBS, Kwong KH, Leung KL, et al. Randomised trial of early versus delayed laparoscopic cholecystectomy for acute cholecystitis. Br J Surg 1998;85:764–767.
12. Rattner DW, Ferguson C, Warshaw AL. Factors associated with successful laparoscopic cholecystectomy for acute cholecystitis. Ann Surg 1993;217:233–236.
13. Cox MR, Wilson TG, Luck AJ, et al. Laparoscopic cholecystectomy for acute inflammation of the gallbladder. Ann Surg 1993;218:630–634.
14. Wiesen SM, Unger SW, Barkin JS, et al. Laparoscopic cholecystectomy: The procedure of choice for acute cholecystitis. Am J Gastroenterol 1993;88:334–337.
15. Peters JH, Gibbons GD, Innes JT, et al. Complications of laparoscopic cholecystectomy. Surgery 1991;110:769–777.
16. Way LW. Bile duct injury during laparoscopic cholecystectomy. Ann Surg 1992;215:195.
17. Flum DR, Koepseh T, Heagerty P, et al. CBD injury during laparoscopic cholecystectomy and the use of IOC. Arch Surg 2001;136:1287–1292.

# Staged Abdominal Repair in the Treatment of Intra-Abdominal Infection: Analysis of 102 Patients

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Surgical treatment of intra-abdominal infections remains a challenge for the surgeon. Staged abdominal repair is being commonly used in patients with intra-abdominal infections. This study presents our experience with staged abdominal repair and analyzes factors affecting mortality. A total of 102 patients who underwent staged abdominal repair procedures for intra-abdominal infections during a 12-year period were retrospectively reviewed. The effects of several risk factors on mortality were evaluated. The investigated risk factors included age, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, number of operations prior to staged abdominal repair, number of repeat laparotomies, anatomic origin of infection, and etiology of intra-abdominal infections. The overall mortality rate was 40% (41/102). The mean number of operations prior to staged abdominal repair (0.72 ± 0.1 in survivors vs. 1.37 ± 0.21 in nonsurvivors), age (24.5% mortality under 55 years vs. 53.6% mortality between 55 and 65 years vs. 75% mortality over 65 years), and APACHE II score (13.4 ± 3.4 in survivors vs. 20.3 ± 6.64 in nonsurvivors) were correlated with mortality rates ($P < 0.05$). Our results showed that the physiologic status of patients, severity of sepsis, and decision time for staged abdominal repair were all associated with higher mortality. (J GASTROINTEST SURG 2003;7:646–651.) 

KEY WORDS: Intra-abdominal infection, staged abdominal repair, APACHE II score

Despite many advances in diagnostic modalities, potent antibiotics, intensive care, and aggressive surgical treatment, severe intra-abdominal infections are associated with a high mortality rate. The mainstays of therapy in intra-abdominal infections are general support for the patient's hemodynamic and respiratory status, antibiotic administration, nutrition, and surgical intervention. The principal goals of the surgical management are to eliminate the source of bacterial contamination, to reduce the degree of bacterial contamination, to prevent recurrent infection, and to treat abdominal compartment syndrome.[1,2]

The operative management of intra-abdominal infections includes the standard operating methods, percutaneous abscess drainage and decompression procedures (open abdominostomy, mesh abdominostomy, and staged abdominal repair [STAR]). The methods of standard operation are plugging the source of infection (suture closure, resection and anastomosis, and exteriorization), purging the abdominal cavity (mechanical cleansing and irrigation), and postoperative irrigation via drains. Although standard operations are adequate in most patients, these techniques have failed to prevent recurrence of intra-abdominal infections in 10% to 15% of patients with peritonitis. Decompression procedures are directed toward the prevention of recurrent intra-abdominal infections and the treatment of abdominal compartment syndrome. Open and mesh abdominostomy procedures have been plagued by intestinal fistulas and abdominal wall defects. STAR was defined by Wittmann et al.[3] as a series of operations planned either before or during the first operation and performed every 24 to 36 hours with temporary closure of the abdomen using different devices. It combines the

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advantages of planned relaparotomy and open management with a minimal rate of complications.[3–5] The results of the many studies of STAR vary considerably because of differences in methods, patient groups, and severity of disease. Although, the value of STAR in intra-abdominal infections has never been studied in well-designed, prospective, randomized trials, Wittmann et al.[3] showed that patients undergoing STAR had a significantly better outcome than patients treated by other operations; a logistic regression model was used for all risk groups. However, at the present time the effectiveness of STAR in intra-abdominal infections remains debatable.

In this study we present our experience with STAR over a 12-year period in our surgical clinic in the management of intra-abdominal infections, and we examine the factors affecting mortality in patients undergoing this procedure.

## PATIENTS AND METHODS

### Patient Selection

Over a 12-year period (January 1988 to December 1999), 115 patients underwent STAR for intra-abdominal infection at Uludag University Hospital. Thirteen patients were excluded because of inadequate data. The charts of the remaining 102 patients were retrospectively reviewed. Data on patient age, anatomic origin of infection, and etiology of intra-abdominal infection were recorded. The number of operations prior to STAR, the number of relaparotomies, and the Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were calculated.[6] The APACHE II score was used for stratification of patients. The worst physiologic parameters over the 24 hours preceding the STAR procedures were considered in these calculations. Indications for STAR were inability to eliminate or adequately control the source of infection, incomplete debridement of necrotic tissue, excessive intra-abdominal edema, second look for bowel ischemia, and critical patient condition precluding definitive repair.

All patients were treated in the surgical intensive care unit until no further relaparotomy or organ support was necessary. Broad-spectrum antibiotic therapy, a combination of penicillin or cephalosporin, aminoglycoside, and metronidazole, was begun preoperatively and subsequently modified according to the results of microbiological cultures. Patients received parenteral and/or enteral nutritional support.

### Surgical Techniques

STAR was performed using the following operative technique: Serial operations were planned either before or during the first (index) operation; these operations were performed every 24 to 48 hours with abdominal decompression and staged reapproximation and finally closure of the abdominal fascia utilizing a mesh. Relaparotomies were performed by incision through the mesh in the operating room. During each consecutive operation, graft size was reduced bringing the edges of the wound closer together so that at the final operation primary closure would be possible.

At the first laparotomy for peritonitis, the source of contamination was eradicated in the usual manner. When bowel resection was required, ostomies rather than anastomoses were performed. The peritoneal cavity was generously irrigated with 8 to 10 liters of saline solution. At the completion of the laparotomy, Mersilene mesh (Ethicon, Johnson-Johnson, Brussels, Belgium) was sutured to the surrounding fascia with running nonabsorbable sutures. At reoperation, all septic tissue and necrotic debris were debrided or removed with gentle suction, and the cavity was irrigated. Exploratory operations were discontinued once clinical evidence of sepsis subsided and the peritoneal cavity appeared to be clean, as determined by the presence of healthy granulation tissue. If possible, the abdomen was primarily closed at the final exploratory operation. In other patients, the defect was either closed with a split-thickness skin graft or allowed to heal by secondary intention.

### Statistical Analysis

The effects of age, anatomic origin of infections, etiology of intra-abdominal infections, number of operations prior to STAR, number of relaparotomies, and APACHE II scores of surviving patients were investigated. Differences in proportions were examined using chi-square analysis, and differences in means were calculated using Student's $t$ and Mann-Whitney U tests. The results were expressed as means $\pm$ standard error of the mean. A value of $P < 0.05$ was considered significant.

## RESULTS

A total of 102 patients (69 males and 33 females) were studied. The mean age was 54.5 years. The mean number of operations prior to the STAR procedure was $1.04 \pm 0.13$ (range 0–4). On average, those who survived had $0.72 \pm 0.1$ operations preceding the STAR compared to $1.32 \pm 0.21$ among those who died. The difference was statistically significant ($P < 0.05$). The mortality rate was increased

according to the number of operations that preceded STAR. The relationship between the mortality rate and the number of operations prior to STAR is shown in Fig. 1. The median number of operations after the index operation per patient was 2.84 ± 0.32 reoperations per patient. The mean number of relaparotomies was 2.45 ± 0.35 in patients who died and 2.78 ± 0.18 in patients who survived. There was no significant difference in the number of relaparotomies between survivors and nonsurvivors ($P > 0.05$).

Among our patients, the mortality rates were as follows: 24.5% for those less than 55 years of age, 53.6% for those between 55 and 65 years, and 75% for those over 65 years of age. There was a significant difference in correlation with outcome ($P < 0.01$). Patients who survived were younger than those who died. Age in relation to outcome is shown in Table 1. The mean APACHE II scores for survivors and nonsurvivors were 13.4 ± 3.6 and 20.3 ± 6.44, respectively. This difference was statistically significant ($P < 0.01$). The mortality rates were as follows: 16% for patients whose APACHE II scores ranged from 0 to 10; 34.4% for the 61 patients whose APACHE II scores ranged from 11 to 20; and 87.5% for the 16 patients who had APACHE II scores of 21 or higher. Table 2 presents the relationship between APACHE II scores and mortality rates.

The causes of infections were anastomotic leakage in 47 patients, generalized peritonitis in 17, intra-abdominal abscess in seven, necrotizing pancreatitis in 14, bowel perforation in 13, and trauma in four. The mechanisms of intra-abdominal infections and associated mortality are shown in Table 3. The anatomic origin of peritoneal contamination and associated mortality are presented in Table 4. The mechanism and anatomic origin were not significantly associated with mortality in our study. Eleven patients died during relaparotomy. The series of staged procedures was successfully completed in 92 patients (90.1%). Ten of these patients underwent reoperation. The reason for reoperation was wound dehiscence due to fasciitis in eight patients and intra-abdominal abscess in two. Three patients underwent percutaneous drainage of their intra-abdominal abscesses. The overall recurrence rate for intra-abdominal infections in our series was 5.4% (5/92). The overall mortality rate was 40% (41/102). Three patients died within 48 hours after the index operation. If these three are excluded, the mortality rate becomes 38% (38/99). Fistulas developed in 11% (7/61) and hernias in 15% (9/61) of surviving patients during hospitalization. Unfortunately, we do not have long-term results for our patients.

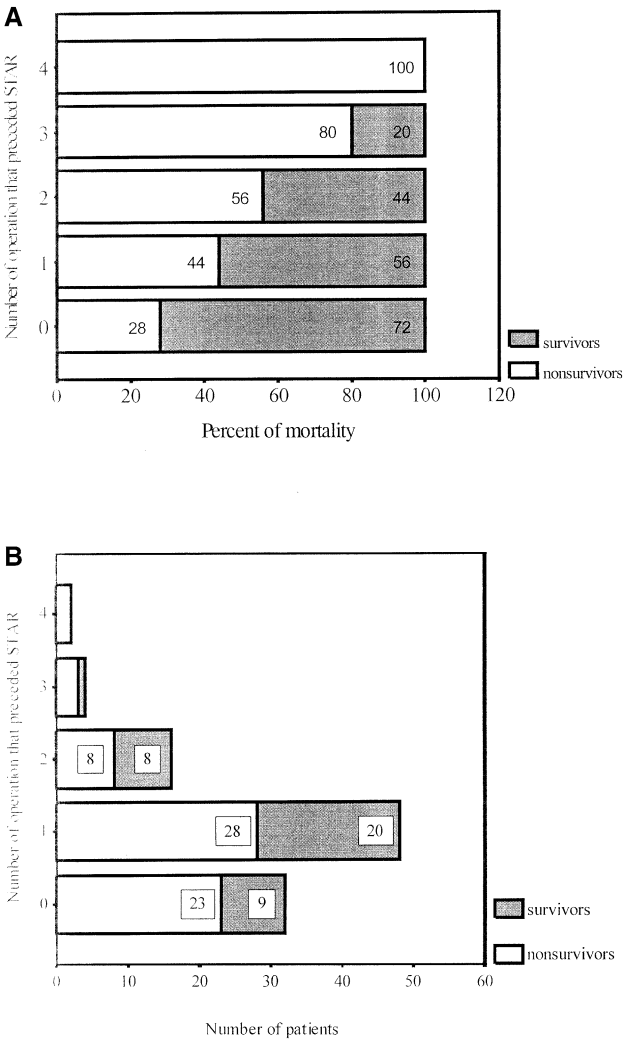


**Fig. 1.** Number of operations that preceded STAR in relation to survival. **A**, Percentage of mortality. **B**, Number of survivors and nonsurvivors.

## DISCUSSION

The mortality rate associated with severe peritonitis did not change dramatically until the 1990s, despite the availability of powerful broad-spectrum antibiotics, critical care units, and radical approaches

**Table 1.** Relationship between age and outcome

| Age (yr) | Total patients | No. of nonsurvivors | Mortality rate (%) |
|---|---|---|---|
| <55 | 53 | 13 | 24.5* |
| 55–64 | 41 | 22 | 53.6 |
| ≥65 | 8 | 6 | 75 |

*$P < 0.01$ vs. age 55–65 years and ≥65 years.

**Table 2.** APACHE II scoring and mortality

| APACHE II score | Total patients | No. of survivors | No. of nonsurvivors | Mortality rate* (%) |
|---|---|---|---|---|
| ≤10 | 25 | 21 | 4 | 16 |
| 11–20 | 61 | 38 | 23 | 37.7 |
| ≥21 | 16 | 2 | 14 | 87.5 |
| Mean APACHE II score†‡ | | 13.4 ± 3.6 | 20.3 ± 6.44 | |

*There were significant differences between groups.
†Values shown are means ± standard deviation.
‡$P < 0.01$ vs. nonsurvivors.

for eliminating bacterial contamination in the abdominal cavity.[2,3] The STAR procedure was clinically accepted as a treatment modality after the work of Wittmann et al.[5,7] clearly defined the indications and the technique for this procedure in the 1990s. STAR was defined by these investigators as a series of operations planned either before or during the index operation and performed every 24 to 36 hours with temporary closure of the abdomen using different devices such as simple mesh, mesh with a zipper, or an artificial burr. In addition to repeated debridement and cleansing of the abdomen, STAR controls the tension exerted on the fascia, prevents abdominal hypertension and, in the end, fascia-to-fascia abdominal closure is possible. According to Wittmann et al.,[3] STAR was found to be superior to conventional operative therapy when patients with equal mortality risks were compared.

The STAR procedure performed at our institution differs in some respects from that described by Wittmann et al.[5] First, Wittmann's relaparotomies were performed at 24-hour intervals. Ours were done at 24- to 48-hour intervals. Hau[8] suggested that repeat laparotomies be performed every 24 hours because the intraperitoneal bacterial content reaches the level of initial inoculation at 24 hours. Because of the adaptation problems of the various surgical teams and also because of the tight scheduling of the operating theaters, sometimes relaparotomies had to be performed at 48-hour intervals. Another important difference between our procedure and that of Wittmann et al. is that we preferred to use ostomies rather than anastomoses. The use of anastomoses rather than ostomies seems to be an advantage of the STAR procedure because the condition of the anastomosis can be assessed at each laparotomy. It was difficult to convince surgeons to perform an intestinal anastomosis when peritonitis was present in the abdomen. We used Mersilene mesh to close the abdomen, and each relaparotomy was performed through this mesh, the size of which was reduced each time, in an attempt to achieve reapproximation of the wound edges and, finally, primary closure. Because of the higher cost and difficulty in obtaining zipper mesh, this material was not used. Similarly, the artificial burr recently described by Wittmann et al.[5] was not yet commercially available and was therefore not used. This may have been the reason

**Table 3.** Etiology of infection and mortality

| Etiology | No. of patients* | No. of nonsurvivors* |
|---|---|---|
| Spontaneous peritonitis | 44 (43.1%) | 19 (43.1%) |
| Generalized (bowel necrosis, fasciitis) | 17 (16.6%) | 7 (41.1%) |
| Necrotizing pancreatitis | 14 (13.7%) | 5 (35.7%) |
| Perforation | 13 (12.7%) | 7 (53.8%) |
| Postoperative peritonitis | 54 (52.7%) | 22 (50%) |
| Anastomotic leak | 47 (46%) | 16 (34%) |
| Intraabdominal abscesses | 7 (6%) | 6 (85.7%) |
| Trauma | 4 (3.9%) | 0 |
| TOTAL | 102 | 41 (40.1%) |

*There were no significant differences between groups.

**Table 4.** Anatomic origin of infection and mortality

| Origin | Total patients | No. of nonsurvivors | Mortality rate (%)* |
|---|---|---|---|
| Large bowel | 43 | 17 | 39.5 |
| Small bowel | 17 | 6 | 35.2 |
| Upper gastrointestinal tract (stomach and duodenum) | 22 | 9 | 40.9 |
| Pancreas | 13 | 7 | 53.8 |
| Other | 7 | 2 | 28.5 |
| TOTAL | 102 | 41 | 40 |

*There were no significant differences between groups.

for the decreased primary closure and increased frequency of fistulas in our series compared with that of Wittmann et al.[5] (11% fistula and 15% hernia vs. 5% fistula and 7% hernia).

Some studies, however, have demonstrated no advantage of STAR over other surgical interventions. In the literature, the mortality rates for intra-abdominal infections associated with different surgical procedures have been reported to range from 19% to 50%.[9–12] Christou et al.[13] reported in their open, consecutive, prospective study that a low serum albumin level, high APACHE II score, and cardiac function status were significantly and independently associated with death, and there was no significant difference in mortality between patients treated with a "closed abdomen" technique (31%) and those treated with variations of the "open abdomen" technique (44%). However, "planned relaparotomy," "open abdomen" technique, and "standard" procedure were not clearly defined in this study. In another retrospective study, the mortality rate for 105 patients treated by planned relaparotomy, was reported to be 54%.[14] Hau et al.[15] have not demonstrated any advantage for planned laparotomies over the other procedures in their nonrandomized prospective studies. When these studies are reviewed in detail, important differences between the described procedures and the classical STAR procedure become evident. In a model of logistic regression analysis using the APACHE II score, the STAR procedure was shown to achieve a higher survival rate than the classical surgical approach. This difference in survival approaches 20% to 40% in patients with APACHE II scores of 10 to 20.[5] Despite all of these findings, the effect of STAR on mortality in the treatment of intra-abdominal infections remains unclear. A precise assessment of the benefits of STAR is difficult because of the heterogeneity of the patients, difficulties arising from stratification of the severity of illness, and the underlying disease processes in studies employing this technique. The mortality rate for our patients who underwent STAR during the index operation (28%) was similar to that achieved by Wittmann et al (24%), but our overall mortality rate was higher. These results suggest that the decision to use the STAR procedure should be made early.

Although our study has the inherent defects of any retrospective study, we believe our results are still meaningful in assessing factors influencing mortality in patients undergoing the STAR procedure. Many factors affect mortality in patients undergoing STAR, such as the severity of illness at the time STAR is considered, the age of the patient, the mechanism and anatomic origin of the infection, the number of operations prior to STAR, and the number of repeat laparotomies.[3,9,14]

The physiologic status of our patients at the beginning of treatment was assessed by means of the APACHE II. An APACHE II score can be translated into an estimation of mortality risk that can be used for comparison with the observed mortality rate.[1,3,16,17] Pacelli et al.[18] reported that the APACHE II score correctly graded the severity of intra-abdominal infections and was strongly correlated with outcome. Koperna et al.[14] found that the preoperative APACHE II score was significantly associated with the risk of persistent abdominal infection. In their study, the mortality rate was 20% in patients with APACHE II scores of less than 20, whereas it rose to 86% with scores of more than 20. It has been found that critically ill patients with scores higher than 25 had a mortality rate of 100% in different studies.[2] Among our patients, the mean APACHE II score in survivors was significantly lower than that in the patients who died. Outcome in our patients with intra-abdominal infections was closely correlated with the severity of the patient's systemic response and his or her physiologic reserves, which were most accurately estimated by means of the APACHE II scoring system.

In our series, the age of patients with intra-abdominal infections who underwent the STAR procedure was significantly correlated with mortality. Although Hau et al.[19] suggested that death after treatment of peritonitis is correlated with the anatomic origin of the infection, our results, as well as those in other studies, did not confirm that relationship.[7,20] Unfortunately, we were not able to obtain complete information about the duration of illness prior to surgery. But we believe that the number of laparotomies performed prior to STAR may provide some of the information concerning the duration of illness. In our study, the mortality rate was increased as was the number of operations that preceded STAR. These findings may indicate that early implementation of the STAR procedure is also a very important factor that influences mortality. This early decision to use the STAR approach may stop ongoing sepsis and prevent multisystem organ failure in these patients. In this respect, our results parallel those of other reports in the literature.[3,6,10]

The severity of the systemic response and the physiologic reserves of patients undergoing STAR are very important factors affecting mortality. We conclude that elderly patients and those with APACHE II scores of 20 or higher should be operated on as soon as possible. If an operative solution is possible, the decision of whether to use the STAR procedure is left to the surgeon's discretion, and this decision should be made on

a case-by-case basis. Relaparotomies should be performed at 24-hour intervals because bacteria regrow to their initial inoculum within 24 hours after irrigation.[8] The most important factor in reducing mortality from intra-abdominal infections is the elimination of the source of infection as soon as possible. Efforts should be focused on early detection and prompt implementation of the STAR procedure.

## CONCLUSION

Our results showed that the physiologic status of the patients, the severity of sepsis, and the number of operations prior to STAR were associated with higher mortality. To improve overall survival in patients undergoing STAR for intra-abdominal infections, the decision to perform STAR should be made early, especially in elderly patients and those with APACHE II scores of 21 or above.

REFERENCES

1. Wittmann DH. Intra-abdominal infections. Introduction. World J Surg 1990;14:145–147.
2. Nathens AB, Rotstein OD. Therapeutic options in peritonitis. Surg Clin North Am 1994;74:677–691.
3. Wittmann DH, Schein M, Cordon RE: Management of secondary peritonitis. Ann Surg 1996;224:10–18.
4. Willson SE. A critical analysis of recent innovations in the treatment of intra-abdominal infection. Surg Gynecol Obstet 1993;177:11–17.
5. Wittmann DH. Staged abdominal repair: Development and current practice of an advanced operative technique for diffuse suppurative peritonitis. Acta Chir Aust 2000;32:171–178.
6. Knauss WA, Draper EA, Wagner DP, Zimmerman JE. A severity of disease classification system. Crit Care Med 1983;13:818–829.
7. Wittmann DH, Aprahamian C, Bergstein JM. Etappenlavage: Advance diffuse peritonitis managed by planned multiple relaparatomies utilising zippers, slide fastener and velcro analogue for temporary abdominal closure. World J Surg 1990;14:218–226.
8. Hau T. Bacteria, toxins and peritoneum. World J Surg 1990;14:167–175.
9. Walsh GL, Chiasson P, Hedderich G, Wexler MJ, Meakins JL. The open abdomen. The Marlex mesh and zipper technique. A method of managing intraperitoneal infection. Surg Clin North Am 1988;68:25–41.
10. Schein M, Saddia R, Freinkel Z, Decker GAG: Aggressive treatment of severe diffuse peritonitis: A prospective study. Br J Surg 1988;75:172–176.
11. Jiffry BA, Sebastian MW, Amin T, Isbister WH. Multiple laparatomies for severe intra-abdominal infection. Aus NZ J Surg 1998;68:139–142.
12. Schein M. Planned reoperations and open management in critical intra-abdominal infections. Prospective experience in 52 cases. World J Surg 1991;15:537–545.
13. Christou NV, Barie PS, Dellinger P, Waymack JP, Stone HH. Surgical Infection Society Intra-abdominal Infection Study. Prospective evaluation of management techniques and outcome. Arch Surg 1993;128:193–198.
14. Koperna T, Schulz F. Relaparotomy in peritonitis: Prognosis and treatment of patients with persisting intra-abdominal infection. World J Surg 2000;24,32–37.
15. Hau T, Ohman C, Wolmershauer A, Wacha H, Young OS, and the Peritonitis Study Group of the SIS. Planned relaparotomy vs. relaparotomy in the treatment of intraperitoneal infections: A case controlled study [abstr]. Curr Opinion Surg Infect 1995;3 (Suppl):28.
16. Levison MA, Zergler D. Correlation of APACHE II score, drainage technique and outcome in postoperative intra-abdominal abscess. Surg Gynecol Obstet 1991;172:89–94.
17. Bosscha K, Reijinders K, Hulstaert PF, Algra A, Vander Werken C. Prognostic scoring systems to predict outcome in peritonitis and intra-abdominal sepsis. Br J Surg 1997;84: 1532–1534.
18. Pacelli F, Doglietto GB, Alfieri S, Piccioni E, Sgadari A, Gui D, Crucitti F. Prognosis in intra-abdominal infections. Multivariate analysis of 604 patients. Arch Surg 1996;131: 641–645.
19. Hau T, Ahrenholz DH, Simmons RL. Secondary bacterial peritonitis: The biologic basis of treatment. Curr Probl Surg 1979;16:1–65.
20. Boscha K, van Vroonhoven JMV, van der Werken CH. Surgical management of severe secondary peritonitis. Br J Surg 1999;86:1371–1377.

# Watermelon Stomach: Pathophysiology, Diagnosis, and Management

*Yuri W. Novitsky, M.D., Kent W. Kercher, M.D., Donald R. Czerniach, M.D., Demetrius E.M. Litwin, M.D., F.A.C.S.*

Watermelon Stomach (WS) has been increasingly recognized as an important cause of occult gastrointestinal blood loss. Clinically, patients develop significant iron deficiency anemia and are frequently transfusion dependent. The histologic hallmark of WS is superficial fibromuscular hyperplasia of gastric antral mucosa with capillary ectasia and microvascular thrombosis in the lamina propria. Endoscopic findings of the longitudinal antral folds containing visible columns of tortuous red ectatic vessels (watermelon stripes) are pathognomonic for WS. Trauma to the mucosal epithelium overlying engorged vessels by gastric acid or intraluminal food results in bleeding. Treatment options for WS include endoscopic, pharmacologic, and surgical approaches. Endoscopic therapy, including contact and non-contact thermal ablations of the angiodysplastic lesions, is the mainstay of conservative therapy. However, many patients fail endoscopic therapy and develop recurrent acute and chronic GI bleeding episodes. Surgical resection may be the only reliable method for achieving a cure and eliminating transfusion dependency. Traditionally, surgery was used only as a last resort after patients failed prolonged medical and/or endoscopic therapy. However, based on the experience garnered from the literature we recommend a more aggressive surgical approach in patients who fail a short trial of endoluminal therapy. (J GASTROINTEST SURG 2003;7:652-661.) 

KEY WORDS: Watermelon stomach, vascular ectasia, occult GI bleeding, Nd:YAG laser, Argon plasma coagulator, gastric surgery, laparoscopy

Watermelon Stomach (WS) is a rare condition associated with chronic GI blood loss. It is often overlooked on endoscopic examinations.[1,2] Clinically, patients develop significant iron deficiency anemia and are frequently transfusion dependent. Rider et al. first described a case of gastric vascular ectasia in 1953, noting "an erosive type of atrophic gastritis with marked veno-capillary ectasia" in a gastrectomy specimen of an elderly woman with occult GI bleed.[3]

Subsequently several patients with vascular lesions of the stomach appearing as "red linear streaks"[4] or "red areas with appearance of dilated blood vessels" in the antrum[5] were reported. In 1984, Jabbari et al.[6] described characteristic endoscopic findings of gastric antral ectasia (longitudinal red columns) and coined the term WS. Since then, this disorder has been increasingly recognized as a distinct entity with characteristic endoscopic and histopathologic features. Several treatment modalities have been employed in an attempt to minimize or eliminate the transfusion requirements in patients with WS. Various pharmacological agents and endoscopic techniques have been used with some success. Surgery, widely recognized as a curative procedure, has been employed infrequently. This hesitance probably stems from early reports of high short- and long-term postoperative morbidity and mortality.[7,8] This review summarizes the clinical presentation, etiology, histopathology, and diagnostic modalities associated with this syndrome which to date has received minimal attention in the surgical literature. Treatment options and outcomes garnered from the literature are reviewed and discussed. Finally, we propose a management algorithm advocating an aggressive surgical approach in patients who fail a short trial of endoluminal therapy.

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## CLINICAL PRESENTATION AND ASSOCIATED ILLNESSES

WS has been increasingly recognized as an important cause of occult gastrointestinal blood loss. The typical patient is an elderly female with a history of chronic iron-deficiency anemia for which no etiology has been recognized despite endoscopic and barium studies.[9] A recent review has identified a 3:1 female preponderance with an 88% incidence of iron deficiency anemia and a 42% incidence of heme-positive stools. Other frequently associated symptoms at presentation include melena, hematochezia, and hematemesis.[10]

Although blood loss rarely exceeds 25 ml per day,[10,11] oral iron replacement alone is usually not sufficient and patients are frequently blood transfusion dependent. Gostout et al.[1] series showed that 62% of patients receive a mean of 10 units of packed red blood cells per 12-month period. Further characteristic findings include hypergastrinemia,[1,9,12,13] hypochlorydia with complete achlorydia in 35% of patients.[8,9,13] Atrophic gastritis is almost uniform,[1,9,14] commonly leading to a misdiagnosis.

Various disorders are thought to cause or to be closely associated with WS (Table 1). Gostout et al[1] found that 62% of patients have a coexistent autoimmune connective tissue disorder, particularly Raynaud's (31%) and sclerodactyly (20%). Liberski et al.[15] reported elevated levels of ANA titers in 7 of 9 tested patients. Other immune system disorders, such as CREST,[16] SLE,[17] systemic sclerosis,[18,19] and scleroderma[20] have been described in patients with WS.

Cirrhosis may be found in 30% to 66% of patients with WS.[15,21] In the setting of cirrhosis, WS can be difficult to distinguish from portal hypertensive gastropathy (PHG), although WS generally affects the gastric antrum as opposed to primary fundus and corpus involvement in PHG. In addition, patients with WS have more severe liver disease, higher gastrin levels, and greater chronic blood loss than the patients with PHG.[22,23] While portal hypertension was initially linked to the development of vascular ectasias, the frequent presence of WS in the absence of portal hypertension, as well as a lack of response to TIPS, contradicts that theory.[24,25] As a result, WS and PHG are considered to be separate clinical entities. Other liver diseases such as primary biliary cirrhosis and nodular regenerative hyperplasia have been described in association with WS.[7,26]

Renal disease[15,27] and, less commonly, diabetes mellitus,[15] hyperthyroidism,[1] and HTN[15] have also been associated with WS. A 40% incidence of gastric lymphomas in a small series of patients with WS[28] was not confirmed in larger series.

## HISTOPATHOLOGY

Microscopic analyses of endoscopic biopsies and surgical resection specimens have yielded a distinct set of pathologic findings. The histologic hallmark of WS is superficial fibromuscular hyperplasia of gastric antral mucosa with capillary ectasia and microvascular thrombosis in the lamina propria. Hypervascularity of the antrum appears to be secondary to an abundance of moderately dilated capillaries[6,13,29] as well as a small number of very large capillaries.[26] Most of the telangiectatic capillaries of the mucosa and submucosa are occluded by fibrin microthrombi.[13,25,26,30]

The antral mucosa is marked by a paucity of inflammatory cells and by focal areas of intestinal metaplasia.[13,29] The lamina propria is marked by fibromuscular hyperplasia, resulting from spindle cell proliferation that extends toward antral glands.[6,9,13,25,29] Typically, there is a perpendicular extension of smooth muscle into the fibrosed lamina propria which is often hyalinized.[26] Additionally, islands of typical neuroendocrine

**Table 1.** Associated pathologies in patients with Watermelon Stomach

| | Immune | Non-immune |
|---|---|---|
| Common | Connective tissue disorders | Cirrhosis |
| | Raynaud's | Renal insufficiency |
| | Sclerodactyly | Hypertension |
| | Telangectasia | |
| | Pernicious anemia | |
| | Primary biliary cirrhosis | |
| | Hypothyroidism | |
| Uncommon | Systemic lupus erythematosus | Diabetes |
| | Scleroderma | Nodular regenerative hyperplasia |
| | Systemic sclerosis | Lymphoma |
| | | Gastric carcinoma |
| | | Aortic stenosis |

cells populate the lower lamina propria. Marked increase in both intraepithelial and extraepithelial neuroendocrine cells with reactivity for serotonin ($5HT_3$) and vasoactive peptide is seen.[29]

Lastly, the submucosa of the gastric antrum contains tortuous dilated vessels extending in a longitudinal direction toward the pylorus. These vessels are congested and surrounded by loosely knit stroma.[6,13,26]

## PATHOGENESIS

The etiology of watermelon stomach is unknown. The heterogeneity of associated conditions, including autoimmune, kidney, and liver disorders, suggests that it may not be uniform. It is unclear whether angiodysplasia is a primary pathologic process or a result of fibromuscular hyperplasia. The former theory proposes that angiodysplasia results in loosening of the attachment of distal gastric mucosa to the muscularis externa, rendering it more susceptible to prolapse and trauma. This, in turn, may result in reactive muscular hyperplasia and fibrosis of the lamina propria.[6] In fact, angiodysplasia could be induced by malfunction of the precapillary sphincters resulting in hyperplasia and dilatation of the capillaries.[27] Prolonged sphincter relaxation induced by high levels of gastrin, may also contribute to local hyperplasia and capillary and venous dilatation. Ectatic vasculature of gastric mucosa is surrounded by neuroendocrine cells that secrete substances such as 5HT-3, VIP, and gastrin. Therefore angiodysplasia may be a result of high local concentrations of these vasodilators.[29] The role of other vasoactive substances such as endogenous nitric oxide, relaxin, endothelin, and prostaglandins still warrants investigation.[31]

Other theories of WS pathogenesis place fibromuscular hyperplasia as an inciting process leading to angiodysplasia and subsequent GI bleeding. Hypergastrinemia may incite spindle cell proliferation and hyperplasia.[23] Increased gastric peristalsis produces repeated mechanical stresses and may induce fibromuscular hyperplasia as well.[24] The resultant chronic low grade obstruction of submucosal veins within hypertrophied muscular layers leads to a rise in hydrostatic pressure and gradual dilatation of veins, venules, and capillaries.[27] The dilatation of submucosal vessels is followed by changes in the mucosal vascular unit and results in typical angiodysplasia.[23,24] Fibrin microthrombi may cause focal ischemia of gastric mucosa resulting in vascular erosion and bleeding.[11]

Overall, angiodysplasia appears to be a common vascular lesion resulting from mechanical or humoral factors. Trauma to the mucosal epithelium overlying engorged vessels by gastric acid or intraluminal food may result in clinically significant bleeding.[26]

## DIAGNOSIS

WS has been increasingly recognized in recent years. It has been diagnosed in patients with lesions that may have been overlooked in the past.[2,32,33] Originally considered a rare entity, seen in only 3 of 10,000 endoscopies,[6] it is now believed to be an important clinical disease with clearly defined endoscopic and microscopic findings. Longitudinal antral folds containing visible columns of tortuous red, ectatic vessels, "watermelon stripes" (Fig. 1), were first described by Jabbari et al.[6] These lesions are sharply demarcated with small marginated red spots.[6,13,34,35] Vessels blanch with pressure and bleed freely when endoscopic biopsies are undertaken.[9,35]

Though originally described as gastric antral vascular ectasia (GAVE), more proximal and diffuse involvement of the stomach is associated with an identical histopathologic and clinical picture. The term "watermelon stomach" is believed to encompass a wide spectrum of involvement of angiodysplastic lesions within the stomach. In fact, four distinct endoscopic patterns are described. The majority of patients have antral disease with classic raised convoluted ridges covered by ectatic vascular tissue radiating out from the py-

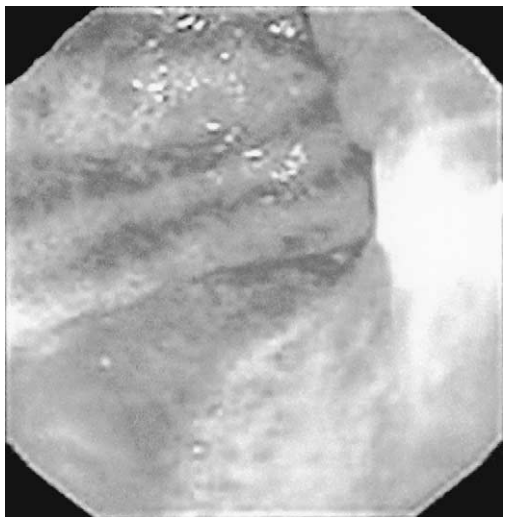

**Fig. 1.** Endoscopic appearance of the gastric antrum in a patient with Watermelon Stomach. Note longitudinal antral folds containing columns of tortuous red ectatic vessels ("watermelon stripes"). Trauma to the mucosal epithelium overlying engorged vessels by gastric acid or intraluminal food may result in clinically significant bleeding.

lorus. Other patterns include lesions arranged in radiating flat stripes, scattered multiple mucosal lesions, or a mixture of the above patterns. It has been suggested that non-cirrhotic patients are likely to have linear lesions within the antrum whereas in cirrhotics the disease is more often diffuse.[22] Histologic findings are similar in all 4 types.[1] In addition, coalesced angiodysplastic giant red lesions, labeled as a "honeycomb stomach" by Chawla et al., are occasionally seen.[5,11,36] This might be a progression from a watermelon stripe appearance to more uniform vascular involvement.[36] A case of diffuse vascular ectasia within the antrum associated with similar lesions in the duodenum and jejunum has been described as well.[25]

Another endoscopic finding in WS is prolapse of the pyloric mucosa.[6] Ectatic elongated vessels and petechial hemorrhages are typically found at the apex of the prolapsing mucosa.[1,6] Other findings include proximal gastric involvement with two-thirds of such patients having a diaphragmatic hernia;[1] atrophic gastritis is seen in uninvolved areas of the stomach.

The watermelon stripes found on endoscopy are believed to be pathognomonic for this entity. Endoscopic biopsy, though associated with potential significant bleeding, is highly sensitive for the diagnosis of watermelon stomach.[30] Although nonspecific, upper GI series may demonstrate prominent mucosal folds extending from the pyloric channels, and CAT scan may show a thickened antral wall.[37] Angiography reveals antral hypervascularity.[35] Endoscopic ultrasound distinctly defines the layers of the stomach wall, localizing ectatic vessels of the mucosa and submucosa. Vascular ectasia appears as distinct echopoor vascular structures in those layers.[38]

## TREATMENT

Treatment options for watermelon stomach depend upon the severity of disease. In many cases, parenteral or oral iron supplementation may be sufficient. However, patients are often transfusion dependent with average requirements of 10 units of blood per year[1] and as high as 50–100 units per year in severe cases. This puts patients at a significant risk of viral transmission despite the current meticulous screening of blood products.[39] In addition to viral infections, RBC-related sepsis and endotoxin-induced septic shock present additional dangers.[40] The above risks are compounded by chronic transfusion dependency. Thus, ultimately, the goal of therapy should be a complete or near-complete elimination of blood transfusion requirements in WS patients.

Endoscopic, pharmacologic, and surgical approaches have been described with a wide variety of outcomes. Though endoscopic therapy is considered to be the mainstay of conservative therapy and may be very successful in controlling symptoms and reducing or eliminating transfusion requirements, many authors agree that antrectomy or other surgical procedures are the only curative measures. Traditionally, operations have been used as a last resort and perioperative mortality as high as 7.4% was reported in a widely quoted early series.[41] As the experience in treatment of WS grows and larger series are being reported, the appropriate management algorithm for eliminating transfusion requirements in patients with WS is coming to light. We have reviewed all cases of WS reported in the English literature, and have evaluated the efficacy and safety of the available treatment regimens.

### Thermal Ablation

Several types of contact and non-contact thermal ablations of the angiodysplastic lesions of watermelon stomach have been described. Neodymium-yttrium-aluminum garnet (Nd:YAG) laser coagulation has been gaining increasing popularity since Fager et al.[42] reported its successful use in 1985. Patients usually require multiple endoscopic sessions, each several weeks apart. While laser therapy is effective in many patients, it is rarely curative. In the five largest series of Nd:YAG therapy, 14 to 50% of initially transfusion-dependent patients required transfusions in the follow-up period, despite multiple treatments (Table 2). Smaller series report variable degrees of success in eliminating transfusion requirements, ranging from complete success to complete failure.[12,18,28,33,41,45–48]

Many patients undergoing Nd:YAG therapy return in the follow-up period with recurrent acute bleeding episodes that require repeat transfusions (Table 3) and immediate interventions. These episodes of failed laser therapy may respond to repeat laser coagulation sessions.[18,41,45,48] Otherwise patients often proceed to surgery for a curative procedure.[44,48]

Endoscopic laser coagulation is not without complications (Table 4). Repeated thermal injury to the antral mucosa in patients with watermelon stomach may result in the development of hyperplastic polyps. These may be large and may contribute to significant recurrent blood loss and anemia.[49] Several investigators[42,44] have also reported the development of antral ulcers. Rigid contractures were noted during endoscopic follow-up in 33% of Gostout's patients.[1] Although asymptomatic, the clinical significance of contracture at the gastric outlet remains unclear.

**Table 2.** Larger series of Nd:YAG laser use

| Author(s) | No. of patients | Follow-up period (mo) | Pretreatment transfusion requirements | Transfusions during follow-up period |
|---|---|---|---|---|
| Gostout et al.[1] | 45 | 1-72 | 28/45 (63%) | 4/28 (14.2%) |
| Liberski et al.[15] | 15 | 24-96 | 14/15 (93%) | 2/14 (14.2%) |
| Sargeant et al.[32] | 16 | 7-44 | 16/16 (100%) | 7/16 (43.8%) |
| Bourke et al.[43] | 11 | 6-60 | 9/16 (56%) | 3/9 (33.3%) |
| Potamino et al.[44] | 8 | 12-60 | 8/8 (100%) | 4/8 (50%) |

More concerning is a recent report of a patient who underwent repeated sessions of Nd:YAG laser coagulation for WS. He presented with non-healing deep ulcerations and ultimately a nodular antrum that proved to contain a carcinoma-in-situ.[47] This case may suggest a possible correlation between prolonged laser therapy and development of gastric neoplasia.

For those patients who obtain long-term relief from Nd:YAG therapy, a reduction in transfusion requirements is usually evident after the first several treatment sessions.[1] With repeated therapy, diminishing returns and increasing complication rates are seen (Table 4).

Many patients, especially those with portal hypertension,[31] are refractory to Nd:YAG therapy and do not gain a timely benefit from laser treatments. In addition, disease along the lesser curvature and posteriorly within the antrum and cardia is difficult to assess[1] and the relative flatness of these lesions makes proximal lesser curvature lesions easy to miss because of the tangential view.[27] Finally, endoscopic laser therapy requires expensive technology that is not yet widely available.[10]

Argon plasma coagulation (APC) is a non-contact method that utilizes ionized gas to provide coagulation at depths of 2–3 mm.[9] This technique allows tangential coagulation of hard to reach lesions for which direct contact is difficult. Two series of APC use have yielded somewhat different results. Abeidi et al.[9] found 44% of patients (4 of 9) remained transfusion dependent during a 3-month follow-up period. Bjorkman et al.[41] have reported a 100% elimination of transfusions in 4 patients (21- to 61-month follow-up), though 75% needed repeated treatments for recurrent acute bleeding episodes during the follow-up period. Overall, APC therapy has been associated with a 22% incidence of recurrent significant rebleeding, with up to 31% of patients requiring ongoing transfusions (Tables 3 and 4). The use of APC for WS has gained in popularity in recent years and may prove to be superior to other thermal ablation techniques as more data becomes available.

A small group of patients has been treated with contact thermal ablation.[16,46,50,51] In a series of 10 patients Petrini and Johnson employed a heat probe achieving a 90% success rate in eliminating transfusion requirements (one patient bled after initiation of aspirin therapy). At 20-month follow-up there were no complications.[51] Other reported trials of therapy with heater probe use were unsuccessful.[16,46]

**Table 3.** Reported failures of endoscopic therapy

| Endoscopic modality | No. of patients | Follow-up period (mo) | Transfusions during the follow-up period |
|---|---|---|---|
| Nd:YAG | 110 | 1–96 | 23/90 (25.6%) |
| APC | 13 | 3–61 | 4/13 (30.8%) |
| Heater Probe | 15 | 13–20 | 2/12 (16.7%) |

## Pharmacologic Therapy

Pharmacologic agents have also produced inconsistent results. Corticosteroids have been used in 8 patients.* Three patients (38%) received blood during the follow-up period. Two patients had to undergo a surgical intervention to control bleeding.[5,34] The use of the serotonin antagonist cyproheptsadine resulted in a significant improvement of antral lesions during a one-year follow-up in one patient.[55] A variety of other medical therapies, including alfa-interferon,[56] octreotide,[57] oral tranexamic acid,[28,58] and ethanol sclerotherapy[59] have been attempted without success.

## Surgery

To date, a wide array of conservative therapies have been utilized to treat patients with transfusion-dependent WS. Although a few of these modalities have shown some promise, none has been uniformly

*References 5, 16, 34, 35, 52–54.

**Table 4.** Common morbidities associated with various therapeutic options

| Treatment modality | Recurrent acute bleeding episodes | Hyperplastic polyps | Antral ulcers | Antral narrowing/ contracture |
|---|---|---|---|---|
| APC | 22% | 0 | 2% | 0 |
| Nd:YAG | 9% | 8% | 3% | 32% |
| Surgery | 0 | 0 | 1% | 0 |

effective in treating this disease. As a result, many authors believe that surgical resection may be the only reliable method for achieving a cure. Traditionally, surgery was used only as a last resort[6,35] after patients failed medical and/or endoscopic therapy. Often these conservative strategies were marked by continuous high transfusion requirements. In the small early series of patients treated with gastric resection, postoperative deaths occurred most commonly in patients who became debilitated by prolonged conservative therapy. Although postoperative mortality rates as high as 7.4% were initially described,[8] no large series of patients treated surgically has been reported to date. Our review of 45 reported surgical cases revealed the results summarized in Table 5. Antrectomy was performed in the vast majority of cases (89%). There were no reported discrete episodes of postoperative bleeding. Only 2 of 45 patients (4.4%) required transfusion during a follow-up period of 1 to 48 months. In one patient, concurrent lesions in the duodenum and jejunum were identified as a source of ongoing blood loss.[25] Lymphoma was incidentally discovered in a partial gastrectomy specimen of another patient.[28] Overall, surgery was highly effective eliminating further bleeding and the need of blood products in transfusion-dependent patients with WS (Table 6).

For all patients with WS who underwent gastric resection, the 30-day mortality rate was 6.6% (3 of 45). Two patients had severe cirrhosis and protracted preoperative bleeding. In each case, surgical blood loss was minimal and bleeding resolved after surgery. Ultimately, both patients died from multiorgan failure.[24] The details of the third patient's case are not available.[44] During long-term follow-up (18–24 mo), 3 additional patients died from unrelated causes.[2,62,63] None of these patients had clinical evidence of upper GI bleeding during the postoperative period.

Although the available surgical data for WS is scarce, gastric resection for a benign condition carries a remarkably low rate of long-term sequelae. Tovey et al.[64] reported a 2.4% rate of late dumping and an absence of continuous diarrhea in 41 patients after Billroth I gastrectomy for benign disease at an average follow-up of 20 years. A recent series of 24 patients who underwent a laparoscopic or laparoscopically assisted gastric resection showed no major functional problems, apart from 2 cases (4.8%) of transient diarrhea, at a mean follow-up of 19 months.[65] Nutritional concerns, including iron, B12, and Vitamin D deficiencies, far outweigh the impact of mechanical post-gastrectomy problems.[66,67] Careful follow-up with dietary counseling and preventive measures should further improve outcomes in the post-gastrectomy population.

Additionally, minimally invasive approaches to gastrectomy have been gaining in popularity. Laparoscopic or laparoscopically assisted gastrectomy patients enjoy shorter hospitalizations and faster functional recovery than the patients after open gastrectomy.[68] The laparoscopic approach appears to result in fewer functional sequelae as well.[65] Quality of life after laparoscopic gastrectomy has also been shown to be significantly better when compared to the conventional approach.[69]

## COMMENTS

Watermelon Stomach, rarely appreciated in the past, has become a recognized distinct clinical entity. Awareness of its characteristic endoscopic findings allows for effective identification of WS in patients with chronic or acute GI bleeding. It is after the diagnosis is established that a physician, often a gastroenterologist, faces the dilemma of choosing an appropriate course of therapy. Although endoscopic, pharmacologic, and surgical modalities may be used in the treatment of WS, each has quantifiable risks and limitations. The ultimate goal in treating a patient with watermelon stomach should be the complete or near-complete elimination of transfusion requirements. How does one proceed along the treatment algorithm to achieve this goal?

After the diagnosis of WS is confirmed and PHG is ruled out, we believe that endoscopic therapy should be initiated promptly (Fig. 2). Whether an Nd:YAG laser or APC probe should be employed remains debatable. The results of this review show that in 75% of patients treated with Nd:YAG laser and in 70% of patients treated with APC (Table 3) transfusion requirements

**Table 5.** Surgical experience with Watermelon Stomach

| Author | No. of patients | Follow-up period (mo) | Pretreatment transfusion requirements | Procedure |
|---|---|---|---|---|
| Wheeler et al.[4] | 2 | 8–12 | + | Antrectomy* |
| Lee et al.[5] | 1 | 18 | + | Antrectomy |
| Jabari et al.[6] | 2 | 24 | + | Antrectomy |
| Gostout et al.[7] | 1 | N/A | + | Antrectomy |
| Arendt et al.[11] | 1 | 21 | + | Antrectomy |
| Fraser et al.[12] | 2 | 36–48 | N/A | Antrectomy |
| Gardiner et al.[13] | 1 | 3 | + | Partial gastrectomy |
| Berk et al.[14] | 1 | N/A | − | Esophagogastrectomy |
| Watson et al.[18] | 2 | N/A | + | Antrectomy |
| Spahr et al.[24] | 4 | <1 | + | Antrectomy |
| Cales et al.[25] | 1 | 1 | + | Total gastrectomy |
| Park et al.[28] | 1 | 18 | + | Partial gastrectomy |
| Lowes et al.[29] | 1 | 12 | + | Antrectomy |
| Gilliam et al.[30] | 5 | N/A | N/A | Antrectomy |
| Rawlinson et al.[34] | 2 | 6 | + | Antrectomy |
| Kruger et al.[35] | 3 | 13–21 | + | Antrectomy |
| Urban et al.[37] | 1 | 3 | + | Antrectomy |
| Manolios et al.[38] | 2 | 6–24 | + | Antrectomy |
| Sargeant et al.[43] | 1 | N/A | + | Total gastrectomy |
| Potamino et al.[44] | 1 | 2 | + | Antrectomy |
| Tanaka et al.[46] | 1 | 1 | + | Antrectomy |
| Barbara et al.[57] | 1 | 24 | + | Antrectomy |
| Gillinsky et al.[60] | 1 | N/A | + | Antrectomy |
| Szold et al.[61] | 3 | N/A | + | Antrectomy |
| Gouldesbrough[62] | 1 | 18 | + | Antrectomy |
| Tovey[63] | 2 | 6–18 | + | Antrectomy |
| Makharia et al.[64] | 1 | N/A | + | Antrectomy |

N/A = not available.
*Includes Billroth I, II, and Roux-en-Y reconstructions.

can be eliminated. However, failure and complication rates remain high. For those patients who do not respond to endoscopic therapy after several sessions, repeated attempts to ameliorate vascular ectasia by endoscopic techniques are probably futile. In addition to the risk of viral transmission associated with ongoing transfusions, the protracted course of this chronic illness, complicated by recurrent episodes of GI bleeding, further worsens these patients' nutritional and immune status. Therefore, it is imperative that these patients are recognized early and moved expeditiously along the treatment algorithm. Inappropriate delays in surgical intervention may significantly adversely affect the morbidity and mortality profiles of these patients. Also, a reported progression to malignancy with repeated laser treatment sessions should not be overlooked.

In some patients, endoscopic therapies, though not completely successful, lead to a marked decrease in transfusion requirements and a near-complete elimination of transfusion dependency. In this population the risks and morbidity of surgery likely outweigh the risks associated with only seldom blood transfusions. These

**Table 6.** Outcomes of surgical approaches

| Operation | No. of patients | Pretreatment transfusion requirements | Recurrent bleeding episodes | Transfusions during follow-up period |
|---|---|---|---|---|
| Antrectomy* | 40 | All | 0 | 1 |
| Partial gastrectomy | 2 | All | 0 | 0 |
| Total gastrectomy | 2 | All | 0 | 1 |
| Esophagogastrectomy | 1 | All | 0 | 0 |

*Includes Billroth I, II, and Roux-en-Y reconstructions.

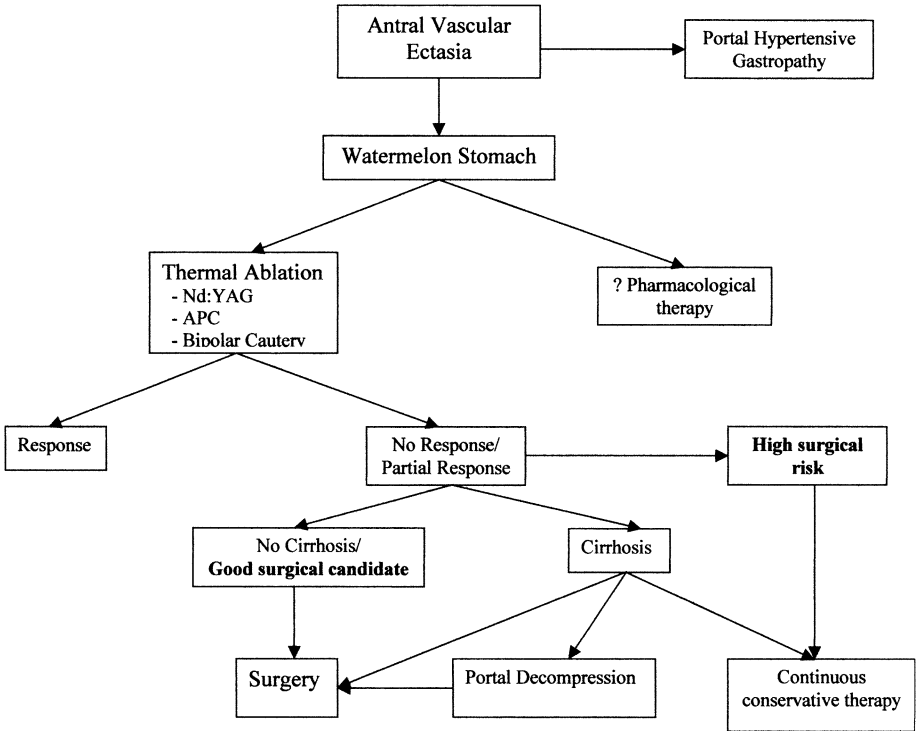


**Fig. 2.** Management algorithm for patients with WS. Initial workup to rule out portal hypertensive gastropathy is paramount since portal decompression is ineffective for WS patients. Prompt surgical referral for patients who fail conservative measures (especially in the absence of significant liver disease) is strongly advocated.

patients require a more tailored approach, with such factors as age, comorbidities, and potential need for systemic anticoagulation considered before the surgical intervention is contemplated.

The appropriate management of patients with WS complicated by cirrhosis or portal hypertension, however, is less clear. This subpopulation usually responds poorly to the endoscopic ablation therapies.[31] In addition, given the fact that both known mortalities associated with antrectomy for WS occurred in cirrhotic patients, aggressive surgical management of these patients may not be warranted. A surgeon should proceed with an additional caution due to the relatively higher perioperative morbidity and mortality associated with gastric surgery in the setting of cirrhosis. We believe that these complicated patients may benefit from a preoperative portal decompression procedure as a bridge to antrectomy. However, for some patients with advanced liver disease surgical risk may be prohibitive and a lifelong conservative therapy (thermal ablation, etc.) may be more appropriate.

WS involving the proximal stomach presents an additional dilemma. While we do not consider proximal or diffuse gastric vascular lesions as absolute contraindications to surgery, those patients will require a more extensive resection and, therefore, warrant additional analysis of the surgical risk-benefit ratio.

The challenge remains in a prompt, accurate identification of patients that will require surgical intervention. Based upon our experience and a review of the available literature, we believe that a short trial or one or two endoscopic sessions will identify the patients with disease amenable to a conservative therapy. For those patients who do not respond to it initially, the low morbidity and mortality observed in surgically treated cases favor an earlier, more aggressive surgical approach.

The development and wider implementation of minimally invasive techniques may have resulted in an additional support for the surgical treatment of gastric pathology in general, and WS in particular. With the increased safety profile and decreased postoperative morbidity and mortality conferred by laparoscopy, gastric surgery may have become a better option. Those patients, previously considered poor surgical candidates, may now benefit from a minimally invasive operative approach to eliminate long-term transfusion requirements and provide cure for this chronic illness.

## REFERENCES

1. Gostout CJ, Viggiano TR, Ahlquist DA, Wang KK, Larson MV, Balm R. The clinical and endoscopic spectrum of the watermelon stomach. J Clin Gastroenterol 1992;15:256–263.

2. Labenz J, Borsch G. Bleeding watermelon stomach treated by Nd-YAG laser photocoagulation. Endoscopy 1993; 25:240–242.
3. Rider JA, Klotz AP, Krisner JB. Gastritis with veno-capillary ectasia as a source of massive gastric hemorrhage. Gastroenterology 1953;24:118–123.
4. Wheeler MH, Smith PM, Cotton PB, Evans DMD, Lawrie BW. Abnormal blood vessels in the gastric antrum. A cause of upper gastrointestinal bleeding. Dig Dis Sci 1979;24:155–158.
5. Lee FI, Costello F, Flanagan N, Vasudev KS. Diffuse antral vascular ectasia. Gastrointest Endosc 1984;30:87–90.
6. Jabbari M, Cherry R, Lough JO, Daly DS, Kinnear DG, Goresky CA. Gastric antral vascular ectasia: The watermelon stomach. Gastroenterology 1984;87:1165–1170.
7. Gostout CJ, Ahlquist DA, Radford CM, Viggiano TR, Bowyer BA, Balm RK. Endoscopic laster therapy for watermelon stomach. Gastroenterology 1989;96:1462–1465.
8. Borsch G. Diffuse gastric antral ectasia: The "watermelon stomach" revisited. Am J Gastroenterology 1987;82:1333–1334.
9. Abedi M, Haber GB. Watermelon stomach. Gastroenterologist 1997;5:179–184.
10. Gretz JE, Achem SR. The watermelon stomach: Clinical presentation, diagnosis, and treatment. Am J Gastroenterol 1998;93:890–895.
11. Arendt R, Barten M, Lakner V, Arendt R. Diffuse gastric antral vascular ectasia: Cause of chronic gastrointestinal blood loss. Endoscopy 1987;19:218–229.
12. Fraser AG, Koelmeyer T, White AC, Nicholson GI. Antral vascular ectasia: The watermelon stomach. N Z Med J 1992;105:338–339.
13. Gardiner GW, Murray D, Prokipchuk EJ. Watermelon stomach, or antral gastritis. J Clin Pathol 1985;38:1317–1318.
14. Berk T, Slemmer JR, Friedman LS. Gastric antral vascular ectasia associated with gastric carcinoma. Am J Gastroenterol 1991;86:768–770.
15. Liberski SM, McGarrity TJ, Hartle RJ, Varano V, Reynolds D. The watermelon stomach: Long term outcome in patients treated with Nd:YAG laser therapy. Gastrointest Endosc 1994;40:584–587.
16. Beales IL. Watermelon stomach in the CREST syndrome. Postgrad Med J 1994;70:766–767.
17. Archimandritis A, Tsirantonaki M, Tzivras M, Hatzis G, Davaris P. Watermelon stomach in a patient with vitiligo and systemic lupus erythematosus. Clin Exp Rheumatol 1996;14:227–228.
18. Watson M, Hally RJ, McCue PA, Varga J, Jimenez SA. Gastric antral vascular ectasia (watermelon stomach) in patients with systemic sclerosis. Arthritis Rhem 1996;39:341–346.
19. Fabian G, Tovari E, Baranyay F, Czirjak L. Watermelon stomach as a cause of chronic iron deficiency anemia in a patient with systemic sclerosis. J Eur Acad Dermatol Venereol 1999;12:161–164.
20. Manolios N, Eliades C, Duncombe V, Spencer D. Scleroderma and watermelon stomach. J Rheumatol 1996;23:776–778.
21. Burak KW, Lee SS, Beck PL. Portal hypertensive gastropathy and gastric antral vascular ectasia (GAVE) syndrome. Gut 2001;49:866–872.
22. Payen JL, Cales P, Voigt JJ, Barbe S, Pilette C, Dubuisson L, Desmorat H, Vinel JP, Kervran A, Chayvialle JA. Severe portal hypertensive gastropathy and antral vascular ectasia are distinct entities in patients with cirrhosis. Gastroenterol 1995;108:138–144.
23. Lingenfelser T, Krige JE. The stomach in cirrhosis. J Clin Gastroenterol 1993;17:92–96.
24. Spahr L, Villenneuve JP, Dufresne MP, Tasse D, Bui B, Willems B, Fenyves D, Pomier-Layrargues G. Gastric antral vascular ectasia in cirrhotic patients: Absence of relation with portal hypertension. Gut 1999;44:739–742.
25. Cales P, Voigt JJ, Payen JL, Bloom E, Berg P, Vinel JP, Pradere B, Broussy P, Pascal JP. Diffuse vascular ectasia of the antrum, duodenum, and jejunum in a patient with nodular regenerative hyperplasia. Lack of response to portosystemic shunt or gastrectomy. Gut 1993;34:558–561.
26. Suit PF, Petras RE, Bauer TW, Petrini JL. Gastric antral vascular ectasia. A historical and morphometric study of "the watermelon stomach." Am J Surg Pathol 1987;11:750–757.
27. Gilmore PR. Angiodysplasia of the upper gastrointestinal tract. J Clin Gastroenterol 1988;10:386–394.
28. Park RH, Danesh BJ, Upadhyay R, Howatson AG, Lee FD, Russel RI. Gastric antral vascular ectasia (watermelon stomach)—therapeutic options. Postgrad Med J 1990;66:720–723.
29. Lowes JR, Rode J. Neuroendocrine cell proliferations in gastric antral vascular ectasia. Gastroenterology 1989; 97:207–212.
30. Gilliam JH 3d, Geisinger KR, Wu WC, Weidner N, Richter JE. Endoscopic biopsy is diagnostic in gastric antral vascular ectasia. The "watermelon stomach." Dig Dis Sci 1989;34:885–888.
31. Brandt LJ. Gastric antral vascular ectasia: Is there to be a consensus. Gastrointest Endosc 1996;44:355–356.
32. Sargeant IR, Loizou LA, Rampton D, Tulloch M, Bown SG. Laser ablation of upper gastrointestinal vascular ectasias: long term results. Gut 1993;34:470–475.
33. Parente F, Petrillo M, Vago L, Porro GB. The watermelon stomach: clinical, endoscopic, endosonographic, and therapeutic aspects in three cases. Endoscopy 1995;27:203–206.
34. Rawlinson WD, Barr GD, Lin BP. Antral vascular ectasia—the "watermelon" stomach. Med J Aust 1986;144:709–711.
35. Kruger R, Ryan ME, Dickson KB, Nunez JF. Diffuse vascular ectasia of the gastric antrum. Am J Gastroenterol 1987;82:421–426.
36. Chawla SK, Ramani K, Presti PL. The honeycomb stomach: Coalesced gastric angiodysplasia. Gastrointest Endosc 1990;36:516–518.
37. Urban BA, Jones B, Fishman EK, Kern SE, Ravich WJ. Gastric antral vascular ectasia ("watermelon stomach"): Radiologic findings. Radiology 1991;178:517–518.
38. Avunduk C, Hampf F. Endoscopic ultrasound in the diagnosis of watermelon stomach. J Clin Gastroenterol 1996; 22:104–106.
39. Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ. The risk of transfusion-transmitted viral infections. The Retrovirus Epidemiology Donor Study. N Engl J Med 1996; 334:1685–1690.
40. Chamberland M, Khabbaz RF. Emerging issues in blood safety. Infect Dis Clin North Am 1998;12:217–229.
41. Bjorkman DJ, Buchi KN. Endoscopic laser therapy of the watermelon stomach. Lasers Surg Med 1992;12:478–481.
42. Frager JD, Brandt LJ, Frank MS, Morechi R. Treatment of a patient with watermelon stomach using transendoscopic laser photocoagulation. Gastrointest Endosc 1988;34:134–137.
43. Bourke MJ, Hope RL, Boyd P, Gillespie PE, Cowen AE, Williams SJ. Endoscopic laser therapy for watermelon stomach. J Gastroenterol Hepatol 1996;11:832–834.
44. Potamiano S, Carter CR, Anderson JR. Endoscopic laser treatment of diffuse gastric antral vascular ectasia. Gut 1994;35:461–463.
45. Tsai HH, Smith J, Danesh BJ. Successful control of bleed-

ing from gastric antral vascular ectasia (watermelon stomach) by laser photocoagulation. Gut 1991;32:93–94.
46. Tanaka T, Mori Y, Morishita Y, Kojima T, Kawamori T, Amano K, Ichihara M, Tarao M, Gotoh A, Mori H. Gastric antral vascular ectasia. Hum Pathol 1991;22:1053–1055.
47. Bernstein CN, Pettigrew N, Wang KK, Greenberg H, Lipschitz J. Multifocal gastric neoplasia after recurrent laser therapy for the watermelon stomach. Can J Gastroenterol 1997;11:403–406.
48. Brennan FN, Cowen AE, Lawrence BH. Successful treatment of two patients with gastric antral vascular ectasia 'watermelon stomach' using endoscopic Nd-YAG laser therapy. Aust N Z J Med 1991;21:439–441.
49. Geller A, Gostout CJ, Balm RK. Development of hyperplastic polyps following laser therapy for watermelon stomach. Gastrointest Endosc 1996;43:54–56.
50. Kamberoglou D, Dakkak M, Bennet JR. Case of watermelon stomach successfully treated by heat probe electrocoagulation. Gut 1991;32:964.
51. Petrini JL, Johnston JH. Heat probe treatment for antral vascular ectasia. Gastrointest Endosc 1989;35:324–328.
52. Moss SF, Ghosh P, Thomas DM, Jackson JE, Calam J. Gastric antral vascular ectasia: Maintenance treatment with oestrogen-progesterone. Gut 1992;33:715–717.
53. Calam J, Walker RJ. Antral vascular lesion, achlorhydria, and chronic gastrointestinal blood loss. Dig Dis Sci 1980; 25:236–239.
54. Suzuki T, Hirano M, Oka H. Long-term corticosteroid therapy for gastric antral vascular ectasia. AJG 1996; 91:1873–1874.
55. Pina Cabral JE, Pontes JM, Toste M, Camacho E, Leitao MC, Freitas D, Monteiro JG. Watermelon stomach: Treatment with a serotonin antagonist. Am J Gastroenterol 1991;86:927–928.
56. Disdier P, Schleinitz N, Perreard M, Monges D, Swiader L, Gerolami A, Harle JR, Weiller PJ. Dramatic improvement of watermelon stomach with alpha-interferon. Am J Gastroenterol 1995;90:1009–1010.
57. Barbara G, De Giorgio R, Salvioli B, Stanghlellini V, Corinaldesi R. Unsuccessful octreotide treatment of the watermelon stomach. J Clin Gastroenterol 1998;26:345–346.
58. McCormick PA, Ooi H, Crosbie O. Tranexamic acid for severe bleeding gastric antral vascular ectasia in cirrhosis. Gut 1998;42:750–752.
59. Rose JDR. Endoscopic injection of alcohol for bleeding from gastroduodenal vascular anomalies. BMJ 1987;295:93–94.
60. Gilinsky NH, Giles OA, O'Conner WN. Gastric antral vascular ectasia ("watermelon stomach"): first bleeding after aortic valve replacement. J Clin Gastroenterol 1987;9:612–613.
61. Szold A, Katz LB, Lewis BS. Surgical approach to occult gastrointestinal bleeding. Am J Surg 1992;163:90–92.
62. Gouldesbrough DR. Gastric antral vascular ectasia: A problem of recognition and diagnosis. Gut 1991;32:954–955.
63. Tovey FI. Gastric antral vascular ectasia: The Watermelon Stomach. Gastroenterol 1985;88:1293.
64. Makharia GK, Behra A, Kaman L, Vaiphei K, Singh K, Kochhar R. Watermelon stomach: A rare cause of upper gastrointestinal bleeding. Indian J Gastroenterol 1999; 18:86–87.
65. Azagra JS, Goergen M, De Simone P, Ibanez-Aguirre J. The current role of laparoscopic surgery in the treatment of benign gastroduodenal diseases. Hepatogastroenterol 1999; 46:1522–1526.
66. Tovey FI, Godfrey JE, Lewin MR. A gastrectomy population: 25-30 years on. Postgrad Med J 1990;66:450–456.
67. Mellstrom D, Rungren A. Long-term effects after partial gastrectomy in elderly men. Scand J Gastroenterol 1982; 17:433–439.
68. Reyes CD, Weber KJ, Gagner M, Divino CM. Laparoscopic vs open gastrectomy: A retrospective review. Surg Endosc 2001;15:928–931.
69. Adachi Y, Suematsu T, Shiraishi N, Katsuta T, Morimoto A, Kitano S, Akazawa K. Quality of life after laparoscopy-assisted Billroth I gastrectomy. Ann Surg 1999;229:49–54.

# Morphology and Function of Canine Small Intestinal Autografts: With Particular Interest in the Influence of Ex Vivo Graft Irradiation

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The intestinal transplantation procedure obligates an early functional deficit in intestinal grafts. Graft irradiation has been used to modulate post-transplant immune reactions; however, irradiation may cause further deterioration of the function of the transplanted intestine. Using the canine model, we investigated the influence of the transplant procedures, with and without ex vivo graft irradiation, on early intestinal graft function and histopathology. Outbred hound dogs underwent autointestinal transplantation with (n = 8) or without (n = 5) 7.5 Gy ex vivo graft irradiation. Mucosal cytochrome P450 and P-glycoprotein, routine immunohistopathology, and intestinal absorptive function were studied. Weight gain was slow after surgery, but was comparable in the irradiated and nonirradiated groups. During the early post-transplant period, both groups showed defects in intestinal absorption, associated with decreased cytochrome P450 3A4 activity and reduced P-glycoprotein expression, regardless of graft irradiation. These changes returned to normal in both groups by day 28. Histopathologically, epithelial apoptosis showed a slight increase 1 hour after transplantation; however, there was no evidence of histopathologic abnormalities including arterial changes associated with irradiation. In addition, the frequency of T and B lymphocytes in the lamina propria were not significantly influenced by the transplant surgery or ex vivo irradiation. Thus, early after transplantation, intestinal function was impaired and effectiveness of orally administered immunosuppressive drugs was significantly altered. Graft irradiation did not induce further defects in intestinal function or cause histopathologic abnormalities. (J GASTROINTEST SURG 2003;7:662–671) 

KEY WORDS: Small intestinal transplantation, graft irradiation, intestinal absorption, canine model

Small intestinal transplantation (SITx) is the ultimate therapeutic option for patients with intestinal failure. Recent developments in immunosuppressive treatment protocols, particularly the introduction of tacrolimus (TAC), have improved the clinical outcome of SITx[1–3]; however, the high mortality and morbidity associated with SITx has heretofore precluded stable long-term intestinal graft function and the widespread use of this procedure. Intestinal graft irradiation has been used to modulate both host-versus-graft and graft-versus-host immune reactions after SITx[4–9]; however, the potential complications associated with irradiation have not been studied in the transplant setting.

Intestinal transplantation obligates extrinsic denervation, partial disruption of intrinsic neural continuity, disruption of lymphatics, and ischemia/reperfusion injury. The consequences of these phenomena complicate the early post-transplant period, resulting in significant defects in nutrient absorption and intestinal motility. These changes, in general, are resolved within a few weeks when allogenic immunity is controlled; however, subtle defects in intestinal function have been shown to persist for a long time.[10–12] The technique of intestinal autotransplantation has provided a useful model for studying these non–alloimmune-related consequences of intestinal transplantation. Accordingly, this study used a large animal autologous SITx model and analyzed clinical outcome, intestinal morphology, and intestinal absorptive function with and without a single dose of 7.5 Gy ex vivo graft irradiation.

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## MATERIAL AND METHODS

### Animals

Female hound dogs (Harlan Sprague Dawley, Inc., Indianapolis, IN), weighing 17 to 23 kg, with a mean age of 20.1 ± 10.6 months, were maintained in the conventional animal facilities at the University of Pittsburgh. All procedures in this study were performed according to the guidelines of the Council on Animal Care at the University of Pittsburgh along with the guidelines of the National Institutes of Health and the Public Health Service policy on the humane use and care of laboratory animals.

### Surgical Procedures

All animals were given oral neomycin sulfate (1 g/day) for 5 days before surgery. Canine autologous intestinal transplantation was performed as previously described.[13] Briefly, anesthesia was induced with intravenous sodium thiopental (25 mg/kg) and maintained with isoflurane (1.0%), nitrous oxide, and oxygen using positive pressure mechanical ventilation. Systemic blood pressure and ECG were continuously monitored during the anesthesia. Through a midline laparotomy, the entire small bowel from the ligament of Treitz to the ileocecal valve, leaving approximately 10 cm of both jejunum and terminal ileum, was isolated along with the superior mesenteric artery and superior mesenteric vein and excised. The intestinal graft was immediately perfused with cold lactated Ringer's solution (300 to 400 ml) containing heparin (1000 U/L) and stored in chilled lactated Ringer's solution in a plastic box. The graft was then irradiated ex vivo with a dose of 7.5 Gy using a 6 mV linear accelerator (Varian Medical Systems, Inc., Palo Alto, CA). The time to achieve this irradiation dose was 3 minutes, and a total of 45 minutes was required for the transport and irradiation of intestinal grafts. After 45 minutes of cold preservation, the intestinal graft was autotransplanted into the same animal with end-to-end vascular anastomosis between the graft and the recipient superior mesenteric artery and superior mesenteric vein. Pieces of the graft jejunum and ileum were obtained 60 minutes after reperfusion for histopathologic examination and other analyses, and intestinal continuity was restored with a two-layer end-to-end anastomosis at the jejunum and ileum.

Postoperatively, all animals received 1 liter per day of lactated Ringer's solution containing 5% dextrose for 3 days. Animals were given subcutaneous sulfamethoxazole trimethoprine (60 mg/kg/day) and oral neomycin (1g/day) for 7 days postoperatively. Torbugesic (0.1 mg/kg) was given intramuscularly as an analgesic. Recipients were allowed liquids after surgery and solids from postoperative day 1. A low-residue solid meal was given for the first 7 days postoperatively; thereafter animals were fed standard kennel food (approximately 1700 kcal/day of 5L18; PMI Nutrition International Inc., Brentwood, MO).

### Experimental Design

Eight recipient animals received 7.5 Gy ex vivo irradiated intestinal grafts and five received nonirradiated grafts. Four of eight recipients of irradiated grafts and 3 of five recipients of nonirradiated grafts received daily oral cyclosporine ([CYS] 20 mg/kg/day of SangCya Oral Solution; Sangstat, Menlo Park, CA) with twice daily administration in equally divided doses, starting on the day after transplantation. The remaining dogs in each group were initially scheduled to receive 2.0 mg/kg/day of oral tacrolimus (TAC) (FK506; Fujisawa Pharmaceutical Co., Osaka, Japan), every 12 hours in equally divided doses, instead of CYS. However, TAC caused severe gastrointestinal side effects (anorexia, vomiting, and diarrhea) in this species. Therefore daily administration of TAC was withdrawn during the second week after SITx, and these recipients were given TAC exclusively for the prescheduled pharmacokinetic study (see below) without continuous treatment.

Animals were killed at 30 days after SITx except for three dogs with irradiated intestine that were followed for more than 200 days. At the time the dogs were killed, graft jejunum, ileum, and mesenteric lymph nodes, as well as recipient jejunum, ileum, liver, kidney, and spleen, were obtained and fixed in 10% formalin for routine histopathologic examination and in optimum cold temperature compound (OCT) for immunohistochemical analysis, and snap-frozen in liquid nitrogen. Three recipients underwent open biopsy of intestinal grafts between 155 and 232 days after SITx for histopathologic analysis.

### Pharmacokinetics

On days 1, 7, 14, and 28 after SITx, the absorption of CYS or TAC was studied by oral administration of 10 mg/kg CYS or 1 mg/kg TAC. As control subjects, normal dogs that did not undergo transplantation were given CYS (n = 3) or TAC (n = 5) on one occasion. Whole-blood samples (1.0 ml) were drawn 0, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours after the oral dose of CYS or TAC. CYS concentrations were determined in the whole blood using a monoclonal antibody–based fluorescence polarization immunoassay (TDx; Abbott Laboratories, North Chicago, IL). Whole-blood concentrations of TAC were determined by means of microparticulate enzyme immunosorbent assay using an IMX analyzer (Abbott Laboratories).

Pharmacokinetic parameters were calculated by model-independent analysis. Peak blood concentration ($C_{max}$) and time to reach $C_{max}$ ($T_{max}$) were observed. Area under the blood concentration–time curve (AUC) was calculated from time 0 - ∞ according to the trapezoidel rule method after a single dose. In cases of multiple dose administration, trapezoidal rule and reverse supersition principle were used.[14]

### Routine and Immunohistopathologic Analyses

Intestinal tissues fixed in 10% buffered formalin were embedded in paraffin, cut into 4 μm sections, and stained with hematoxylin and eosin. Histologic changes were evaluated in a blind fashion. The degree of epithelial injury was determined by architecture and by the frequency of apoptosis in crypt epithelial cells. Muscle layer thickness was determined by ocular micrometer measurement of both the internal circular and external longitudinal muscle layers at 10 different locations for each specimen.

For immunohistochemical staining of T cells, paraffin-fixed sections of intestine were deparaffinized and rehydrated through sequential immersions in xylene, followed by changes in graded concentrations of ethanol. Sections were then incubated in target unmasking solution (DAKO Corp., Carpinteria, CA) for target antigen retrieval. For staining of B cells, 4 μm sections were cut from OCT-fixed frozen intestinal samples, air-dried, and fixed in acetone. Prepared sections were stained by means of the immunoperoxidase method[15] using monoclonal antibodies (mAbs) that recognize canine T cells (CD3-12, rat $IgG_1$) and canine B cells (CA2.1D6, mouse $IgG_1$) (both from Serotec Ltd., Kidlington, Oxford, UK). Sections were then incubated with biotinylated horse antimouse IgG (Vector Laboratories, Inc., Burlingame, CA) or biotinylated goat antirat IgG (Jackson ImmunoResearch Laboratories, Inc., West Grove, PA) and finally with horseradish peroxidase (HRP)–labeled streptavidin (Vector Laboratories). Endogenous peroxidase was quenched with 0.5% hydrogen peroxide diluted in methanol. HRP-binding–positive cells were visualized with 0.02% AEC chromogen (ScyTek Laboratories, Logan, UT).

### Intestinal Cytochrome P450 Activity

Cytochrome P450 3A4 (CYP3A4) activity in the intestinal microsomes was determined by measuring the conversion of testosterone to 6β-hydroxytestosterone. Intestinal mucosal tissue was stripped and microsomes were prepared in the presence of protease inhibitors. The microsomal protein was quantitated by the method of Lowry.[16] Microsomal samples (1.0 mg/ml of protein in a final concentration) were incubated at 37° C with 200 μmol/L testosterone, 1 mmol/L EDTA, 10 mmol/L $MgCl_2$, and sodium phosphate buffer for 30 minutes. At the end of incubation, the samples were centrifuged and any protein was precipitated with an equal volume of methanol. 6β-Hydroxytestosterone in the supernate was measured by means of high-performance liquid chromatography.[17] Briefly, 100 μl of the culture medium was injected into a LiChrospher 100 RP-18 column (Merck KGaA, Darmstadt, Germany) and a mobile phase of methanol/water (60:40 v/v) at a flow rate of 1.2 ml/min was used to separate various components. 6β-Hydroxytestosterone was measured at 242 nmol/L by comparing the absorbency to a standard curve of 6β-hydroxytestosterone in William's E medium.

### Intestinal P-Glycoprotein Expression

The intestinal mucosal tissue was stripped and homogenized with a plunger in the presence of protease inhibitors. After samples were centrifuged at 7000 rpm for 5 minutes at 4° C, the supernate was collected and the protein concentrations were determined. Protein samples (50 μg) were loaded onto an 8% polyacrylamide separating gel and transferred onto polyvinylidene fluoride membrane (NEN Life Science Products, Boston, MA). The membrane was incubated for 1 hour at room temperature with mouse anti-P-glycoprotein (P-gp) mAb C494 (1:100; Signet Laboratories, Inc., Dedham, MA), followed by HRP-conjugated sheep antimouse antibody (1:2000; Amersham Life Science, Inc., Arlington Heights, IL). Immune complexes were detected with a chemiluminescence reagent (NEN Life Science Products).

### Statistical Analyses

Data in this study were expressed as mean ± standard deviation (SD). One-way analysis of variance (ANOVA) was used to analyze statistical significance of the differences in various parameters among groups. The differences were considered significant at $P \leqslant 0.05$.

## RESULTS

### Clinical Course After Small Intestinal Transplantation

No major surgical complications occurred in this study, such as vascular thrombosis or intestinal leakage, which are associated with mortality. All recipients were followed for a minimum of 30 days after SITx and all were included for analyses in this study.

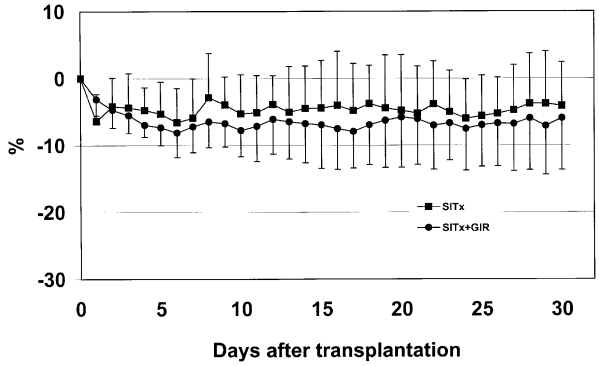


**Fig. 1.** Changes in mean body weight after intestinal autotransplantation (*SITx*) with and without a single 7.5 Gy dose of ex vivo intestinal graft irradiation (*GIR*).

The dogs all had watery diarrhea (2 to 3 stools/day) during the first week after SITx, which slowly improved by 14 days, regardless of the 7.5 Gy intestinal irradiation. By 30 days after SITx, most of the recipients resumed the passage of formed stools; however, it took more than 3 months for normal stool conditions to return. A gradual weight loss was noted during the first 7 to 10 days after SITx (Fig. 1). Subsequent weight gain was slow, and weight gain at 30 days after transplantation was between −14.2% and +7.2%. There was no statistical difference whether recipients had irradiated grafts or continuous CYS administration. Three recipients with irradiated grafts who were followed for more than 200 days were extremely healthy with good appetites, normal stools, and steady weight gain (5.3% ± 0.3% at day 200).

At the time they were killed on day 30 after SITx, recipients had minimal to no ascites, no lymphadenopathy or adhesions, and healthy appearing intestines. No macroscopic differences were noted between 7.5 Gy ex vivo irradiated and nonirradiated intestinal grafts.

## Routine Histopathologic Examination

Intestinal graft tissues obtained 1 hour after reperfusion showed a slight increase in crypt apoptosis compared to the normal nontransplanted intestine (0.7 ± 0.4 apoptosis/10 crypts). Irradiated grafts tended to have more apoptosis (2.8 ± 1.2 apoptosis/10 crypts) than nonirradiated grafts (2.3 ± 1.0 apoptosis/10 crypts); however, no statistical difference was observed (Fig. 2). Intestinal grafts in both groups were otherwise essentially normal with no villous denudation or inflammatory infiltration. By 30 days after SITx, the frequency of crypt apoptosis normalized and no further abnormalities were noted in any of the intestinal graft tissues. Graft vessels in irradiated intestine, especially small arteries in the submucosa that were believed to be more susceptible to irradiation-induced vasculopathy, showed no abnormalities. The lack of any abnormalities in the vascular component of the intestines was also confirmed in intestinal specimens obtained by open biopsy from three recipients with irradiated grafts more than 200 days after SITx (see Fig. 2).

The thickness of both circular and longitudinal muscle layers showed a slight increase at 30 days after SITx in both irradiated and nonirradiated grafts compared to normal intestine (Table 1). Interestingly, the muscular layer thickness at more than 200 days was similar to that seen at 30 days (1.69 mm, 39% increase), suggesting that muscle layer thickening might have been induced during the early post-transplant period and was not progressive.

Irradiation may intervene in the normal homing of the lymphocytes into the intestine.[18] This possibility was explored by quantifying T and B lymphocytes in the lamina propria at 30 days after SITx (see Table 1). Irradiated grafts tended to have fewer $CD3^+$ cells compared to nonirradiated grafts and normal intestine. On the other hand, the frequency of B cells in the lamina propria was comparable in the normal, irradiated, and nonirradiated intestines.

## Intestinal Absorption

***Pharmacokinetics.*** Absorption of CYS, which also represents the ability of the intestine to absorb fat-soluble compounds, was significantly decreased early after SITx (Fig. 3). In normal unoperated dogs, the whole-blood concentration of CYS rapidly increased after 10 mg/kg CYS by mouth, with a peak of 1482 ± 444 ng/ml at 2 hours, and quickly decreased to 518 ± 74 and 184 ± 40 ng/ml at 6 and 12 hours, respectively. During the first week after SITx, CYS absorption was extremely low (less than 42% compared to normal dogs). These abnormalities were seen in both irradiated and nonirradiated intestinal autografts and gradually improved with time after SITx, and a nearly normal absorption pattern was seen at 30 days after SITx.

TAC (1.0 mg/kg) frequently caused vomiting after oral administration, and only a limited number of pharmacokinetic studies were completed. In normal nonoperated dogs, the peak TAC level was 22.6 ± 16.3 ng/ml at 1 hour after 1 mg/kg by mouth. Absorption of TAC tended to be enhanced early after SITx, more so without irradiation (Fig. 4); however, there was a large individual difference in the TAC blood concentration vs. time profile during the early post-transplant period. As seen in CYS absorption, intestinal absorption of TAC normalized with time, and a nearly normal absorption pattern was

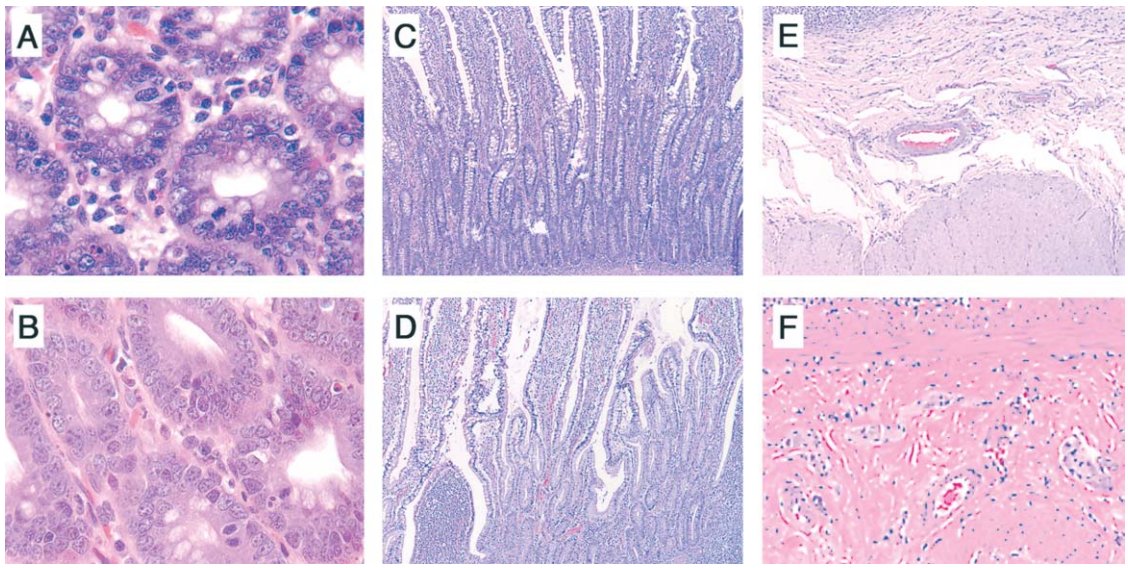


**Fig. 2.** Routine histopathologic examination demonstrates mild increase in crypt apoptosis at 60 minutes after reperfusion of nonirradiated (**A**) and 7.5 Gy ex vivo irradiated (**B**) intestinal autografts. Otherwise, the architecture of both intestinal grafts is well preserved. At day 30, both nonirradiated (**C**) and 7.5 Gy irradiated (**D**) grafts show long slender villi with normal frequency of apoptosis. The vascular components in the 7.5 Gy irradiated intestine show no abnormality and no sign of endoarteritis at 30 days (**E**) and 265 days (**F**) after SITx. (Hematoxylin and eosin stain; original magnifications ×400 for **A** and **B**, and ×40 for **C** to **F**).

seen by 30 days after SITx in both irradiated and nonirradiated grafts.

***Pharmacokinetic Parameters.*** Analysis of $C_{max}$, $T_{max}$, and AUC distinctively represented changes seen in CYS and TAC absorption after SITx (Figs. 5 and 6). A significant reduction in CYS $C_{max}$ and prolongation of $T_{max}$ were seen 1 day after SITx; however, both gradually recovered to near-normal values by 30 days (see Fig. 5, *A* and *B*). Accordingly, AUC of CYS was substantially reduced at 1 day after SITx to less than half the normal value (see Fig. 5, *C*); this subsequently increased with time and returned to normal by 30 days in recipients of both irradiated and nonirradiated intestinal grafts.

Changes in the pharmacokinetic parameters of TAC after SITx were less clear compared to those of CYS, because of the variation among animals (Fig. 6). SITx increased the $C_{max}$ and AUC of TAC, and irradiation tended to normalize the changes caused by SITx.

## Cytochrome P3A4 Activity

Activity of intestinal mucosal CYP3A4 was relatively preserved in the intestine before reperfusion; however, it was significantly decreased in intestinal autografts after graft reperfusion (Fig. 7). Ex vivo graft irradiation did not further influence CYP3A4 activity.

## P-Glycoprotein Expression

The expression of P-gp in the grafted intestinal mucosa was slightly decreased at 1 hour after reperfusion compared to that before SITx. The decrease in

**Table 1.** Muscle layer thickness and frequency of T and B cells in the lamina propria 30 days after small bowel intestinal transplantation with and without graft irradiation

| | Muscle layer thickness* | | | $CD3^+$ cells | B cells |
|---|---|---|---|---|---|
| | day 0 (mm) | day 30 (mm) | % increase | ($\times 10^{-3}$ cells/mm$^2$) | ($\times 10^{-3}$ cells/mm$^2$) |
| Normal | 1.22 ± 0.24 | NA | NA | 2.15 ± 0.33 | 0.96 ± 0.18 |
| SITx | 1.17 ± 0.09 | 1.44 ± 0.18 | 23 ± 11 | 2.11 ± 0.39 | 1.06 ± 0.19 |
| SITx + GIR | 1.20 ± 0.18 | 1.64 ± 0.23 | 41 ± 37 | 1.79 ± 0.28 | 1.01 ± 0.26 |

SITx = small intestinal transplantation; NA = not applicable; GIR = 7.5 Gy ex vivo intestinal graft irradiation.
*Total thickness of circular and longitudinal muscle layers.

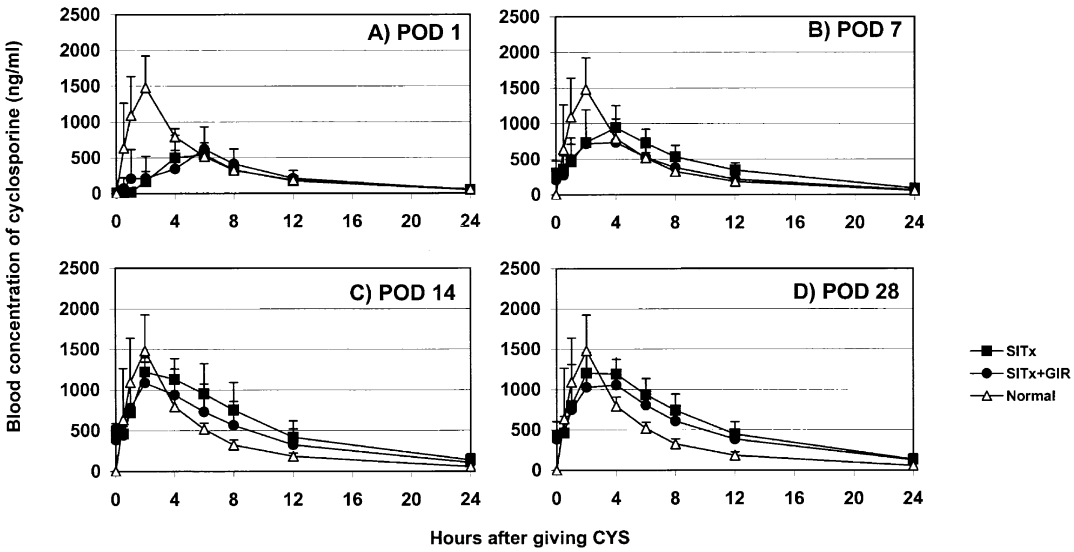


**Fig. 3.** Sequential changes in cycloporine (*CYS*) pharmacokinetics after intestinal autotransplantation (*SITx*) with (n = 4) and without (n = 3) 7.5 Gy ex vivo graft irradiation (*GIR*). After oral administration of CYS (10 mg/kg) on days 1, 7, 14, and 28 after SITx, whole-blood samples were taken 0, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours for measurement of CYS concentrations. Normal untransplanted dogs (n = 3) served as controls.

P-gp expression was observed in both irradiated and nonirradiated intestines (Fig. 8).

## DISCUSSION

Intestinal absorptive function is modulated by several factors including absorptive surface area, intraluminal environment, motility (extrinsic and enteric innervation), and humoral factors (autocrine, paracrine, and juxtacrine effectors). All of these factors are influenced by intestinal transplantation, and several previous studies have shown decreased intestinal function during the early post-transplant period in a rejection-free autotransplantation model.[10–12,19] In this study, intestinal absorptive function was studied by analyzing blood levels of oral CYS and TAC, which are essential for the survival of transplanted organs. These immunosuppressive drugs are actively transported into the enterocyte, where they are either metabolized by intestinal CYP3A4, or exsorbed into the intestinal lumen by P-gp, an intrinsic membrane protein that functions as an ATP-dependent efflux pump.[20–22] Consequently, in addition to passive transport of these drugs via the periepithelial pathway, additional factors that control oral bioavailability and blood levels of CYS and TAC include activity of cytochrome P enzymes and P-gp efflux pump in

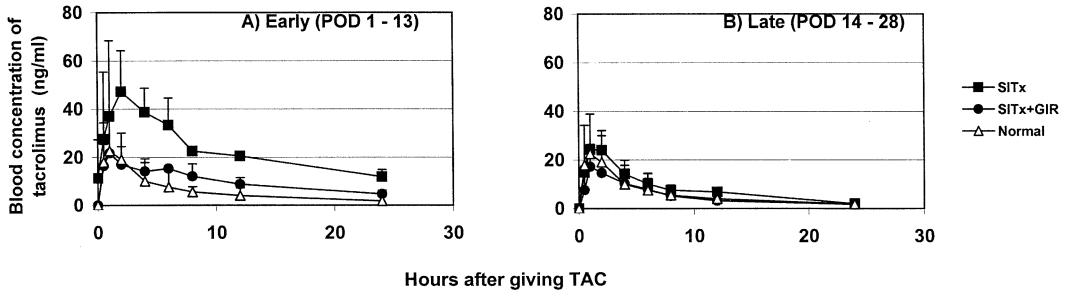


**Fig. 4.** Changes in tacrolimus (*TAC*) pharmacokinetics after intestinal (*SITx*) autotransplantation with and without 7.5 Gy ex vivo graft irradiation (*GIR*). After oral administration of TAC (1 mg/kg) at 1, 7, 14, and 28 days after SITx, whole-blood samples were taken at 0, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours for measurement of TAC concentrations. Results are summarized as early (1 and 7 days, n = 3) and late (14 and 28 days, n = 6) phases and compared to those of unoperated normal dogs (n = 5).

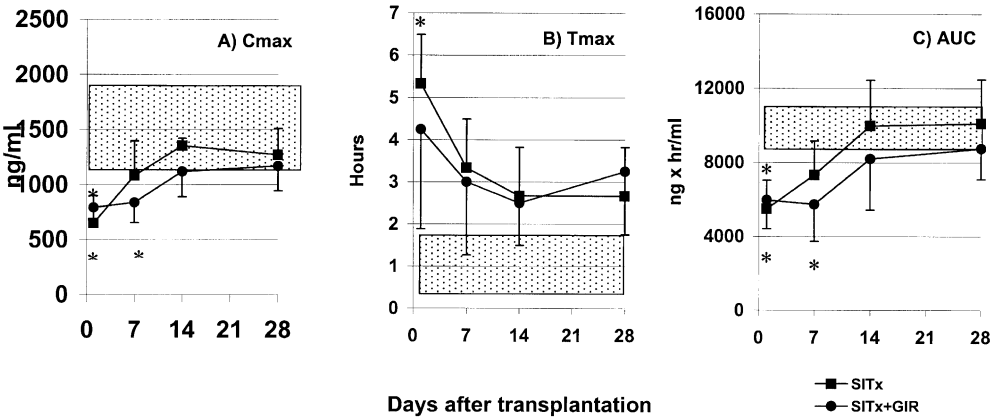


**Fig. 5.** Changes in $C_{max}$ (**A**), $T_{max}$ (**B**), and AUC (**C**) of cyclosporine after intestinal autotransplantation (*SITx*) with and without 7.5 Gy ex vivo intestinal graft irradiation (*GIR*). *Shaded area* in each figure represents mean ± SD of $C_{max}$, $T_{max}$, and AUC of normal untransplanted dogs. $^*P \leq 0.05$ vs. normal control dose (ANOVA).

the intestine. Reduction of the intestinal CYP3A4 enzyme activity and P-gp expression in this study explains, in part, the altered pharmacokinetics of CYS and TAC early after intestinal transplantation.[23,24] Although whole-body irradiation has been shown to cause intestinal dysmotility via the changes in motor activity,[25] intestinal graft irradiation, per se, did not induce any further reduction in CYP3A4 activity and P-gp expression beyond what was induced by SITx, resulting in the similar degrees of early functional impairment.

It is well known that energy dissipated from ionizing irradiation generates a series of biochemical events inside the cell and possibly leads to cell damage and death. The acute radiation injuries in the intestine result primarily from the depletion of rapidly proliferating mucosal cells that support the healthy turnover of villous epithelium (normally every 5 or 6 days).[26] Increasing doses and durations of irradiation have been known to cause cell loss from the intestinal villi and failure to maintain the homeostatic cell renewal system when it exceeds the repopulation

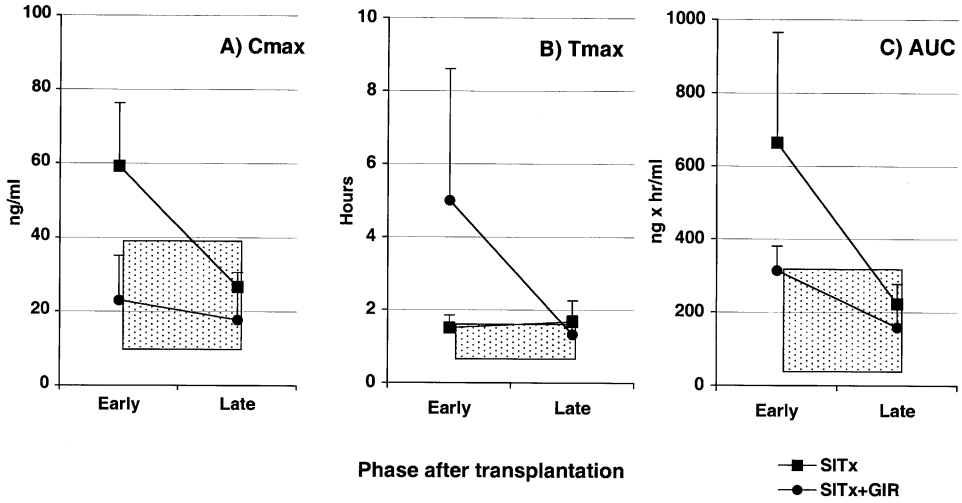


**Fig. 6.** Changes in $C_{max}$ (**A**), $T_{max}$ (**B**), and AUC (**C**) of tacrolimus early (1 to 7 days) and late (14 to 28 days) after intestinal autotransplantation with and without 7.5 Gy ex vivo intestinal graft irradiation (*GIR*). *Shaded area* in each figure represents mean ± SD of $C_{max}$, $T_{max}$, and AUC of normal untransplanted dogs.

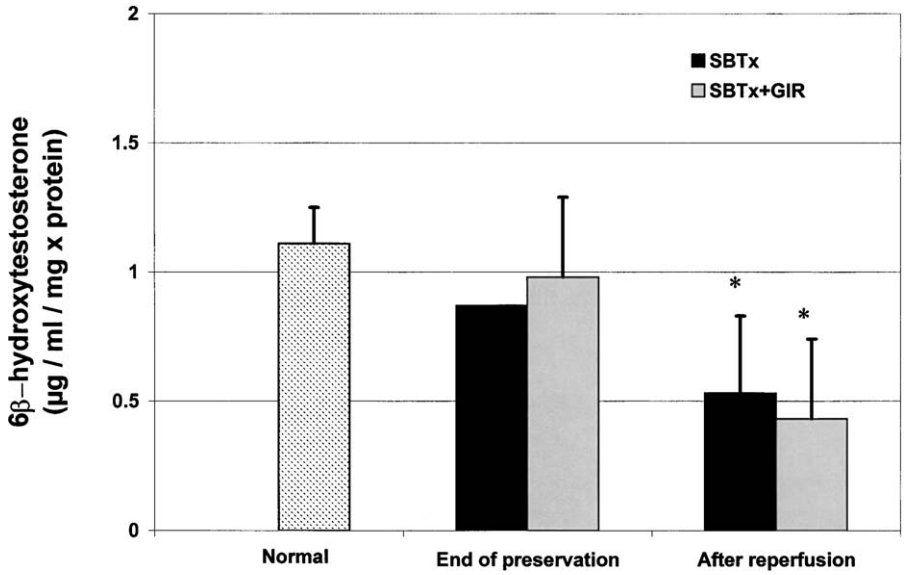


**Fig. 7.** Intestinal CYP450 3A4 activity before and 60 minutes after reperfusion of nonirradiated (n = 1 to 5) and 7.5 Gy irradiated (n = 3 to 8) intestinal grafts. Microsomal protein was isolated from intestinal samples, and CYP450 3A4 activity was determined by measuring conversion of testosterone to 6β-hydroxytestosterone. GIR ex vivo 7.5 Gy graft irradiation. $^{*}P \leq 0.05$ vs. normal intestine (n = 4) (ANOVA).

capacity of the crypt cells. Subsequent villous shortening and sloughing results in reduction of the total epithelial surface area. Although we did not notice any significant histopathologic changes in this study, early acute radiation injuries are histopathologically characterized as mucosal atrophy and infiltration of the lamina propria with plasma cells and polymorphonuclear cells.[27] The radiation dose significantly correlates with the risk of inducing radiation injury, and a dosage of less than 40 Gy has rarely been shown to cause intestinal damage.[28,29]

On the other hand, late radiation injury is indirect and is the result of progressive vasculitis, which is characterized by obliterative endoarteritis of the small vessels.[30,31] These complications may be life threatening and lead to severe disturbances of intestinal function. However, as shown in the rodent model,[8] vascular changes are not seen in this large animal study in which 7.5 Gy ex vivo irradiation was used for a follow-up period of 200 days. The reason for this may be that ex vivo irradiation is considered to be less harmful compared to irradiation to tissues with blood circulation. In addition, the single 7.5 Gy dose applied in this study was far below the dosages used in most oncology studies.[30–32] Another possible long-term complication of irradiation is intestinal wall fibrosis and collagen deposition. The direct effects of radiation on collagen or other constituents

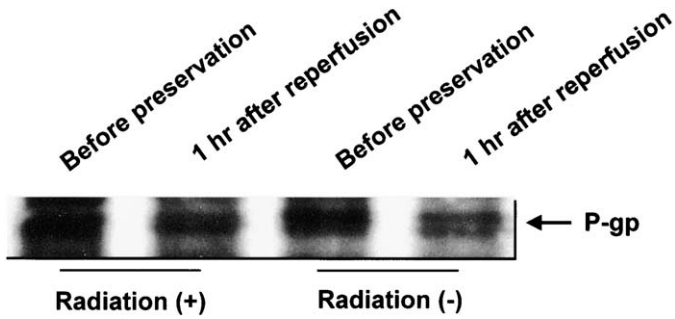


**Fig. 8.** Intestinal P-glycoprotein (P-gp) expression before harvesting and 60 minutes after reperfusion of nonirradiated and 7.5 Gy irradiated intestinal grafts. P-gp levels were measured by Western blotting using mouse anti-P-gp monoclonal antibody C494.

of the extracellular matrix and indirect effects via injured cells and inflammatory cytokine production are believed to cause these changes.[33,34] Both routine and immunohistopathologic analyses of the irradiated intestine in this study confirm the lack of changes associated with fibrosis.

Although this study suggests that intestinal graft irradiation may not cause significant adverse effects, it should also be considered that the harmful effects of radiation may surface when intestinal grafts suffer other injuries associated with transplantation, especially ischemia/reperfusion injuries and allograft rejection. The main target of ischemia/reperfusion injuries is believed to be microcirculation.[35] It has been postulated that oxygen free radicals produced at the time of reperfusion play a pivotal role in injuries to the endothelial cells lining the microvessels in the villous core. Because vascular endothelial cells are also the targets of irradiation, prolonged ischemia may possibly enhance injuries. In addition, ischemia/reperfusion does not necessarily damage the epithelial crypt; however, the denudation and villous loss seen after severe ischemia/reperfusion injuries require prompt epithelial cell proliferation and intact crypt function, both of which possibly are damaged by irradiation. Further studies will be required to address these issues.

In summary, this canine autotransplant study shows that the SITx procedure results in impaired absorptive function of the transplanted intestine during the early post-transplant period, as previously reported by several investigators.[10–12, 19] Reductions in intestinal CYP3A4 enzyme activity and P-gp expression after SITx, are in part, responsible for absorptive dysfunction. Intestinal graft irradiation does not augment any of the damage that is induced by SITx.

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REFERENCES

1. Todo S, Tzakis AG, Abu-Elmagd K, et al. Intestinal transplantation in composite visceral grafts or alone. Ann Surg 1992;216:223–233.
2. Grant D. Current results of intestinal transplantation. The International Intestinal Transplant Registry. Lancet 1996; 347:1801–1803.
3. Abu-Elmagd K, Reyes J, Todo S, et al. Clinical intestinal transplantation: New perspectives and immunologic considerations. J Am Coll Surg 1998;186:512–525.
4. Lee KK, Schraut WH. In vitro allograft irradiation prevents graft-versus-host disease in small-bowel transplantation. J Surg Res 1985;38:364–372.
5. Grant D, Duff J, Zhong R, et al. Effect of ex vivo allograft irradiation combined with cyclosporine therapy in a pig intestinal transplant model. Transplant Proc 1989;21(1 Pt 3): 2879–2880.
6. Williams JW, McClellan T, Peters TG, et al. Effect of pretransplant graft irradiation on canine intestinal transplantation. Surg Gynecol Obstet 1988;167:197–204.
7. Foster PF, Sankary HN, Kociss K, et al. The interaction of gamma irradiation of the allograft and recipient administration of cyclosporine in rat small bowel transplantation. Transplant Proc 1992;24:1175–1176.
8. Murase N, Ye Q, Nalesnik MA, et al. Immunomodulation for intestinal transplantation by allograft irradiation, adjunct donor bone marrow infusion, or both. Transplantation 2000; 70:1632–1641.
9. Abu-Elmagd K, Reyes J, Bond G, et al. Clinical intestinal transplantation: A decade of a single center experience. Ann Surg 2001;234:404–417.
10. Sarr MG, Duenes JA, Walters AM. Jejunal and ileal absorptive function after a model of canine jejunoileal autotransplantation. J Surg Res 1991;51:233–239.
11. Thompson JS, Rose SG, Spanta AD, Quigley EM. The long-term effect of jejunoileal autotransplantation on intestinal function. Surgery 1992;111:62–68.
12. Sugitani A, Reynolds JC, Tsuboi M, Todo S. Extrinsic intestinal reinnervation after canine small bowel autotransplantation. Surgery 1998;123:25–35.
13. Yoshimi F, Nakamura K, Zhu Y, et al. Canine total orthotopic small bowel transplantation under FK 506. Transplant Proc 1991;23:3240–3242.
14. Gibaldi M, Perrier D. Pharmacokinetics.. New York: Marcel Dekker; 1982.
15. Demetris AJ, Qian S, Sun H, et al. Early events in liver allograft rejection. Delineation of sites of simultaneous intragraft and recipient lymphoid tissue sensitization. Am J Pathol 1991;138:609–618.
16. Lowry OH. Protein measurement with the Folin phenol reagent. J Biol Chem 1951;193:265–275.
17. Kostrubsky VE, Ramachandran V, Venkataramanan R, et al. The use of human hepatocyte cultures to study the induction of cytochrome P-450. Drug Metab Dispos 1999;27:887–894.
18. Brennan PC, Carr KE, Seed T, McCullough JS. Acute and protracted radiation effects on small intestinal morphological parameters. Int J Radiat Biol 1998;73:691–698.
19. Wassef R, Cohen Z, Nordgren S, Langer B. Cyclosporine absorption in intestinal transplantation. Transplantation 1985;39:496–499.
20. Van Asperen J, Van Tellingen O, Beijnen JH. The pharmacological role of P-glycoprotein in the intestinal epithelium. Pharmacol Res 1998;37:429–435.
21. Wacher VJ, Silverman JA, Zhang Y, Benet LZ. Role of P-glycoprotein and cytochrome P450 3A in limiting oral absorption of peptides and peptidomimetics. J Pharm Sci 1998; 87:1322–1330.
22. Lown KS, Mayo RR, Leichtman AB, et al. Role of intestinal P-glycoprotein (mdr1) in interpatient variation in the oral bioavailability of cyclosporine. Clin Pharmacol Ther 1997; 62:248–260.
23. Masuda S, Uemoto S, Hashida T, et al. Effect of intestinal P-glycoprotein on daily tacrolimus trough level in a living-donor small bowel recipient. Clin Pharmacol Ther 2000;68:98–103.

24. Benet LZ, Izumi T, Zhang Y, et al. Intestinal MDR transport proteins and P-450 enzymes as barriers to oral drug delivery. J Control Release 1999;62:25–31.
25. Erickson BA, Otterson MF, Moulder JE, Sarna SK. Altered motility causes the early gastrointestinal toxicity of irradiation. Int J Radiat Oncol Biol Phys 1994;28:905–912.
26. Sher ME, Bauer J. Radiation-induced enteropathy. Am J Gastroenterol 1990;85:121–128.
27. Trier JS, Browning TH. Morphologic response of the mucosa of human small intestine to x-ray exposure. J Clin Invest 1966;45:194–204.
28. Kinsella TJ, Bloomer WD. Tolerance of the intestine to radiation therapy. Surg Gynecol Obstet 1980;151:273–284.
29. Rodier JF. Radiation enteropathy—incidence, aetiology, risk factors, pathology and symptoms. Tumori 1995;81(3 Suppl):122–125.
30. Fajardo LF, Berthrong M. Vascular lesions following radiation. Pathol Annu 1988;23(Pt 1):297–330.
31. Chuang VP. Radiation-induced arteritis. Semin Roentgenol 1994;29:64–69.
32. Himmel PD, Hassett JM. Radiation-induced chronic arterial injury. Semin Surg Oncol 1986;2:225–247.
33. Wang J, Zheng H, Hauer-Jensen M. Influence of short-term octreotide administration on chronic tissue injury, transforming growth factor beta (TGF-beta) overexpression, and collagen accumulation in irradiated rat intestine. J Pharmacol Exp Ther 2001;297:35–42.
34. Zheng H, Wang J, Hauer-Jensen M. Role of mast cells in early and delayed radiation injury in rat intestine. Radiat Res 2000;153(5 Pt 1):533–539.
35. Jaeschke H. Preservation injury: Mechanisms, prevention and consequences. J Hepatol 1996;25:774–780.

# A Comparison of Pancreaticogastrostomy and Pancreaticojejunostomy Following Pancreaticoduodenectomy

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This retrospective study compares the results of pancreaticogastrostomy (PG) and pancreaticojejunostomy (PJ) in our institution, which has extensive experience in both techniques. Between the years of June 1995 and June 2001, 214 patients underwent pancreaticoduodenectomy (PD) at our institution. Of these 177 had PG and 97 had pancreatojejunostomy (PJ). There were 117 (54.6%) males and 97 (45.3%) females with a mean age of 64.2 ± 12.4 years. Indications for surgery were pancreatic adenocarcinoma in 101 (47.2%), ampullary adenocarcinoma in 36 (16.9%), distal bile duct adenocarcinoma in 22 (10.2%), duodenal adenocarcinoma in 9 (4.2%), and miscellaneous causes in 46 (21.4%) of patients. Preoperatively, significant differences in the groups were that the patients undergoing PJ were significantly younger than those undergoing PG. Also noted preoperatively, was that the patients undergoing PG had a significantly lower direct bilirubin than those undergoing PJ. With regard to intraoperative parameters, operative time was significantly shorter in the PJ group when compared to the PG group. When the patients who did not develop fistula (N = 186) were compared to those who developed fistula (N = 28) the significant differences were that the patients who developed fistula were more likely to have hypertension preoperatively and a higher alkaline phosphatase. They also showed a significantly higher drain amylase and were likely to have surgery for ampullary, distal bile duct or duodenal carcinoma rather than pancreatic adenocarinoma. In addition, those patients who developed fistula had a significantly longer postoperative stay, a larger number of intraabdominal abscesses and leaks at the biliary anastomosis. Thirty-day mortality was significantly higher in the PJ group compared to the PG (4 vs. 0, $P = 0.041$). There was a significantly larger number of bile leaks in the PJ group when compared to the PG (6 vs. 1, $P = 0.048$). In addition, the PJ group required a significantly larger number of new CT guided drains to control infection (8 vs. 2, $P = 0.046$) and the PJ group required a larger number of re-explorations to control infection or bleeding (5 vs. 0, $P = 0.018$). However, the pancreatic fistula rate was not different between the two groups (12% [PG] vs. 14% [PJ]). This retrospective analysis shows that safety of PG can be performed safely and is associated with less complications than PJ and proposes PG as a suitable and safe alternative to PJ for the management of the pancreatic remnant following PD. (J GASTROINTEST SURG 2003;7:672-682.) 

KEY WORDS: Pancreaticoduodenectomy, pancreaticojejunostomy, pancreaticogastrostomy, pancreatic fistula, periampullary carcinoma

When the one-stage pancreaticoduodenectomy was first introduced as treatment for tumors of the pancreas and periampullary carcinoma, it was associated with high mortality and morbidity.[1] Recently, the mortality following pancreaticoduodenectomy in large series has been reported to be <4%.[2–8] However, the morbidity associated with the procedure remains high. The major cause for morbidity and mortality following pancreaticoduodenectomy is thought to be leakage from the pancreaticoenteric anastomosis. Because of this, several approaches have been suggested to minimize leak from the pancreaticoenteric anastomosis. Suture ligation of the pancreatic duct,[9–10] pancreatic duct injection with neoprene,[11] duct stenting,[12] modifications of the jejunal anastomosis, i.e., end-to-end versus end-to-side and type of pancreaticojejunal anastomosis (invagination versus duct to mucosa[13,14]), the use of an isolated Roux-en-Y limb to

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drain the pancreas[15] and total pancreatectomy[16] have been suggested as solutions to the incidence of postoperative pancreatic leak and fistula and its associated morbidity and mortality.

This retrospective study was designed to compare the results of pancreaticogastrostomy and pancreaticojejunostomy in our institution, which has extensive experience in the use of both techniques.

## PATIENTS AND METHODS

A retrospective chart review was conducted on all patients who underwent pancreaticoduodenectomy (PD) at Loyola University Medical Center between June 1995 and June 2001. Charts were reviewed to determine the patient's age, sex, and preoperative clinical status of jaundice, hypertension, diabetes, previous cancer, chronic lung disease, atrial fibrillation, coronary artery disease, peripheral vascular disease, hypothyroidism, peptic ulcer disease, pancreatic, and stent placement. Preoperative laboratory variables evaluated included hemoglobin and hematocrit, white blood cell, platelet count, liver enzymes, total bilirubin and direct bilirubin, albumin, creatinine, BUN, and serum amylase. Charts were further reviewed for intraoperative variables including operative time, blood loss, amount of units transfused, the use of preoperative antibiotics, and postoperative octreotide. Also reviewed were the pathology for which the patients underwent PD and postoperative complications including mortality and morbidity and postoperative length of hospital stay. Each of the above parameters were compared to the type of management of the pancreatic remnant, whether pancreaticogastrostomy (PG) or pancreaticojejunostomy (PJ). Some of the above parameters were compared to patients who developed a pancreatic fistula irrespective of the type of anastomosis of the pancreatic remnant. Finally, postoperative outcomes and interventions were compared to type of pancreatic anastomosis.

### Surgical Technique

There have been several techniques suggested for pancreaticogastrostomy.[17,18] In this series PG (Fig. 1) was constructed in a single 3-0 silk invagination technique.[19] The pancreaticogastrostomy was constructed at least 5 cm away from the cut end of the stomach. Pancreaticojejunostomy was constructed in a single layer of 3-0 silk or 3-0 Maxon suture invaginating the pancreatic remnant into the site of the jejunum (81 patients); in some cases a duct-to-mucosa anastomosis to the side of the jejunum (8 patients) or an end-to-end anastomosis invaginating the pancreas into the end of the jejunum (8 patients) were performed (Fig. 2). All patients underwent the classic pancreaticoduodenectomy that included distal gastrectomy. No fibrin glue was used to reinforce any of the anastomoses. No pancreatic duct stents were used in either the PG or PJ group. Stenting of the hepaticojejunal anastomosis was done rarely and at the discretion of the operating surgeon. The same surgeon did all 117 pancreaticogastrostomies. In the pancreaticojejunostomy group, 92 of the operations were done by one single surgeon and the other 5 by three different surgeons. All patients received prophylactic antibiotics, but postoperative octreotide was used at the discretion of the operating surgeon. At the end of the procedure, two drains were placed, one to drain the biliary anastomosis and the other to drain the pancreatic anastomosis. Each was brought out through a separate incision below the abdominal incision and anchored to the skin with 3-0 nylon suture.

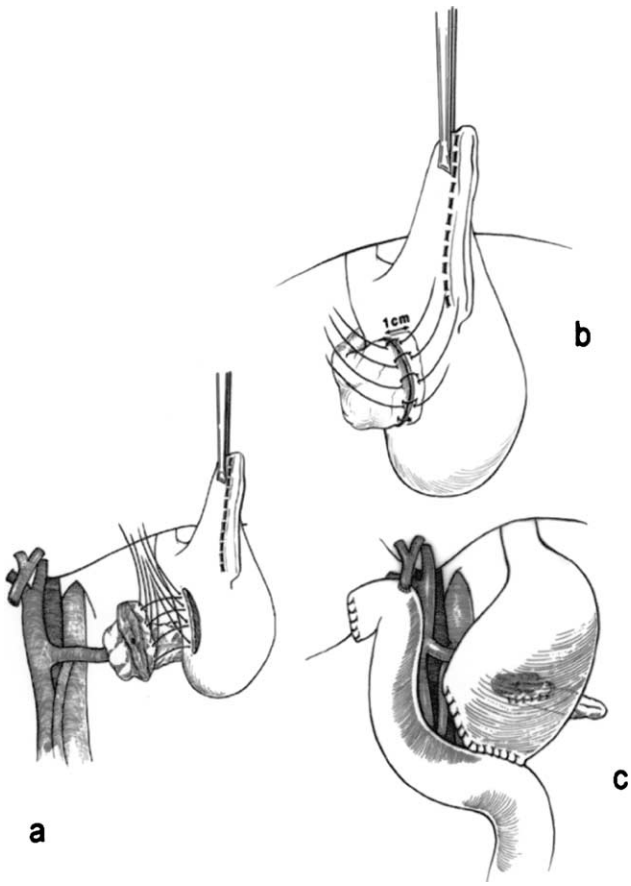


**Fig. 1.** Illustration showing construction of pancreaticogastrostomy (**A**) sutures from posterior superior gastric wall to anterior pancreas body, (**B**) sutures from posterior inferior gastric wall to posterior pancreas body, and (**C**) completed hepaticojejunostomy, gastrojejunostomy, and pancreaticogastrostomy.

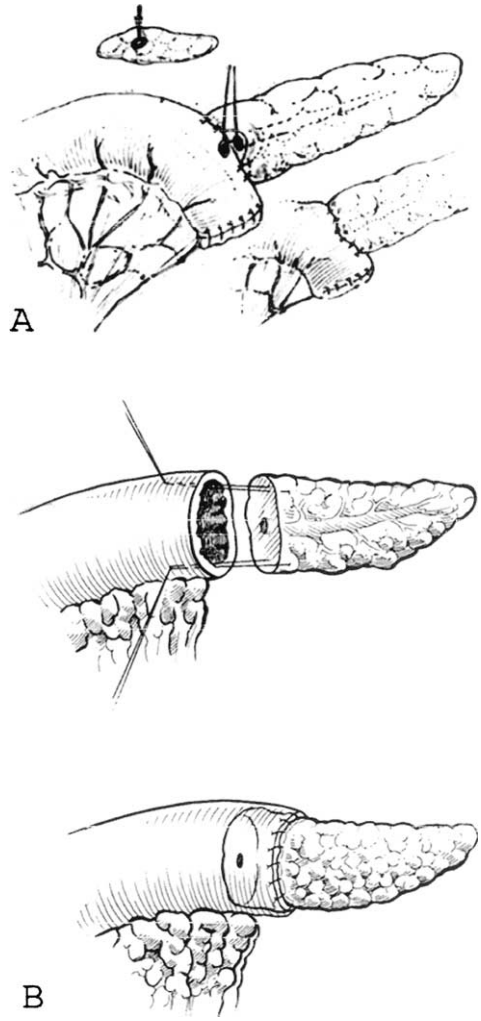


**Fig. 2.** Illustration showing (**A**) duct to mucosa end-to-side pancreaticojejunostomy, and (**B**) end-to-end anastomosis, invaginating pancreatic remnant into end of jejunum.

### Postoperative Management

All patients received $H_2$-receptor antagonist (ranitidine) during their postoperative course as prophylaxis for stress ulceration. The patients also received erythromycin lactobionate (250 mg intravenous every 6 hours) from postoperative day four until they were on a general diet. The majority of patients also received metoclopramide. A pancreatic leak was defined as amylase-rich fluid greater than 50 cc in volume (drain amylase greater than 3 times serum amylase) on the first day after regular diet. A pancreatic fistula was defined as a pancreatic leak that persisted beyond 14 days. If no leak was determined, then the drains were removed prior to the patient's hospital discharge. If a leak was diagnosed then the pancreatic drain was left in place and the patient discharged on an oral diet and instructed to measure drain volumes daily at home. Those patients who were discharged with drains had their drains removed when drainage ceased or the amylase levels were found to be consistent with closure of the fistula.

### Statistical Methods

Descriptive statistics are reported as a mean (SD) for continuous/ordinal variables N (%) for categorical variables. Univariate analysis included the Wilcoxin Rank Sum test to compare continuous/ordinal variables between (PG vs. PJ or no fistula vs. fistula). Chi-square or Fisher's Exact test were used as appropriate to compare categorical variables with other categorical variables. To identify independent predictors of morbidity and treatment group (PG vs. PJ) we performed multivariate logistic regression using stepwise model selection.

## RESULTS

### Patient Characteristics and Preoperative/ Intraoperative Variables

Two hundred fourteen patients underwent PD between June 1995 and June 2001 at our institution. Of these, 117 had PG and 97 had PJ. There were 117 (54.6%) males and 97 (45.3%) females with a mean age of 64.2 $\pm$ 12.4 years. Table 1 reflects the patient characteristics and preoperative variables. Significant preoperative variables noted were that patients undergoing PJ were younger and that patients undergoing PG had a lower direct bilirubin than those undergoing PJ. While the difference in age may be attributed to chance, the difference in direct bilirubin may be explained by the fact that a larger number of patients undergoing PG had preoperative biliary stents placed. Table 2 reflects the intraoperative parameters. Here the operative time for patients underoing PJ was significantly shorter than those underoing PG. There were no differences in blood loss, blood replacement, or indication for surgery. Also noted, was that there was no difference between the two groups in the use of preoperative antibiotics or postoperative octreotide. One hundred sixty-eight pancreaticoduodenectomies were done for periampullary malignancy (Table 2). Forty-six were done for miscellaneous causes and these included cystic tumors of the pancreas, chronic pancreatitis, villous adenomas of the ampulla, stromal tumors of the duodenum and pancreas, and sclerosing cholangitis of the distal bile duct.

**Table 1.** Patient characteristics and preoperative variables

| Characteristics | PG (n = 117) | PJ (n = 97) | *P* value |
|---|---|---|---|
| Age (yr) | 65.5 ± 12.3 | 62.2 ± 11.9 | 0.033 |
| Gender | | | 0.28 |
| Male | 59 (50) | 56 (58) | |
| Female | 58 (50) | 41 (42) | |
| Preoperative history | | | |
| Hypertension | 42 (36) | 27 (28) | 0.21 |
| Diabetes | 15 (13) | 18 (19) | 0.25 |
| Previous cancer | 16 (14) | 12 (12) | 0.8 |
| COPD/Asthma | 7 (6) | 5 (5) | 0.8 |
| Atrial fibrillation | 9 (8) | 5 (5) | 0.5 |
| CAD | 19 (16) | 11 (11) | 0.3 |
| Peripheral vascular disease | 4 (3) | 7 (7) | 0.2 |
| Peptic ulcer | 3 (3) | 8 (8) | 0.07 |
| Hypothyroid | 10 (9) | 5 (6) | 0.4 |
| Pancreatitis | 2 (2) | 3 (3) | 0.7 |
| Jaundice | 99 (87) | 75 (82) | 0.34 |
| Stent | 75 (64) | 50 (52) | 0.064 |
| Preoperative laboratory values | | | |
| HGB | 12.6 ± 1.6 | 12.6 ± 1.8 | 0.7 |
| HCT | 36.6 ± 4.8 | 37.1 ± 4.8 | 0.27 |
| WBC | 8.3 ± 4.1 | 9.0 ± 3.3 | 0.084 |
| PLT | 276 ± 110 | 287 ± 129 | 0.8 |
| Alkaline phosphotase | 318 ± 295 | 330 ± 261 | 0.5 |
| ALT | 173 ± 203 | 181 ± 203 | 0.8 |
| AST | 104 ± 108 | 121 ± 130 | 0.4 |
| T-bilirubin | 5.2 ± 7.0 | 5.7 ± 6.0 | 0.32 |
| D-bilirubin | 3.0 ± 3.4 | 5.0 ± 4.3 | 0.045 |
| ALB | 3.4 ± .66 | 3.4 ± .68 | 0.9 |
| S-amylase | 60.7 ± 38.8 | 64.6 ± 60.7 | 0.8 |
| Creatinine | .89 ± .32 | 1.01 ± .75 | 0.5 |
| BUN | 14.9 ± 7.7 | 15.9 ± 10.6 | 0.7 |

PG = pancreaticogastrostomy; PJ = pancreaticojejunostomy; ± values are mean ± standard deviation; values in parentheses are percentages; *P* values are from the Chi-square or Fisher's exact test as appropriate for categorical scaled variables; Mann-Whitney U test for continuous scaled variables.

## Pancreatic Leak/Fistula

The overall incidence of pancreatic leak was 37/214 (17.3%) and that of fistula was 28/214 (13%). Table 3 outlines the relationship of patient characteristics, preoperative, intraoperative, and postoperative variables in patients without fistula (N = 186) versus those who had fistula (N = 28). Regarding demographics and preoperative variables, there was no difference between the patient's age, gender, the presence of diabetes, jaundice, stent, hematocrit, WBC count, total bilirubin, albumin, or creatinine. However, patients who had hypertension or a higher alkaline phosphatase were more likely to develop a fistula. Regarding intraoperative parameters, there was no difference between blood loss, blood replacement, operative time, the use of octreotide, antibiotics, or the type of anastomosis (PG vs. PJ). However, patients who developed a fistula had a significantly higher drain amylase. Also, patients having PD for pancreatic carcinoma were less likely to develop fistula. Because this is a retrospective study, the texture of the pancreatic remnant could not be evaluated. Since all 117 PG were performed by one surgeon and 92 of the PJ by a single surgeon, outcome, i.e., fistula rate, morbidity, and mortality could not be related to surgeon's experience. Decision to do PG or PJ was related in all circumstances to individual surgeon's preference. In 81 patients the pancreatic remnant was invaginated into the site of the jejunum. Of these 11 (13.5%) developed pancreatic fistula; three of the four deaths occurred in this group. In 8 patients the end of the pancreas was invaginated into the end of the jejunum. In this group 1 (12.5%) developed a pancreatic fistula; one of four deaths occurred in this group. In 8 patients, the

**Table 2.** Intraoperative parameters

| Parameter | PG (n = 117) | PJ (n = 97) | *P* value |
|---|---|---|---|
| Blood | | | |
| Blood loss (cc) | 1085 ± 668 | 1178 ± 996 | 0.61 |
| Blood replacement (number of units) | 0.81 ± 1.5 | 1.16 ± 1.9 | 0.5 |
| Operative time (hours) | 6.8 ± 0.96 | 6.2 ± 1.3 | 0.004 |
| Pathology | | | 0.1 |
| Pancreatic adenocarcinoma | 49 (42) | 52 (54) | |
| Duodenal adenocarcinoma | 5 (4) | 4 (4) | |
| Ampullary adenocarcinoma | 25 (21) | 11 (11) | |
| Distal bile duct carcinoma | 9 (8) | 13 (13) | |
| Other | 29 (25) | 17 (18) | |
| Octreotide | 93 (82) | 79 (83) | 0.8 |
| Antibiotic | 117 (100) | 97 (100) | NA |

PG = pancreaticogastrostomy; PJ = pancreaticojejunostomy; NA = not applicable; ± values are mean ± standard deviation; values in parentheses are percentages; *P* values are from the Chi-square or Fisher's exact test as appropriate for categorical scaled variables; Mann-Whitney U test for continuous/ordinal scaled variables.

end of the pancreas was anastomosed to the side of the jejunum in two layers, 1) duct to mucosa and 2) the pancreatic capsule to the serosa of the jejunum. In this group 2 (25%) patients developed a pancreatic fistula; no deaths occurred in this group. A longer hospital stay was associated with having a fistula. As far as postoperative parameters go, there was no difference in the groups in relation to mortality, wound infection, postoperative pneumonia, myocardial infarction, or arrhythmia. However, those patients who developed intraabdominal abscess or bile leak were more likely to have pancreatic fistula postoperatively. To summarize, those patients that developed postoperative pancreatic fistulas had a higher incidence of hypertension, elevation of alkaline phosphatase, a higher drain amylase, and were more likely to have had their PD for ampullary carcinoma, distal bile duct carcinoma or duodenal carcinoma. In addition, those patients who developed fistula had a higher incidence of intraabdominal abscess, and a higher incidence of bile leak, and a longer hospital stay.

## Postoperative Morbidity/Mortality in Relation to PG vs. PJ

Table 4 lists the postoperative morbidity, mortality, and interventions in patients undergoing PG versus those undergoing PJ. In univariate analysis, patients undergoing PJ, mortality was significantly higher when compared to those undergoing PG ($P = 0.041$). Three of four deaths were due to leakage at the pancreaticojejunal anastomosis and one death was due to hemorrhage. There was no difference between groups in relation to pancreatic leak, pancreatic fistula, intraabdominal abscess, wound infection, delayed gastric emptying, urinary tract infection, pneumonia, arrhythmia, myocardial infection, hospital stay, or days to closure of fistula. However, there was a statistically significant higher incidence of bile leaks in those patients who had PJ. The one patient who had bile leak following PG, and 4 of 6 patients who had bile leaks following PJ, were diagnosed by percutaneous transhepatic cholangiography and had stents placed at the same time. The remaining two patients in the PJ group were identified by the presence of bile in the right subcostal drain and were treated by maintaining the drain until the bile leakage ceased. All the patients who had bile leaks also had either a pancreatic leak or a pancreatic fistula.

Patients with PJ had significantly more postoperative percutaneous CT-guided drains placed (to drain infection or fluid collections) and significantly more reexplorations. There was no significant difference in the number of new PTC drains placed to control bile leaks when comparing PJ to PG. Although not statistically significant, fistulas resulting from a PJ anastomotic breakdown took longer to close when compared to fistulas resulting from a PG anastomotic breakdown.

## Results of Multivariate Analysis

We performed logistic regression analysis using forward stepwise model selection based on the likelihood ratio test to identify independent predictors of morbidity (pancreatic leak, fistula, intraabdominal abscess, wound infection, urinary tract infection, arrhythmia, or myocardial infarction, and length of hos-

**Table 3.** Patient characteristics, preoperative, intraoperative and postoperative variables vs. fistula

| Characteristics | No fistula (n=182) | Fistula (n=28) | *P* value |
|---|---|---|---|
| Demographics | | | |
| Age (yr) | 63.9 ± 12.5 | 65.1 ± 10.5 | 0.9 |
| Gender | | | |
| Male | 97 (86) | 16 (14) | 0.7 |
| Female | 85 (88) | 12 (12) | |
| Preoperative history | | | |
| Hypertension | | | 0.027 |
| No | 129 (90) | 14 (10) | |
| Yes | 53 (79) | 14 (21) | |
| Diabetes | | | 0.065 |
| No | 151 (85) | 27 (15) | |
| Yes | 31 (97) | 1 (3) | |
| Jaundice | | | 0.9 |
| No | 25 (81) | 6 (19) | |
| Yes | 150 (88) | 21 (12) | |
| Stent | | | 0.32 |
| No | 73 (84) | 14 (16) | |
| Yes | 109 (89) | 14 (11) | |
| Preoperative laboratory values | | | |
| HCT | 36.8 ± 4.7 | 37.7 ± 5.3 | 0.23 |
| WBC | 8.6 ± 4.0 | 8.0 ± 1.9 | 0.9 |
| Alkaline phosphatase | 334 ± 282 | 215 ± 210 | 0.029 |
| T-bilirubin | 5.4 ± 6.4 | 5.9 ± 0.06 | 0.7 |
| ALB | 3.5 ± 0.67 | 3.4 ± 0.67 | 0.8 |
| Creatinine | 0.94 ± 0.57 | 0.95 ± 0.39 | 0.4 |
| Intraoperative parameters | | | |
| Blood loss (cc) | 1065 ± 621 | 1279 ± 738 | 0.12 |
| Blood replacement (number of units) | 0.87 ± 1.3 | 1.18 ± 1.5 | 0.29 |
| Drainage Amylase | 826 ± 4406 | 15976 ± 15343 | <0.0001 |
| Pathology | | | <0.0001 |
| Pancreatic adenocarcinoma | 98 (98) | 2 (2) | |
| Duodenal adenocarcinoma | 5 (63) | 3 (38) | |
| Ampullary adenocarcinoma | 26 (77) | 8 (24) | |
| Distal bile duct carcinoma | 18 (82) | 4 (18) | |
| Other | 35 (76) | 11 (24) | |
| Operative time (hours) | 6.6 ± 1.14 | 7.0 ± 0.90 | 0.11 |
| Octreotide | | | 0.8 |
| No | 33 (89) | 4 (11) | |
| Yes | 145 (86) | 23 (14) | |
| Antibiotic | | | 0.9 |
| No | 5 (100) | 0 (0) | |
| Yes | 177 (86) | 28 (14) | |
| Type of Pancreatic Anastomosis | | | 0.5 |
| PG | 103 (88) | 14 (12) | |
| PJ | 79 (85) | 14 (15) | |
| Hospital stay (days) | 10.5 ± 4.8 | 16.8 ± 7.7 | <0.0001 |
| Postoperative parameters | | | |
| Intraabdominal abscess within 30 days postoperatively | | | <0.0001 |
| No | 175 (90) | 20 (10) | |
| Yes | 7 (47) | 8 (53) | |
| Wound infection | | | 0.9 |
| No | 173 (87) | 26 (13) | |
| Yes | 9 (82) | 2 (18) | |

*Table 3 continued.*

**Table 3.** *Continued*

| Characteristics | No fistula (n = 182) | Fistula (n = 182) | P value |
|---|---|---|---|
| Pneumonia | | | 0.9 |
| No | 179 (87) | 28 (14) | |
| Yes | 3 (100) | 0 (0) | |
| Arrhythmia or myocardial infarction | | | 0.9 |
| No | 174 (88) | 23 (11) | |
| Yes | 8 (62) | 5 (39) | |
| Bile leak | | | <0.0001 |
| No | 181 (89) | 23 (11) | |
| Yes | 1 (17) | 5 (83) | |

± values are mean ± standard deviation; values in parentheses are percentages; *P* values are from the Chi-square or Fisher's exact test as appropriate for categorical scaled variables; Mann-Whitney U test for continuous scaled variables.

pital stay) and treatment group (PG vs. PJ). Death within 30 days postoperatively or in hospital could not be analyzed with multivariate logistic regression because there were too few deaths. Similarly, there were too few patients with either bile leak, delayed gastric emptying, or pneumonia to analyze with multivariate logistic regression.

The following explanatory variables were included in the forward stepwise model selection procedure: 1) age; 2) gender; 3) history of hypertension, diabetes, cancer, COPD or asthma, atrial fibrillation, CAD, peripheral vascular disease, peptic ulcer, pre-op total bilirubin, pre-op alkaline phosphatase, stent; 4) operation time; 5) estimated blood loss during surgery; 6) preoperataive use of antibiotics; 7) postoperative use of octreotide; and 8) pathology of pancreas. Surgery method (PG vs. PJ) was also included as an explanatory variable in the models for predicting morbidity. None of the stepwise model selection procedures identified statistically significant explanatory variables in a multivariate model for any of the response variables.

## Post-Discharge Interventions in Patients Discharged With or Without Pancreatic Fistula

***Pancreaticogastrostomy.*** Of the 14 patients discharged with a pancreatic fistula, two patients returned for the placement of new drains for un-drained intraabdominal collections, and 1 patient developed a small bowel fistula, which healed with conservative management. In addition, one patient not discharged with a fistula returned with severe upper GI bleeding and was diagnosed to have a pseudoaneurysm of the gastroduodenal artery and had emergency angiography with angiographic embolization of the right hepatic artery. This patient survived and lived for three years after his pancreaticoduodenectomy.

***Pancreaticojejunostomy.*** Of the 14 patients in this group discharged with a pancreatic fistula, six patients returned to have new drains placed to drain intraabdominal collections. In addition, in those patients who were discharged without a fistula, one patient returned with delayed gastric emptying and on CT was found to have an abscess and had to have a new drain placed, another patient was readmitted with a liver abscess and had this drained by CT guidance, and a third patient was admitted with small bowel obstruction and underwent lysis of adhesions with a placement of a PEG/PEJ tube, a fourth patient was admitted with a wound infection and on further workup was found to have a liver abscess that was drained using CT guidance, and a fifth patient was admitted for delayed gastric emptying and was managed medically. One patient in the PJ group discharged with a fistula, was readmitted within a month of discharge with severe cardiac disease, had to be placed on a balloon pump, underwent a coronary angioplasty, and was also found to have a post-op abscess that needed to have a new drain placed. In short while there were several readmissions in both groups, discharged with or without fistula, all complications were managed conservatively or with the help of the interventional radiologist and one needed reoperation for lysis of adhesions. There were no postoperative deaths in these patients.

## DISCUSSION

The management of the pancreatic remnant following pancreaticoduodenectomy continues to be the source of much discussion.[13,14,20,21] Because leakage at the pancreaticoenteric anastomosis results in major morbidity and mortality following PD, many

**Table 4.** Postoperative outcomes and interventions in relation to type of pancreatic anastomosis

| Outcomes/Interventions | PG (n = 117) | PJ (n = 97) | *P* value |
|---|---|---|---|
| Outcomes | | | |
| Death within 30 days postoperatively | 0 (0) | 4 (4) | 0.041 |
| Pancreatic leak | 19 (16) | 18 (19) | 0.7 |
| Fistula | 14 (12) | 14 (14) | 0.6 |
| Bile leak | 1 (1) | 6 (6) | 0.048 |
| Intraabdominal abscess | 6 (5) | 10 (10) | 0.15 |
| Wound infection | 7 (6) | 4 (4) | 0.8 |
| Delayed gastric emptying | 2 (2) | 6 (6) | 0.15 |
| Urinary tract infection | 8 (7) | 8 (8) | 0.7 |
| Pneumonia | 1 (1) | 2 (2) | 0.6 |
| Arrhythmia or myocardial infarction | 7 (6) | 7 (7) | 0.7 |
| Hospital stay (days) | 11.2 ± 5.3 | 11.5 ± 6.1 | 0.7 |
| Days to closure of fistula | 20.1 ± 18.2 | 43.8 ± 33.6 | 0.069 |
| Interventions | | | |
| New CT drains | 2 (2) | 8 (8) | 0.046 |
| Reexploration | 0 (0) | 5 (5) | 0.018 |
| New PTC drains | 1 (1) | 4 (4) | 0.18 |

PG = pancreaticogastrostomy; PJ = pancreaticojejunostomy; values in parentheses are percentages; *P* values are from the Chi-square or Fisher's exact test as appropriate, intraabdominal abscess is within 30 days postoperatively; days to closure of fistula based on N = 9 in PG group and N = 11 in PJ group.

techniques have been proposed for the management of the pancreatic remnant.[9–16,18] Initially, ductal ligation was thought to be a safer procedure,[9] but the data suggests that this is associated with at least 50% incidence of pancreatic fistula.[10,13] Injection of the pancreatic duct with the neoprene has been proposed by Dicarlo.[11] In 51 patients they observed a 33.3% overall morbidity and a 5.8% operative mortality. Another solution suggested was removal of the remaining pancreas, i.e., performing a total pancreatectomy.[16] The most recent results of this procedure reveal a mortality, morbidity, and survival equivalent to that of PD.[16] In addition, total pancreatectomy is associated with severe endocrine and exocrine abnormalities. It is for this reason that total pancreatectomy presently is reserved for selected individuals. The high incidence of pancreatic fistula following pancreatic duct ligation, the 100% incidence of pancreatic insufficiency, and the high incidence of diabetes following pancreatic duct injection, and the equivocal results of total pancreatectomy has prevented the widespread applications of these methods for the treatment of the pancreatic remnant. More recently, a Roux-en-Y anastomosis has been proposed as safe management of the pancreatic remnant.[15] A mortality of 0.95% and a morbidity of 11.2% in 105 patients have been reported.[15] It was felt by the authors that the use of a defunctionalized limb to drain the pancreatic remnant contributed to the lower morbidity and mortality. This modification, however, requires further study. Therefore, we are left with PJ and PG as the most commonly used methods of reconstruction following PD.

After the inception of the one-stage PD, postoperative mortality of 50% was the norm.[1] In fact, mortality rates continued to be so high in the 1950s and the 1960s that there were suggestions that the operation be abdandoned.[22] In the late 1980s, mortality rates were considerably lower and were reported between 10–20%.[23,24] More recently, mortality rates of 10% are reported,[25,26] though in some institutions mortality rates following PJ of less than 5% are being reported.[27–29] It is estimated that up to 50% of the mortality from a leak after PD with a PJ anastomosis was due to leakage at the PJ anastomosis.[5,6] Because of this, PG was offered as a safer alternative to PJ following PD. The success of anastomosing the pancreas to the stomach was first described by Tripodi and Sherwin[30] and later confirmed by Person and Glenn in the laboratory.[31] Waugh and Clagett were the first to use PG in the clinical setting in 1946.[32] Thereafter, a large number of investigators have written and reported on the successful use of PG as reconstruction following PD.[32–47] Many theories have been put forward to support using PG over PJ.[42] Pancreatic enzymes are inactivated by the acidic gastric fluid. Also, the stomach does not contain enterokinase, which is required for conversion of trypsinogen to trypsin and subsequent activation to other proteolytic enzymes. A lack of enzymatic activation may help prevent auto digestion of the anastomosis. Initially, the

alkaline pancreatic secretions may aid in preventing marginal ulceration. The proximity of the pancreas to the posterior wall of the stomach allows for potentially less tension on the anastomosis. The excellent blood supply to the stomach wall is favorable to an anastomotic healing and thickness of the stomach wall holds sutures well. Nasogastric decompression provides for continuous emptying of the stomach, and therefore, less tension on the anastomosis, a benefit not possible with a PJ anastomosis. PG avoids a long jejunal limb between the pancreatic and biliary anastomosis where biliary and pancreatic secretions can collect and cause increased pressure resulting in tension at both the pancreatic and biliary anastomoses.

Analysis of four large series of pancreaticojejunostomy following pancreaticoduodenectomy in the 1980s reveals the following. Of 772 patients, 116 (15%) required reexploration for a leak at the PJ anastomosis, and of these 116, 11 (9.4%) died.[5,6,28,48] A more recent publication from the Johns Hopkins Medical Center summarizes results in 650 consecutive PD in the 1990s.[3] In this study 71% of patients had PJ and 29% had PG. Twenty-six (4%) of the patients in the study needed reexploration for hemorrhage, intraabdominal abscess, and fascial dehiscence. There were nine deaths (1.4%) due to leak at the pancreaticoenteric anastomosis in this study. All nine deaths occurred in the 26 patients who required reexploration. In other words, 34.6% of the reexplorations resulted in death. The authors do not relate reexplorations or mortality to type of the anastomosis, whether PJ or PG. A recent review by Mason of PG between 1946 and 1997 reveals the following.[49] Between 1946 and 1990, a total of 199 cases were described in the literature. A mortality of 4.5% (9/199) and a leakage rate of 1% (2/199) were reported. None of the nine deaths during this time were attributed to PG. From the time period 1991 to 1997, the number of PG described in literature was 614. The incidence of leakage for this period when compared to the previous rose to 4.7% (29/614) and mortality was 3.3% (20/614). In this group of the 20 persons who died only 3 of the deaths (15%) were related to the PG anastomosis, 1 from hemorrhage and 2 from sepsis. In our series of 102 patients published recently, there were 4 deaths. Only 1 of the 102 (1%) was attributed to a complication at the pancreaticogastric anastomosis and was due to hemorrhage and not leakage.[47] Bartoli[50] did a meta-analysis of 15 years of literature on pancreatic fistula and relative mortality in malignant disease after PD. They compared the data on PG versus PJ anastomosis done in three different ways, i.e., pancreaticojejunal end to side, pancreaticojejunal end to end, and Wirsung duct to jejunal end to side anastomosis. In all cases PG was found to be associated with lower morbidity and mortality rates. Miyagawa et al.[51] also found PG to be superior to PJ in a retrospective comparative study.

However, it should be noted that the only randomized study comparing PG to PJ (at the Johns Hopkins Hospital) showed no difference in the rate of fistula following the two procedures.[52] The fistula rate was 12.3% for PG and 11.1% for PJ. Factors influencing the development of fistula in that series were the surgeon's experience, the texture of the pancreatic remnant, and the primary pathology for which the operation was being done.

In our present series of 214 patients, there were 4 deaths in the PJ group, and none in the PG group. Three of the 4 deaths in the PJ group were directly related to the leakage at the PJ anastomosis. The fourth death was due to hemorrhage. This was a statistically significant difference in mortality between PJ or PG. There was no difference in pancreatic leak, fistula rate, intraabdominal infection, wound infection, delayed gastric emptying, urinary tract infection, pneumonia, arrhythmias, myocardial infarction or hospital stay between the PG and PJ groups. However, in the PJ group who had leakage at the pancreatic anastomosis, there was a higher incidence of leakage at the biliary anastomosis. This resulted in a larger number of patients in the PJ group requiring a PTC drain to control leakage at the biliary anastomosis. It was also seen in our series that a significantly larger number of patients who had leaks at the PJ anastomosis needed new CT drains and/or reexploration to control infection. In the PG group one patient needed a new PTC drain and no patients needed reexploration. To be noted also was that fistulas following a PG anastomotic breakdown took a shorter time to close than those following a PJ breakdown ($20.1 \pm 18.2$ vs. $43.8 \pm 33.6$ days), ($P = 0.069$).

## CONCLUSION

This retrospective analysis shows that PG can be performed safely and with fewer complications than PJ and we propose it as a suitable alternative to the latter for the management of the pancreatic remnant following PD. While the pancreatic leak and fistula rate were not different between groups, it is possible that leakage at the PJ anastomosis is more likely to be fatal, more likely to be associated with bile leaks at the hepaticojejunal anastomosis, more likely to require reexploration and new CT drains to control infection, and results in pancreatic fistulae that take longer to close.

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REFERENCES

1. Brunswig A. One stage pancreaticoduodenectomy. Surg Gynecol Obstet 1943;77:581.
2. Cameron JL, Pitt HA, Yeo CJ, Lillemoe KD, Kaufman HS, Coleman J. One hundred and forty-five consecutive pancreaticoduodenectomies without mortality. Ann Surg 1993; 217:430–438.
3. Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA, Hruban RH, Ord SE, Sauter PK, Coleman J, Zahurak ML, Grochow LB, Arbrams RA. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990's. Pathology, complications and outcomes. Ann Surg 1997;226: 248–260.
4. Sohn TA, Yeo CJ, Cameron JL, Koniaris L, Kaushal S, Abrams RA, Sauter PK, Coleman J, Hruban RH, Lillemoe KD. Resected adenocarcinoma of the pancreas—616 patients: results, outcomes, and prognostic indicators. J. Gastro Surg 2000;4:568–579.
5. Crist DW, Sitzmann JV, Cameron JL. Improved hospital morbidity, mortality and survival after the Whipple procedure. Ann Surg 1987;206:358–365.
6. Grace PA, Pitt HA, Tompkins RK, Denbesten L, Longmire Jr WP. Decreased morbidity and mortality after pancreatoduodenectomy. Am J Surg 1986;151:141–149.
7. Geer RJ, Brennan MF. Prognostic indicators for survival after resection of pancreatic adenocarcinoma. Am J Surg 1993;165:68–73.
8. Conlon KC, Klimstra DS, Brennan MF. Long term survival after curative resection for pancreatic ductal adenocarcinoma. Clinico pathologic analysis of 5-year survivors. Ann Surg 1996;223:273–279.
9. Goldsmith HS, Ghosh BC, Huvos AG. Ligation versus implantation of the pancreatic duct after pancreaticoduodenectomy. Surg Gynecol Obstet 1971;132:87–92.
10. Papachristou DN, Fortner JG. Pancreatic fistula complicating pancreatectomy for malignant disease. Br J Surg 1981; 68:238–240.
11. Dicarlo V, Chiesa R, Pontiroli AE, Carlucci M, Staudacher C, Zerbi A, Cristallo M, Braga M, Pozza G. Pancreaticoduodenectomy with occlusion of the residual stump with neoprene injection. World J Surg 1989;13:105–111.
12. Roder JD, Stein HJ, Bottcher KA, Busch R, Claus-Dieter H, Steinert JR. Stented versus nonstented pancreaticojejunostomy after pancreaticoduodenectomy. A prospective study. Ann Surg 1999;1:41–48.
13. Aston SJ, Longmire Jr WP. Management of the pancreas after pancreaticoduodenectomy. Ann Surg 1974;179:322–327.
14. Marcus SG, Cohen H, Ranson JHC. Optimal management of the pancreatic remnant after pancreaticoduodenectomy. Ann Surg 1995;221:635–648.
15. Papadimitriou JD, Fotopoulos AC, Smyrniotis B, Prahalias AA, Kostopanagiotou G, Papadimitriou LJ. Subtotal pancreaticoduodenectomy. Use of a defunctionalized loop for pancreatic stump drainage. Arch Surg 1999;134:135–139.
16. Sarr MG, Behrns KE, van Heerden JA. Total pancreatectomy. An objective analysis of its use in pancreatic cancer. Hepato-Gastroenterol 1993;40:418–421.
17. Telford GL, Mason GR. Improved technique for pancreaticogastrostomy after pancreaticoduodenectomy. Am J Surg 1981;142:386–387.
18. Takao S, Shimazu H, Maenohara S, Shinchi H. Modified pancreaticogastrostomy following pancreaticoduodenectomy. Am J Surg 1993;165:317–321.
19. Aranha GV. A technique for pancreaticogastrostomy. Am J Surg 1998;175:328–329.
20. Yeo CJ, Cameron JL. Alternative techniques for performing the Whipple operation. Advances in Surgery 1997;30:293–310.
21. Reissman P, Perry Y, Cuenca A, Bloom A, Eld A, Shiloni E, Rivkind A, Durst A. Pancreaticojejunostomy versus controlled pancreaticocutaneous fistula in pancreaticoduodenectomy for periampullary carcinoma. Am J Surg 1995;169: 585–588.
22. Shapiro TM. Adenocarcinoma of the pancreas: A statistical analysis of biliary bypass vs. Whipple resection in good risk patients. Ann Surg 1975;182:715–721.
23. Connolly MM, Dawson PJ, Michelassi F, Moosa PR. Survival in 1001 patients with carcinoma of the pancreas. Ann Surg 1987;206:366–373.
24. Forrest JF, Longmire WP. Carcinoma of the pancreas and periampullary region. A study of 279 patients. Ann Surg 1979; 189:129.
25. Strasberg SM, Drebin JA, Soper NJ. Evolution and current status of the Whipple procedure: An update for gastroenterologists. Gastroenterology 1997;113:983–994.
26. Sikora SS, Posner MC. Management of the pancreatic stump following pancreaticoduodenectomy. Surg Gynecol Obstet 1943;77:581.
27. Trede M, Schwall G, Saeger HD. Survival after pancreaticoduodenectomy 118 consecutive resections without an operative mortality. Ann Surg 1990;211:447–458.
28. Trede M, Schwall G. The complications of pancreatectomy. Ann Surg 1988;207:39–47.
29. Pellegrini CA, Heck CF, Raper S, Way LW. An analysis of the reduced morbidity and mortality rates after pancreaticoduodenectomy. Arch Surg 1989;124:778–781.
30. Tripodi AM, Sherwin CF. Experimental transplantation of the pancreas into the stomach. Arch Surg 1934;28:345–356.
31. Person Jr EC, Glenn F. Pancreaticogastrostomy, experimental transplantation of the pancreas into the stomach. Arch Surg 1939;39:530–550.
32. Waugh JM, Clagett OT. Resection of the duodenum and head of the pancreas for carcinoma. An analysis of thirty cases. Surgery 1946;20:224–232.
33. Ingebrigtsen R, Langfeldt E. Pancreaticogastrostomy. Lancet 1952;2:270–271.
34. Dill-Russell AS. Pancreaticogastrostomy. Lancet 1952;1: 589–590.
35. Wells CA, Shepherd JA, Gibbon N. Pancreaticogastrostomy. Lancet 1952;1:588–589.
36. Silverstone M. Pancreaticoduodenectomy and pancreaticogastrostomy. A five-year survival with notes on the metabolism. Br J Surg 1956;44:299–302.
37. Strauch GO. The use of pancreatogastrostomy after blunt traumatic pancreatic transection. A complete and efficient operation. Ann Surg 1972;176:16–18.
38. Millbourn E. Pancreatico-gastrostomy in pancreatico-duodenal resection for carcinoma of the head of the pancreas or the papilla of vater. Acta Chir Scandinav 1958;116:12–27.
39. Flautner L, Tihanya T, Szecseny A. Pancreaticogastrostomy: An ideal complement to pancreatic head resection with preservation of the pylorus in the treatment of chronic pancreatitis. Am J Surg 1985;150:608–611.
40. Madiba TE, Thomson SR. Restoration of continuity following pancreaticoduodenectomy. Brit J Surg 1995;82:158–165.
41. Icard P, Dubois F. Pancreaticogastrostomy following pancreaticoduodenectomy. Ann Surg 1988;207:253–256.
42. Pikarsky AJ, Muggia-Sullam M, Eid A, Lyass S, Bloom AI, Durst AL. A retrospective analysis of 28 patients. Arch Surg 1997;132:296–299.
43. Delcore R, Thomas JH, Pierce GE, Hermreck AS. Pancreaticogastrostomy: A safe drainage procedure after pancreaticoduodenectomy. Surgery 1990;108:641–647.

44. Kapur BML, Misra M, Seenu V, Goel AK. Pancreaticogastrostomy for reconstruction of pancreatic stump after pancreaticoduodenectomy for ampullary carcinoma. Am J Surg 1998;176:274–278.
45. Ihse J, Axelson J, Hansson L. Pancreaticogastrostomy after subtotal pancreatectomy for cancer. Dig Surg 1999;16:389–392.
46. Mackie JA, Rhoads JE, Park D. Pancreaticogastrostomy: A further evaluation. Ann Surg 1975;181:541–545.
47. Morris DM, Ford RS. Pancreaticogastrostomy: Preferred reconstruction for Whipple resection. J Surg Res 1994;54: 122–125.
48. O'Neil S, Pickleman JR, Aranha G. Pancreaticogastrostomy following pancreaticoduodenectomy. World J Surg 2001; 25:567–571.
49. Cullen JJ, Sarr MG, Ilstrup DM. Pancreatic anastomotic leak after pancreaticoduodenectomy: Incidence, significance, and management. Am J Surg 1994;168:295–298.
50. Mason GR. Pancreatogastrostomy as reconstruction for pancreatoduodenectomy: Review. World J Surg 1999; 23:221–226.
51. Bartoli FG, Arnone GB, Ravera G, Bachi V. Pancreatic fistula and relative mortality in malignant disease after pancreaticoduodenectomy. Review and statistical meta-analysis regarding 15 years of literature. Anticancer Research 1991; 11:1831–1848.
52. Miyagawa S, Makuuchi M, Lygidakis NJ, Noguchi T, Nichimaki K, Hashikura Y, Harada H, Hayashi K, Kakazu T. A retrospective comparative study of reconstruction methods following pancreaticoduodenectomy-pancreaticojejunostomy vs pancreaticogastrostomy. Hepato-Gastroenterol 1992;39:381–384.
53. Yeo CJ, Cameron JL, Maher MM, Sauter PK, Zahurak MI, Talamini MA, Lillemoe KD, Pitt HA. A prospective randomized trial of pancreaticogastrostomy versus pancreaticojejunostomy after pancreaticoduodenectomy. Ann Surg 1995;222:580–592.

# Intra-Abdominal Hemorrhage Due to Rupture of a Splenic Vein Aneurysm: A Case Report

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Splenic vein aneurysm (SVA) is extremely rare. Most patients with an SVA have portal hypertension. In this report we describe the first recorded case of intra-abdominal hemorrhage due to rupture of an SVA in a patient without evidence of portal hypertension. A 72-year-old man was admitted to our medical center in a state of shock, with complaints of acute abdominal pain and abdominal distention. Preoperatively, abdominal ultrasonography demonstrated an echo-free space in the abdomen, suggesting the presence of a fluid collection. In addition, computed tomography revealed an enhanced lesion with contrast material in the pancreatic tail. An emergency operation showed bleeding from the SVA near the pancreatic tail. Consequently, a distal pancreatectomy with splenectomy was performed. Histologically the lesion was diagnosed as an SVA surrounded by pancreatic tissue with chronic inflammatory changes. The patient's postoperative course was uneventful. (J GASTROINTEST SURG 2003;7:683–686) 

KEY WORDS: Splenic vein, rupture, chronic pancreatitis

Clinically, intra-abdominal hemorrhage is associated with shock and therefore requires emergency treatment. This critical condition is mainly attributable to abdominal injury, resulting in rupture of the liver, spleen, or major vessels, whereas rupture of hepatocellular carcinomas, arterial aneurysms, and other conditions causing intra-abdominal hemorrhage are rare.[1–4] Here we describe a patient with rupture of a splenic vein aneurysm (SVA) presenting as intra-abdominal hemorrhage; to our knowledge this is the first such report in the English literature.

## CASE REPORT

A 72-year-old man was admitted to our medical center with acute abdominal pain and abdominal distention. He had suffered from chronic heart failure for the past 7 years. On admission, his blood pressure was 76/35 mm Hg and his pulse rate was 120 beats per minute. He had severe pain in the right lower abdomen with rebound tenderness. No abdominal mass was present, and the liver and spleen were not palpable.

A plain abdominal x-ray film showed a normal bowel pattern without free gas. The blood chemistry data were as follows: hemoglobin, 9.8 g/dl (range 12.4 to 17.4 g/dl); serum glucose, 211 mg/dl (range 55 to 110 mg/dl); creatinine, 1.4 mg/dl (range 0.6 to 1.1 mg/dl); amylase, 199 U/L (range 55 to 170 U/L), and white blood cell count, $12.1 \times 10^9$/L (range 4.0 to 9.0); other results were negative. Abdominal ultrasound imaging demonstrated a massive echo-free space in the abdomen, suggesting the presence of a fluid collection. Computed tomography (CT) showed an enhanced lesion with contrast material in the pancreatic tail along with fluid collection (Fig. 1). From these findings we determined that the intra-abdominal bleeding had been caused by rupture of a lesion in the pancreatic tail, possibly a hypervascular tumor. The patient underwent an emergency operation in March 2001.

On celiotomy, 2 liters of blood was found in the abdomen, and the liver appeared normal with no evidence of portal hypertension. After the major omentum was divided, the anterior surface of the pancreas was revealed, and blood was found to be spurting from a hard tumor, 2 cm in diameter, in the pancreatic tail. Subsequently, a distal pancreatectomy with splenectomy was performed. After the blood was removed, the lesion became soft. The cut surface of

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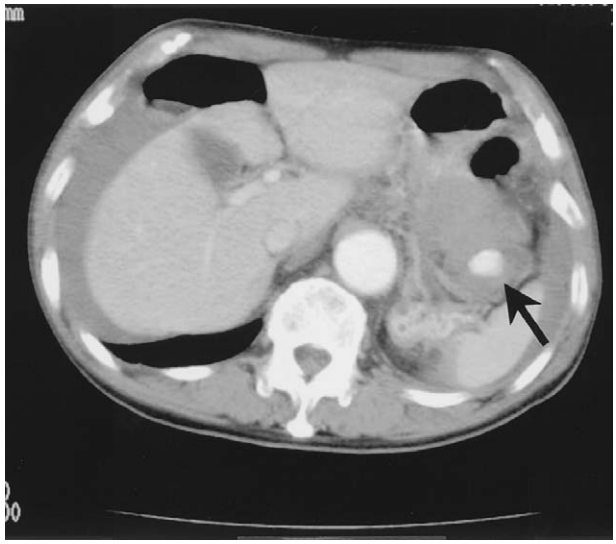

**Fig. 1.** CT findings. There was an enhanced lesion (measuring approximately 2 cm) in the pancreatic tail (*arrow*) with fluid collection in the abdomen.

the resected specimen showed a cystic lesion in the pancreas (Fig. 2). Histologically, the cystic lesion was confirmed to be a true aneurysm of the splenic vein, 2 cm in diameter, which had penetrated the pancreatic parenchyma and then ruptured into the abdominal cavity. The SVA was surrounded by the pancreas, which had significant fibrosis due to chronic pancreatitis (Fig. 3). There was no connection between the SVA and the splenic artery, and there were no findings suggestive of a pancreatic tumor. The postoperative course was uneventful, and the patient was discharged from the hospital 41 days after operation.

## DISCUSSION

Portal system aneurysms can be divided into two types: extrahepatic and intrahepatic. SVA is a true aneurysm and belongs to the extrahepatic category.[5–10] Since Lowenthal and Jacob[5] described the first case of SVA, fewer than 50 cases of portal system aneurysm and eight cases of SVA, including the present one, have been reported in the English literature.[6–8] The eight patients with SVA included five women and three men whose mean age was 50 years.[9–14]

Although the exact etiology of SVA is not fully understood, it may include congenital and acquired factors. The SVA was associated with portal hypertension and liver cirrhosis in four of the eight patients. Shirohara et al.[10] reported that in a patient with liver cirrhosis, the SVA enlarged with the development of esophageal varices. Furthermore, Tolgonay et al.[13] reported that the reduction in the size of the aneurysm was related to a decrease in splenic vein blood flow. These observations suggest that the persistent stagnation of blood flow in the portal system may have played a major role in the development of the SVA. In our patient, histologic examination showed that the SVA was surrounded by the pancreas, which showed chronic inflammatory changes consistent with either severe fibrosis or chronic pancreatitis, and that the SVA had ruptured into the abdominal cavity. It was suspected that the inflammation of the pancreas had caused the development of the SVA. However, acute or chronic pancreatitis has never been reported as a cause of rupture of the splenic vein. In the remaining three patients the etiology was unknown, suggesting that an inherent weakness of the vessel

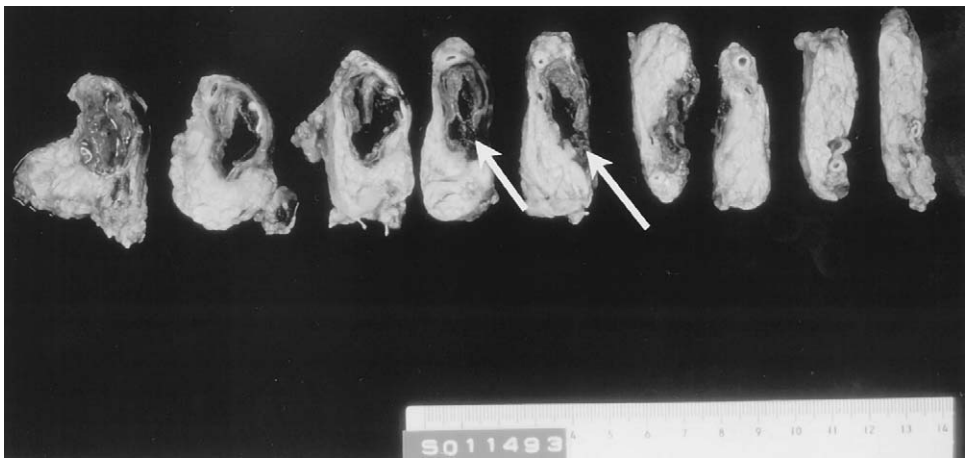


**Fig. 2.** Cut surface of the resected specimen. There was a cystic lesion in the pancreas. The cyst was confirmed to be a dilated splenic vein (*arrows*).

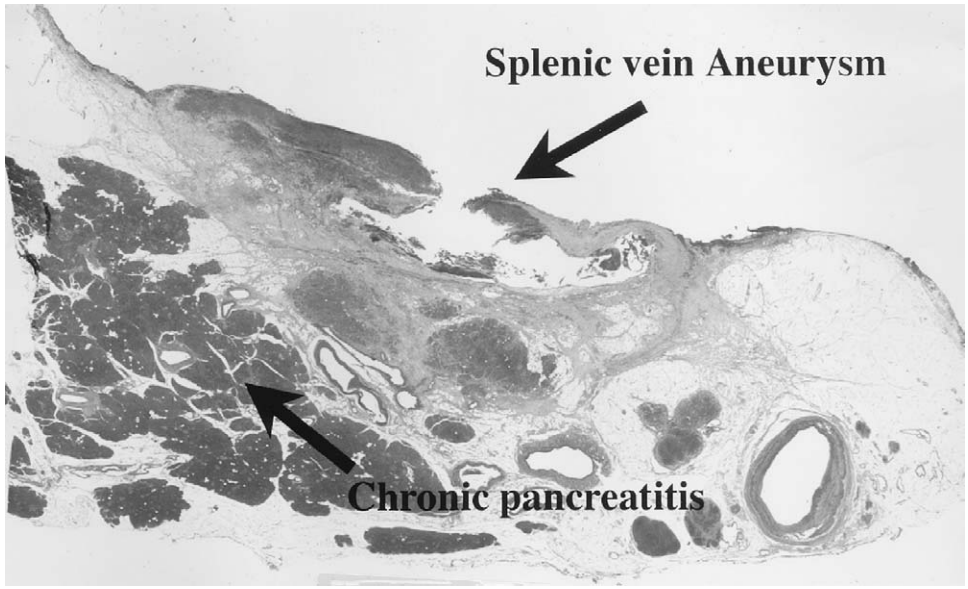


**Fig. 3.** Histologic findings of the resected specimen. This cystic lesion was diagnosed as a true splenic vein aneurysm, 2 cm in diameter, which was surrounded by pancreas tissue with significant fibrosis due to chronic pancreatitis.

wall or a congenital factor resulted in development of the aneurysm.[9,12,14] SVA can develop in patients with portal hypertension and liver cirrhosis, but this is a rare occurrence. Clinically, various factors including hemodynamic changes in the portal system, inflammation, and inherent weakness may have contributed to formation of the aneurysm.

Most abdominal venous aneurysms, including SVA, are found incidentally. However, six of the eight patients had clinical complaints: four had abdominal pain and all had abdominal fullness and hepatic dysfunction. Our patient was the first to present in a state of shock with intra-abdominal bleeding due to SVA rupture. Rupture of an extrahepatic-type portal vein aneurysm has been reported in four cases and is manifested by continuous gastrointestinal bleeding or massive intra-abdominal bleeding.[7,8,15–17]

To make a diagnosis of SVA, noninvasive imaging modalities can be used. In three patients with liver cirrhosis and portal hypertension, follow-up CT and ultrasound imaging were useful in detecting SVA.[5,10,11] In one patient who was suspected to have a pseudocyst of the pancreas, the lesion was confirmed as an SVA by color Doppler ultrasound imaging, thereby avoiding an unnecessary biopsy.[13] Because in our patient CT showed an enhanced lesion in the pancreatic tail with massive intra-abdominal fluid collection, rupture of a hypervascular tumor of the pancreas was suspected. The lesion could not have been detected by means of ultrasound because of its location. At the time of the emergency operation, blood was spurting from the tail of the pancreas. Macroscopically the lesion appeared to be a hypervascular tumor.

Treatment of SVA is controversial. Because its natural course is not well understood, it is difficult to decide on the timing and type of treatment. In three of the eight patients, the SVA was resected; in addition, splenectomy, splenorenal shunt, aneurysm resection, and distal pancreatectomy have also been performed.[5,9] The remaining five patients did not undergo surgery and were still alive at the time of this report. Therefore we recommend careful follow-up of SVA with the use of CT, magnetic resonance imaging, and color Doppler ultrasound unless a patient is symptomatic. In our patient, although the SVA was less than 2 cm in diameter, it had ruptured. This suggests that physicians must bear in mind that an SVA carries a risk of rupture when inflammation is present. If adequate treatment is selected and timed correctly, a good outcome can be expected.

REFERENCES

1. Yoshida H, Onda M, Tajiri T, Umehara M, Mamada Y, Matsumoto S, Yamamoto K, Kaneko M, Kumazaki T. Treatment of spontaneous ruptured hepatocellular carcinoma. Hepatogastroenterology 1999;46:2451–2453.
2. Stengel D, Bauwens K, Sehouli J, Pozsolt F, Rademacher G, Mutze S, Ekkernkamp A. Systematic review and meta-analysis of emergency ultrasonography for blunt abdominal trauma. Br J Surg 2001;88:901–912.
3. Inoguchi H, Mii S, Sakata H, Orita H, Yamahita S. Intrahepatic pseudoaneurysm after surgical hematomesis for a

delayed hemorrhage due to blunt liver injury: Report of a case. Surg Today 2001;31:367–370.
4. Omert LA, Salyer D, Dunham CM, Porter J, Silva A, Protetch J. Implication of the "contrast blush" finding on computed tomographic scan of the spleen in trauma. J Trauma Injury Infect Crit Care 2001;51:272–277.
5. Lowenthal M, Jacob H. Aneurysm of splenic vein—Report of a case. Acta Med Orient 1953;12:170–174.
6. Boyez M, Fourcade Y, Sebag A, Valette M. Aneurysmal dilatation of the portal vein: A case diagnosed by real-time ultrasonography. Gastrointest Radiol 1986;11:319–321.
7. Glazer S, Gaspar MR, Esposito V. Harrison L. Extrahepatic portal aneurysm: Report of a case treated by thrombectomy and aneurysmorphy. Ann Vasc Surg 1992;6:338–342.
8. Barzilai R, Kleckner MS. Hemocholecyst following ruptured aneurysm of portal vein. Report of a case. Arch Surg 1956;72:725–727.
9. Torres G, Hines GL, Monteleone F, Hon M, Hon M, Diel J. Splenic vein aneurysm: Is it a surgical indication? J Vasc Surg 1999;29:719–721.
10. Shirohara H, Endo M, Sakai K, Tabaru A, Otsuki M. Enlarging splenic vein aneurysm associated with stagnation of splenic venous blood flow. Am J Gastroenterol 1996;91:385–387.
11. Ohhira MO, Ono M, Ohhira MA, Matsumoto A, Ohta H, Namiki M. Case report: Splenic vein aneurysm—report of a lesion that progressively expanded. Br J Radiol 1994;67: 656–658.
12. Soo MS, Khoury MB, Lupetin AR. Splenic vein aneurysm: MR appearance—a case report. Angiology 1991;42:590–593.
13. Tolgonay G, Ozbek SS, Oniz H, Oniz H, Suzer E, Yurdakul LO. Regression of splenic vein aneurysm following resolution of splenomegaly. J Clin Ultrasound 1998;26:98–102.
14. Schmidt HG. Splenic vein aneurysm: Diagnosis with color-coded duplex ultrasound. Leber Magen Darm 1995;25: 227–228.
15. Chin KT, Abercrombie JF, Burroughs AK, Ashby BS. Spontaneous rupture of a normal portal vein causing severe retroperitoneal and intraperitoneal bleeding. Br J Surg 1993;80:892.
16. Thomas TV. Aneurysm of the portal vein: Report of two cases, one resulting in thrombosis and spontaneous rupture. Surgery 1967;61:550–555.
17. Calligaro KD, Ahmed S, Dandora R, Doughertyet MJ, Savarese RP, Doerr KJ, McAffee S, et al. Venous aneurysm: Surgical indications and review of the literature. Surgery 1995;117:1–6.

# Intraoperative Imprint Cytology for Evaluation of Sentinel Lymph Nodes From Visceral Malignancies

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Although originally described for breast cancer and melanoma, sentinel lymph node (SLN) mapping techniques are being investigated in the treatment of visceral malignancies. There is no literature evaluating intraoperative analysis of SLNs from visceral sites. We evaluated the utility of touch preparation intraoperative imprint cytology (IIC) in evaluating SLNs harvested in the setting of visceral malignancy. SLN mapping procedures involving 50 cases of visceral malignancy (37 colon, 12 gastric, and 1 small bowel), from February 1999 through August 2001, were studied. In each case, subserosal injections of isosulfan blue were used to identify the SLN. The SLNs were then sent fresh to the pathology laboratory for evaluation by IIC. A standard lymphadenectomy was performed in all cases. Postoperatively, the SLNs were evaluated by means of using hematoxylin and eosin staining. If these stains were normal, immunohistochemical analyses using carcinoembryonic antigen and cytokeratin were subsequently performed. SLNs were successfully identified in 46 cases (92%), and a total of 95 SLNs were harvested. The average number of SLNs was 1.9 with a range of one to six. More SLNs were found with gastric than with colonic lesions (2.8 vs. 1.8; $P = .017$). Evaluable IIC in 41 cases revealed metastatic disease in 10 SLNs, representing seven patients. Of the 34 patients with normal IIC, five were found to have positive SLNs on hematoxylin and eosin staining. An additional three patients were found to have positive SLNs only on immunohistochemical analysis. The overall sensitivity and specificity of IIC was 64% and 100%, respectively. This resulted in a positive predictive value of 100% and a negative predictive value of 86%. The use of IIC to evaluate SLNs from visceral malignancies is clearly feasible. When the IIC of the SLN is positive, the surgeon may feel confident that disease is actually present in the SLN. If there is a negative result, the technique may miss disease that is present on subsequent permanent sections. We do not recommend routine use of IIC; however, it may be of use in clinical trials. (J GASTROINTEST SURG 2003;7:687–691) 

KEY WORDS: Lymphatic mapping, colon cancer, gastric cancer, staging

Pathologic evaluation of resected specimens has long been a critical part of the practice of modern surgical oncology. Traditionally this analysis occurred well after the actual operation was completed. The interval between surgical intervention and final pathologic diagnosis inevitably increases anxiety for many patients. In addition, the inability to render an intraoperative diagnosis may change the nature of the operative procedure or result in return trips to the operating room for additional procedures. Various techniques have been implemented in an effort to provide intraoperative tissue diagnosis. Of these, frozen-section analysis has been the most widely used. Recently additional techniques have been introduced including the use of intraoperative imprint cytology (IIC). There are data supporting the use of IIC for evaluating sentinel lymph nodes (SLNs) in the setting of breast cancer and melanoma.

The SLN concept has emerged as a critical facet of the management of breast cancer and malignant

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melanoma only within the past decade. However, interest in lymphatic visceral mapping appeared as early as 1923 when Braithwaite[1] evaluated the flow of lymphatics near the ileocecal valve with indigo carmine. Then, in 1950, a vital blue dye (pontine sky blue) was used experimentally to map lymphatic drainage and was studied for toxicity, which was found to be low.[2] During the 1950s, vital dyes were used as an aid to identify the thoracic duct and to visualize nodes from gastric and pulmonary carcinomas to improve the completeness of lymphadenectomy.[3,4] The use of the term "sentinel lymph node" was first used by Cabanas[5] in his description of a technique to identify the first node draining a penile carcinoma. It was the pioneering work of Morton et al.[6] that made SLN mapping a standard procedure. The use of SLN techniques for melanoma and breast cancer has become routine. Consequently evaluation of this procedure for visceral malignancy is a natural progression of experience with the SLN technique.

Currently there is far less experience with SLN mapping for visceral malignancy than for melanoma and breast cancer. The utility of SLN techniques in visceral tumors such as gastric and colon cancer is being investigated. To the best of our knowledge, there is no literature evaluating the potential value of IIC for visceral SLN. We evaluated the feasibility of IIC in the intraoperative analysis of SLNs harvested from visceral malignancies.

## METHODS

SLN mapping was performed in 50 cases involving visceral malignancy from February 1999 to August 2001. Most of these cases involved colon cancer (n = 37), with fewer cases of gastric cancer (n = 12) and a single case that involved small bowel carcinoma. The protocol was approved by the institutional review board and all patients signed consent forms before surgery. The visceral SLN mapping technique has been described elsewhere,[7–9] but a brief description is provided here. After mobilization of the involved segment of bowel, the tumor was localized by palpation. Patients found to have gross nodal disease were excluded from this trial. Using a 25-gauge needle, 1 mL of isosulfan blue (Lymphazurin; U.S. Surgical Corp., Norwalk, CT) was injected into the subserosal plane around the edges of the tumor in four quadrants (Fig. 1). The subserosal injection was confirmed by a wheel raised in the bowel wall. The mesentery was observed for egress of the isosulfan blue via lymphatic vessels. Blue nodes or those nodes at the end of an afferent blue channel were considered SLNs. Typically a node demonstrated uptake of the dye within five minutes (Fig. 2). As soon as one lymph node demonstrated uptake of the isosulfan blue, this node was excised and sent for pathologic evaluation. Standard surgical resection (including lymphadenectomy) was then undertaken. The rest of the tissue was processed as a routine specimen.

Following harvest, the SLNs were sent fresh to the pathology laboratory for evaluation. IIC was performed on all SLNs. Hematoxylin and eosin and Diff-Quick stains were used for IIC, and diagnosis of positive or negative for metastatic disease was rendered. Standard lymphadenectomy was performed in all cases regardless of the IIC results. Postoperatively the SLNs were evaluated by standard hematoxylin and eosin staining techniques. If the hematoxylin and eosin studies were negative for disease, the SLNs were then subjected to immunohistochemical analysis using carcinoembryonic antigen and cytokeratin. If initial review of the hematoxylin and eosin–stained section was negative, an SLN protocol (consisting of an additional 3 hematoxylin and eosin–stained levels cut at 50 μ intervals in conjunction with immunohistochemical staining for cytokeratin and carcinoembryonic antigen) was performed on the first of the three levels. Immunohistochemical studies were carried out using the avidin-biotin-peroxidase complex method described previously. Immunohistochemical stains for cytokeratin were considered positive if strong immunoreactivity in cell clusters or individual cells that demonstrated anatomic and cytologic features of metastatic tumor cells were identified.

For the purposes of this report, a significant difference was defined as $P < 0.05$. Groups were compared via Student's $t$ tests and chi-square analysis as appropriate.

## RESULTS

The study group consisted of 50 patients undergoing exploratory operations for resection of primary malignancies: 35 colon, 14 gastric, and one small bowel carcinoma. SLNs were subsequently identified and harvested in 46 (92%) of the 50 patients. In the remaining four patients, the SLN could not be identified (n = 2) or the technique was abandoned secondary to the presence of bulk nodal disease (n = 2). Of the patients who were successfully mapped, 33 had colon cancer (18 males and 15 females, average age 67 years). Gastric cancers were successfully mapped in 12 patients (8 males and 4 females, average age 64 years). One of the colon lesions was a lymphoma, which was successfully mapped and stained true positive by IIC. The small

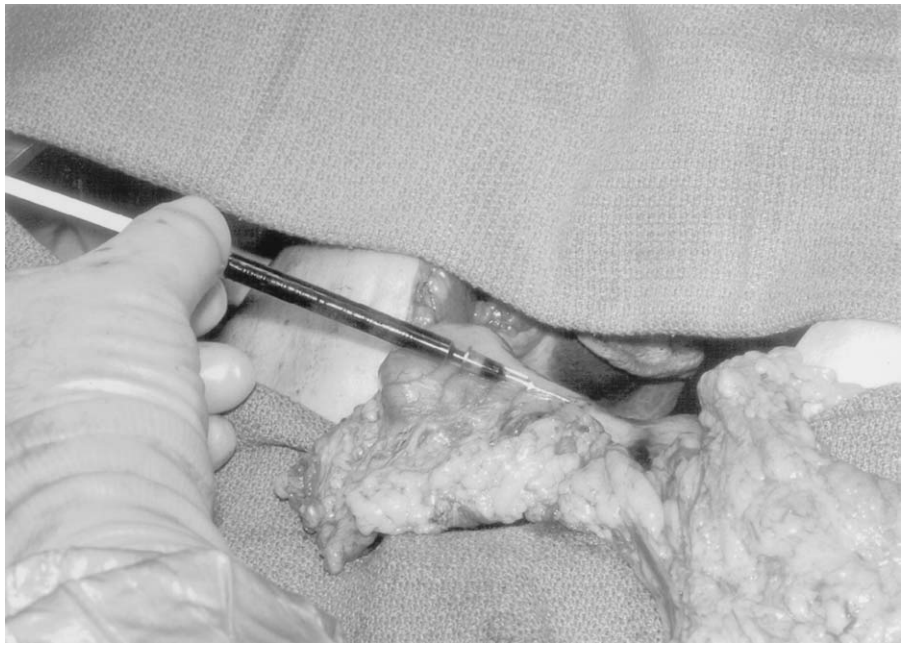

**Fig. 1.** Injection of isosulfan blue in a subserosal plane.

bowel adenocarcinoma occurred in a 27-year-old man. In five successfully mapped patients, IIC was not used, leaving 41 cases for analysis of IIC.

Gastric lesions had significantly more SLNs identified than did colonic lesions (2.8 [SD = 1.34] vs. 1.8 [SD = 1.04]; $P = 0.017$). A total of 33 SLNs were found in the patients with gastric cancer and 60 in those with colon cancer. For the entire group, the number of SLNs found in each case ranged from one to six, with an average of 1.9. IIC revealed metastatic disease in 10 SLNs, representing seven patients (17%). Of the seven patients with positive IIC, five had macrometastases (>2 mm) and two had micrometastases (<2 mm). Thirty-four patients (83%) were found to have negative SLNs by IIC. However, five patients found to have negative SLNs by IIC

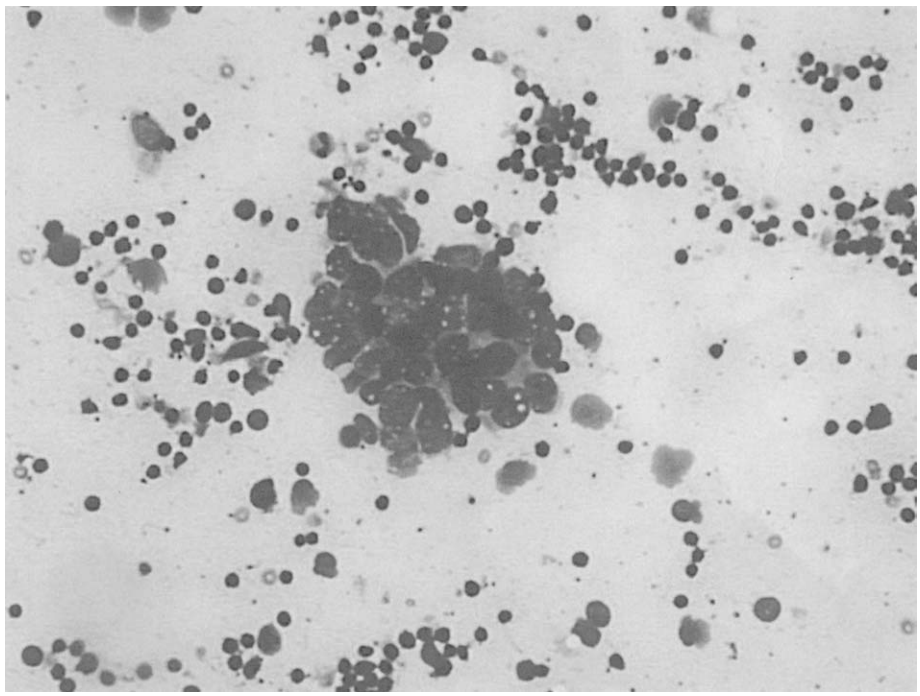

**Fig. 2.** Intraoperative imprint cytology or "touch preparation" of SLN from a patient with colon cancer.

were noted to have positive SLNs on subsequent hematoxylin and eosin evaluation. An additional three patients were found to have metastatic disease only on immunohistochemical analysis. Therefore, a total of 15 patients were found to be node positive after complete pathologic evaluation. Overall sensitivity and specificity of IIC was found to be 64% and 100%, respectively. This produced a positive predictive value of 100% and a negative predictive value of 86%. The sensitivity for the colonic and gastric lesions was 50% and 87%, respectively.

## DISCUSSION

A large body of literature supports the premise that SLN mapping and microscopic evaluation can reliably predict the remainder of the regional lymph node basin for breast cancer and melanoma. This approach may spare the patient a traditional lymphadenectomy and yield more data on nodal metastasis. Another key advantage of SLN mapping techniques is improved staging of nodal disease, which has resulted in upstaging in a significant number of mapped patients. Despite the wealth of experience with SLN mapping for solid tumors, very little is known about the applicability of SLN mapping for visceral malignancies. Furthermore, to the best of our knowledge this represents the first evaluation of intraoperative analysis of SLN from visceral sources in the literature.

At present there is no consensus on the use or the optimal method of intraoperative analysis of SLNs, although several techniques have been examined.[10] In 1999, the College of American Pathologists recommended that SLNs from breast cancer be examined intraoperatively by cytologic methods.[11] Previous SLN studies evaluating the use of frozen-section analysis have reported variable results, with accuracy ranging from 83% to 98%, sensitivity ranging from 58% to 87%, and specificity ranging from 99% to 100%.[11]

Several groups have studied the use of IIC in the evaluation of SLNs. The accuracy of these studies varies from 78% to 98%, sensitivity ranges from 29% to 94%, and specificity ranges from 88% to 100%.[11] Finally, a few groups have examined the utility of intraoperative evaluation of SLNs using combined frozen-section analysis and imprint cytology. The accuracy, sensitivity, and specificity of these studies are similar to that of frozen-section analysis or imprint cytology alone. Regardless of the methodology used, the wide disparity between the accuracy of these studies is, in part, due to the nonuniformity of the SLN examination and, in some studies, the low number of patients examined. Overall, for breast cancer and melanoma, sensitivity and accuracy are similar between frozen-section analysis and imprint cytologic evaluation.[10–14] The sensitivity of 47% found in this trial is similar to that reported for breast cancer and melanoma. However, the cost of frozen-section analysis is significantly greater than the cost of IIC. At our institution (as of December 2001) the cost of evaluating two SLNs is $131 via IIC vs. $356 by frozen-section analysis. Furthermore, similar to IIC for other sites, sensitivity seems to be much better for macrometastases (>2 mm) than for micrometastases.[13]

Lymphatic mapping and SLN techniques have revolutionized the practice of surgical oncology. The demand for optimal techniques for intraoperative tissue diagnosis has never been greater. Traditionally, frozen-section analysis has been the "gold standard" for rendering intraoperative diagnoses. However, IIC has been found to be a preferred alternative to frozen-section analysis in the evaluation of the SLNs harvested in the setting of breast cancer and melanoma. IIC has several advantages over frozen-section analysis. First, it is easy to perform, quick, and can be done at a fraction of the cost of frozen-section analysis. In addition, IIC conserves tissue and avoids freezing artifact, which allows for later evaluation of SLN by hematoxylin and eosin staining or immunohistochemical analysis. However, use of IIC requires expert cytopathologic support, which may not be available at all centers. We found that IIC can be effectively applied to visceral malignancies. When IIC of the SLN is positive, the surgeon may feel confident that disease is actually present in the SLN. However, the technique often misses disease that is present on subsequent permanent sections, resulting in poor sensitivity. IIC performed in the setting of visceral malignancy has a similar specificity and sensitivity when compared to the more well-known applications of the technique in breast cancer and melanoma.[13]

The rich lymphatics found in the stomach had once been thought to be a barrier to SLN procedures in gastric lesions. This does not seem to be a clinical problem as we and others have found.[3,9,10,16–19] However, the greater number of SLNs found in the gastric vs. the colon lesions underscores the differences in lymphatic drainage between the stomach and the colon.

The optimal extent of lymphadenectomy for gastric carcinoma has been the subject of intense debate for decades.[3,4] However, it seems clear that any benefit of lymphadenectomy is likely limited to those patients with nodal metastasis. The use of SLN mapping techniques to evaluate first-echelon nodal disease could serve as a trigger for extended nodal

dissection, if the presence of nodal disease can be confirmed intraoperatively. Unfortunately, the sensitivity of IIC found in this trial does not support using the results of IIC alone as an indication for more extensive lymphadenectomy. The greatest utility of SLN mapping for gastric cancer, however, does not hinge on its ability to predict the nodal basin or limit the lymphadenectomy, but rather on identifying the one node most likely to harbor metastasis. Once identified, this node can be studied more intensively than is practical to study all of the nodes. Evaluation of the SLN with immunohistochemical techniques has been employed in the management of breast cancer, upstaging approximately 10% of patients. This intensive pathologic analysis may yield micrometastases in gastric cancers that would elude traditional techniques.[15–19] Improvements in staging may be of particular importance in light of recent data confirming a survival benefit for patients with stage IB to III gastric cancers who receive adjuvant chemoradiotherapy.[20]

Lymphadenectomies associated with radical resection of the colon are not commonly thought of as morbid procedures. This has led some to question the utility of SLN for colonic adenocarcinoma. Unlike patients with breast cancer or melanoma, those undergoing resection for colon cancer are most likely to benefit through improved staging or the identification and resection of aberrant nodal drainage.

In our study, SLNs were resected to facilitate intraoperative analysis. SLNs can also be harvested after resection, either on a back table in the operating room or in the pathology laboratory. Although such ex vivo techniques can facilitate SLN mapping, they do have limitations for intraoperative evaluation. Specifically, dissection of the SLN after resection does not allow for evaluation of aberrant drainage pathways. In addition, sending the lymph nodes after resection could engender some delay in proceeding with the operative procedure. However, ex vivo SLN dissection is a reasonable option if no SLN is found in vivo, or if intraoperative analysis is not a consideration.

We believe that continued study of the technique of SLN mapping for visceral carcinoma is warranted. Similar to SLN applications for breast cancer and melanoma, IIC seems to have significant advantages over frozen-section analysis. The clinical impact of intraoperative analysis of SLNs in this setting is currently limited. However, the use of IIC for SLNs from visceral sources may become a valuable technique when such analysis will change the conduct of the operative procedure. However, we do not recommend IIC for cases of routine visceral SLNs, but we believe that it may be a useful tool to support clinical investigations.

REFERENCES

1. Braithwaite LR. Flow of lymph from the ileocecal angle. Br J Surg 1923;11:7.
2. Weinberg J, Greaney EM, Rawlings B, Haley TJ. The use and toxicity of pontamine sky blue. Science 1951;114:41–42.
3. Weinberg J, Greaney EM. Identification of regional lymph nodes by means of a vital staining dye during surgery of gastric cancer. Surg Gynecol Obstet 1950;90:561–567.
4. Cohn I, Leon W, Strug LH. Vital staining of the thoracic duct. Ann Surg 1958;148:867–870.
5. Cabanas RM. An approach for the treatment of penile carcinoma. Cancer 1977;39:456–466.
6. Morton DL, Wen DR, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch Surg 1992;127:392–399.
7. Saha S, Wiese D, Badin J, et al. Technical details of sentinel lymph node mapping in colorectal cancer and its impact on staging. Ann Surg Oncol 2000;7:120–124.
8. Waters GS, Geisinger KR, Garske DD, et al. Sentinel lymph node mapping for carcinoma of the colon: A pilot study. Am Surg 2000;66:943–946.
9. Hundley JC, Shen P, Shiver SA, et al. Lymphatic mapping for gastric adenocarcinoma. Am Surg 2002;68:931–935.
10. Joosten JJA, Strobbe LJA, Wauters CAP, et al. Intraoperative lymphatic mapping and the sentinel node concept in colorectal carcinoma. Br J Surg 1999;86:482–486.
11. Petris GD, Lev R, Siew S. Peritumoral and nodal muciphages. Am J Surg Pathol 1998;22:545–549.
12. Creager AJ, Geisinger KR, Shiver SA, et al. Intraoperative evaluation of sentinel lymph nodes for metastatic breast carcinoma by imprint cytology. Mod Pathol 2002;15:1140–1147.
13. Creager AJ, Shiver SA, Shen P, et al. Intraoperative evaluation of sentinel lymph nodes for metastatic melanoma by imprint cytology. Cancer 2002;94:3016–3022.
14. Fitzgibbons PL, Page DL, Weaver D, et al. Prognostic factors in breast cancer: College of American Pathologists Consensus Statement. Arch Pathol Lab Med 1999;124:966–978.
15. Sano T, Katai H, Sasako M, Maruyama K. Gastric lymphography and detection of sentinel lymph nodes. Recent Results Cancer Res 2000;157:253–258.
16. Siewart JR, Sendler A. Potential and futility of sentinel node detection for gastric cancer. Recent Results Cancer Res 2000;157:259–269.
17. Hiratsuka M, Miyashiro I, Ishikawa O, et al. Application of sentinel node biopsy to gastric cancer surgery. Surgery 2001;129:335–340.
18. Aikou T, Higashi H, Natsugoe S, et al. Can sentinel node navigation surgery reduce the extent of lymph node dissection in gastric cancer? Ann Surg Oncol 2001;8(9 Suppl):90S–93S.
19. Kitagawa Y, Kubota T, Otani Y, et al. Clinical significance of sentinel node navigation surgery in the treatment of early gastric cancer. Nippon Geka Gakkai Zasshi 2001;102:753–757.
20. McDonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345:725–730.

# The Hypertensive Lower Esophageal Sphincter: A Motility Disorder With Manometric Features of Outflow Obstruction

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The aim of this study was to define the clinical presentation, motility characteristics, and prevalence and patterns of gastroesophageal reflux in patients with hypertensive lower esophageal sphincter (HTLES). HTLES was defined by a resting pressure measured at the respiratory inversion point on stationary manometry of greater than 26 mm Hg (ninety-fifth percentile of normal). One hundred consecutive patients (80 women, 20 men; mean age 54.7 years, range 23 to 89 years), diagnosed with HTLES at our institution between September 1996 and October 1999, were studied. Patients with achalasia or other named esophageal motility disorders or history of foregut surgery were excluded, but patients with both HTLES and "nutcracker esophagus" were included. The most common symptoms in patients with HTLES were regurgitation (75%), heartburn (71%), dysphagia (71%), and chest pain (49%). The most common primary presenting symptoms were heartburn and dysphagia. The intrabolus pressure, which is a manometric measure of outflow obstruction, was significantly higher in patients with HTLES compared to normal volunteers. The residual pressure measured during LES relaxation induced by a water swallow was also significantly higher than in normal persons. There were no significant associations between any of the relaxation parameters studied (residual pressure, nadir pressure, duration of relaxation, time to residual pressure) and either the presence or severity of any symptoms or the presence of abnormal esophageal acid exposure. Seventy-three patients underwent 24-hour pH monitoring, and 26% had increased distal esophageal acid exposure. Compared to a cohort of patients with gastroesophageal reflux disease but no HTLES (n = 300), the total and supine periods of distal esophageal acid exposure were significantly lower in the patients with HTLES and abnormal acid exposure. Patients with HTLES frequently present with moderately severe dysphagia and typical reflux symptoms. Approximately one quarter of them have abnormal esophageal acid exposure on pH monitoring. Patients with HTLES have significantly elevated intrabolus and residual relaxation pressures on liquid boluses, suggesting that outflow obstruction is present. (J GASTROINTEST SURG 2003;7:692–700) 

KEY WORDS: Esophagus, sphincter, hypertensive, obstruction, dysphagia

The hypertensive lower esophageal sphincter (HTLES) was first described by Code et al.[1] in 1960. The subsequent small numbers of studies that have reported on this motility condition have included relatively few patients, and some studies reported heterogeneous study groups that included patients with achalasia, patients with diffuse esophageal spasm, and patients who had undergone antireflux surgery, in addition to those with HTLES.[2–5] Clinical features of HTLES have not been thoroughly defined and, in particular, the relationship between this condition and gastroesophageal reflux disease (GERD) is unclear. As a result, the importance of finding HTLES on manometric examination remains uncertain.

This study was undertaken to define, in a large number of patients, the clinical and manometric features of patients with HTLES. An additional aim was to identify associations between the presence of HTLES and esophageal acid exposure, compared to the pattern in a control group of patients with abnormal acid exposure but no HTLES.

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## PATIENTS AND METHODS

### Study Population

The medical and esophageal laboratory records of 100 consecutive patients with HTLES investigated at this institution over the 3-year period from September 1996 to October 1999 were retrospectively reviewed. The diagnosis of HTLES was made when the lower esophageal sphincter (LES) resting pressure measured at the respiratory inversion point on stationary manometric examination was greater than 26 mm Hg (ninety-fifth percentile of normal).[6] Exclusion criteria were a history of previous foregut surgery or the presence of achalasia, scleroderma, diffuse esophageal spasm, and nonspecific esophageal motility disorders. Because we also investigated the association between dysphagia and HTLES, patients were excluded if dysphagia might have been caused by significant esophageal body hypomotility, which was defined as a mean contraction amplitude in the distal two esophageal body channels of less than 25 mm Hg. Patients with "nutcracker esophagus" were included because it is recognized that HTLES and nutracker esophagus are overlapping conditions and, to some extent, represent part of a spectrum of hypercontraction of the distal esophagus.

All patients completed a structured symptom questionnaire. Table 1 outlines the scoring system used to measure symptom severity for heartburn. Regurgitation was graded as follows: 0 (none); 1 (minimal, occasional episode after straining or a large meal); 2 (moderate, predictable with position change or straining); or 3 (severe, affects daily life, possibly with a history of aspiration). Dysphagia was graded as 0 (none), 1 (occasionally with coarse foods; lasting a few seconds), 2 (moderate; requiring clearing with liquids), or 3 (severe; requiring a semiliquid diet and with a history of meat impaction). Patients were requested to identify the primary symptom driving their need for medical attention.

### Manometry

***Standard Stationary Manometry.*** Stationary manometry was performed using a water-perfused eight-channel catheter (Synectics Medtronic, Stockholm, Sweden; and Arndorfer, Greendale, Wisconsin). The gastric baseline pressure was used as a zero reference for pressure measurement. The distal border of the LES was marked by a persistent rise in pressure of more than 2 mm Hg above the gastric baseline pressure, whereas the proximal border of the LES was recorded as the point at which the pressure fell to the negative pressure of the intrathoracic esophageal body. The resting pressure of the LES was measured at the respiratory inversion point, as described previously.[6] The intra-abdominal length of the LES was measured as the length from the distal border of the LES to the respiratory inversion point.

Esophageal body function was assessed by placing the most proximal pressure port of the motility catheter 1 cm below the lower border of the upper esophageal sphincter with the other four pressure ports trailing at 5 cm intervals. The mean contraction amplitudes measured at the distal two recording levels in the esophagus in response to ten 5 ml water swallows were recorded.

***Measurement of LES Relaxation.*** LES relaxation in response to five swallows of 5 ml water was measured via a catheter with four circumferential side holes positioned within the LES high-pressure zone, as described previously.[7] Two LES relaxation pressure measurements, the residual pressure and the nadir pressure, were made. The residual pressure in the LES was measured at the moment when the bolus was judged to be flowing through the sphincter. This moment was determined as follows: the upstroke of the peristaltic wave in the transducer 5 cm proximal to the sphincter was recorded. This point indicates luminal closure, and consequently the bolus is distal to this proximal transducer. Combined radiologic and manometric studies indicate that a 5 ml bolus has reached the sphincter at that point.[8] The upstroke of the peristaltic wave 5 cm proximal to the LES is an objective and readily identifiable moment at which to measure the residual pressure in the LES. The method is shown in Fig. 1. The LES relaxation nadir pressure is simply the pressure at the lowest point of the relaxation.

Two time measurements for LES relaxation were made: the time from the onset of relaxation to the residual pressure, and the total duration of relaxation. For both measurements, the onset of LES relaxation was considered to occur at the time of the swallowing event measured in the pharynx. The time from onset of LES relaxation to the residual pressure was measured. The duration of the relaxation was measured from the onset of relaxation to the end of relaxation. The end of relaxation was marked by the onset of the postrelaxation contraction. LES relaxation parameters were compared with those of 40 volunteers.[9]

**Table 1.** Symptom severity scoring system for heartburn

| | |
|---|---|
| 0 | No symptoms |
| 1 | Mild symptoms, minimal or occasional episodes, no prior medical visit |
| 2 | Moderate symptoms, frequent or prolonged episodes, reason for visit |
| 3 | Severe symptoms, constant disability in activities of daily life |

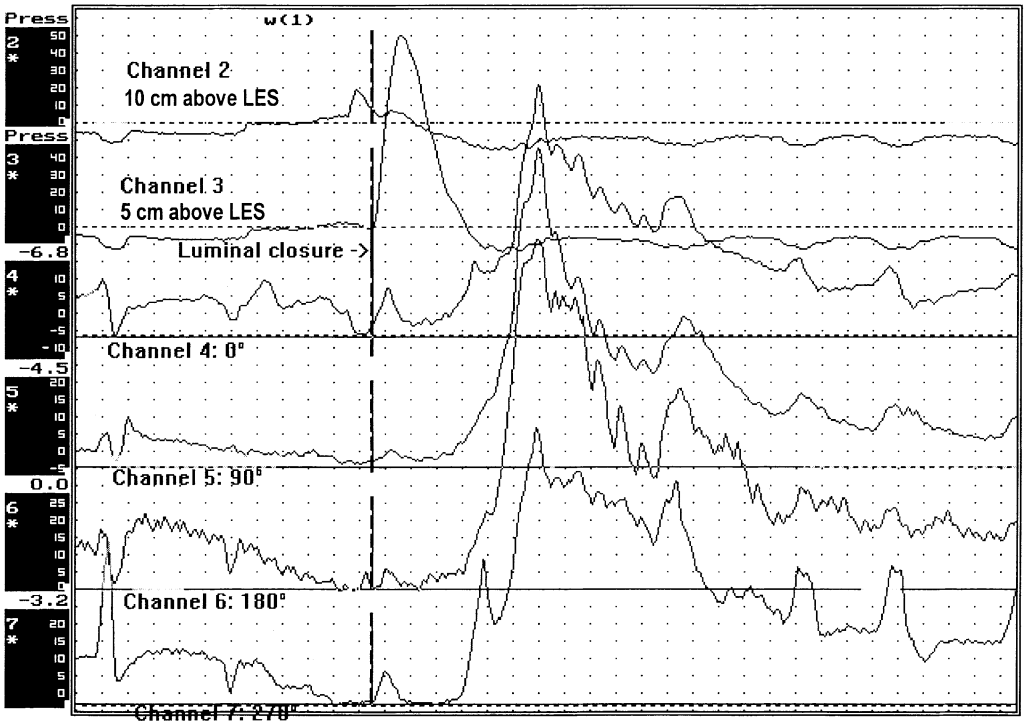


**Fig. 1.** Tracing demonstrating relaxation of the LES in response to a swallow. The residual pressure is measured at the point where the upstroke of the peristaltic wave in the channel 5 cm above the LES indicates luminal closure. (From Crookes et al. Static and dynamic function of the lower esophageal sphincter before and after laparoscopic nissen fundoplication. J GASTROINTEST SURG 1997;1:499–504.)

***Measurement of the "Ramp" Intrabolus Pressure.*** The ramp intrabolus pressure is a waveform on esophageal manometry that precedes the peristaltic upstroke resulting from a swallow and may be an indicator of outflow resistance.[10] Features of the ramp intrabolus pressure were measured in the esophageal body channel positioned 5 cm above the LES relaxation channels, as described elsewhere[10] and as shown in Fig. 2. The mean of the measurements made in response to five wet swallows, each 5 ml of water, were used. The bolus pressure parameters measured were the overall mean pressure, halfway mean pressure, bolus tail pressure, and bolus duration (see Fig. 2). The duration was measured from the onset of the bolus when the amplitude increased above baseline pressure to the termination at the onset of the peristaltic manometric upstroke (see Fig. 2). The intrabolus pressure measurements were compared to those obtained in 53 healthy individuals.[11]

### 24-Hour pH Monitoring

Twenty-four-hour distal esophageal pH monitoring was performed in 73 patients (73%). Proton pump inhibitor medications were discontinued at least 2 weeks before testing, and other medications were discontinued at least 72 hours before testing. The pH monitoring was performed, as previously described, by positioning a glass pH electrode (Mui Scientific, Toronto, Ontario, Canada) 5 cm above the manometrically measured upper border of the LES.[12] The electrode was connected to a digital recording device (Microdigitrapper; Synectics Medical, Irving, TX) and pH was continually monitored for 24 hours. The patients' diets were limited to foods having a pH in the range of 5 to 7. The stored data were transferred to a personal computer and analyzed using a standard software package (Multigram; Gastrosoft, Irving, TX). A composite score greater than 14.7 (ninety-fifth percentile of normal) denoted abnormal esophageal acid exposure.[13]

### Statistical Analysis

Statistical analysis was performed using SSPS version 8.0 software (SPSS, Inc., Chicago, IL). The Mann-Whitney U test was used to compare the distribution of continuous data between individual groups. Values are expressed as medians and interquartile range (twenty-fifth to seventy-fifth percentiles).

## RESULTS

Eighty of the 100 patients were female, and the median age for all patients was 54.5 years (range 23

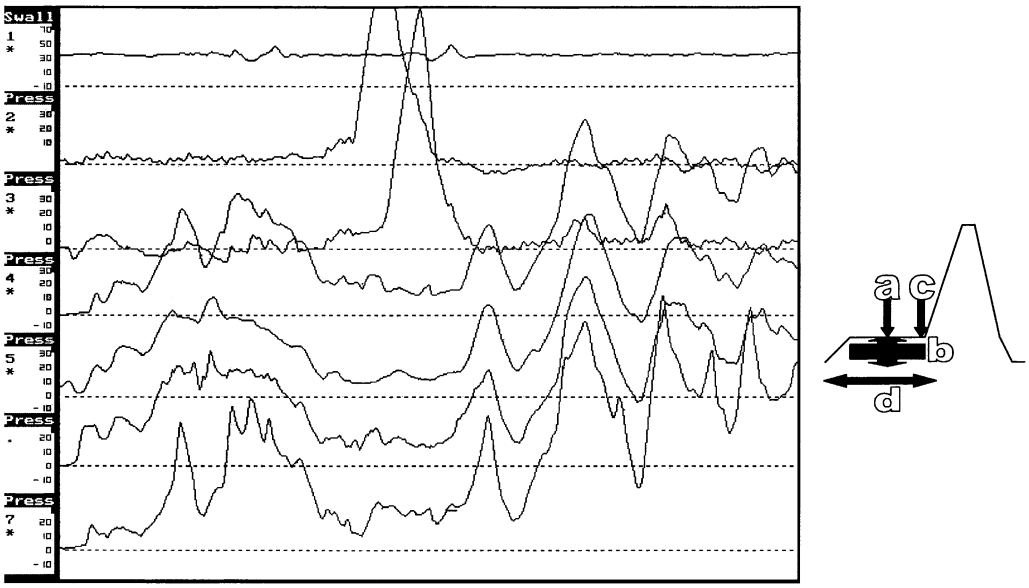


**Fig. 2.** (*Left*) Motility tracing of a hypertensive LES. Channels 4–7 demonstrate the 4 circumferential side holes positioned in the LES high pressure zone. In response to 5 ml water increased residual pressures are measured at the time of the upstroke of the peristaltic wave in the tracing 5 cm above the LES (channel 3). (*Right*) Schematic analysis of the "ramp" intrabolus pressure 5 cm above the LES: *a*, half–way mean intrabolus pressure; *b*, overall mean intrabolus pressure; *c*, bolus tail pressure; *d*, duration of intrabolus pressure.

and 89 years). HTLES was present in 7.2% of the total 1390 standard manometries performed at this institution during the 3-year study period.

The most frequently reported symptoms for patients with HTLES were regurgitation in 75 patients (75%), heartburn in 71%, dysphagia in 71%, chest pain in 49%, and nausea in 51%. Twenty-one percent of patients had all five of these symptoms, 41% had four or more, and 72% had three or more. No patient was asymptomatic. The distribution of the severity of these five symptoms is presented in Fig. 3. As shown, moderately severe symptoms were frequently reported for the symptoms regurgitation and heartburn, whereas the symptom that patients considered most frequently to be severe was dysphagia. Although regurgitation was the most frequently reported symptom overall, heartburn and dysphagia were the most common primary presenting

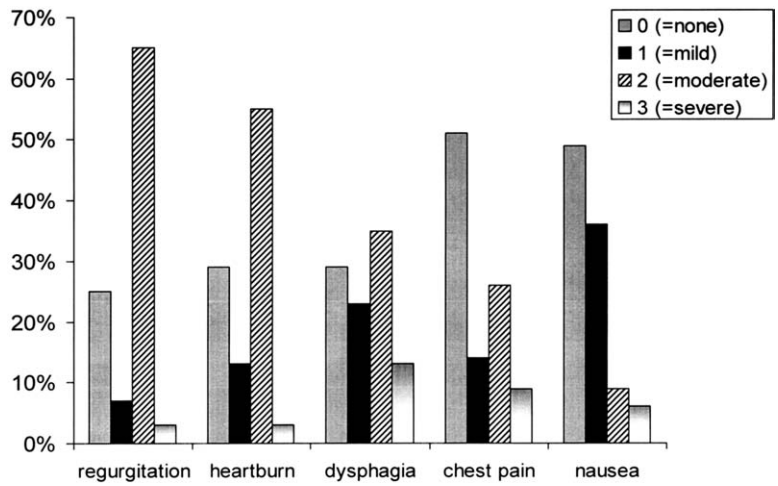


**Fig. 3.** Distribution of the severity of the five most frequently reported symptoms for patients with HTLES.

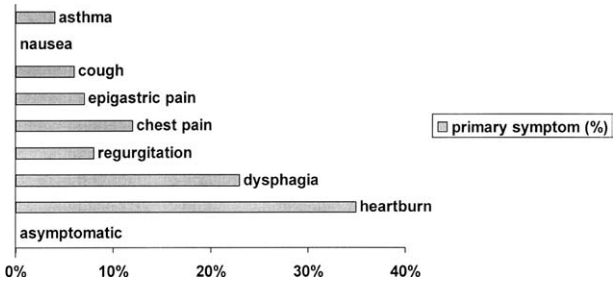


**Fig. 4.** Frequency of primary presenting symptoms for patients with HTLES.

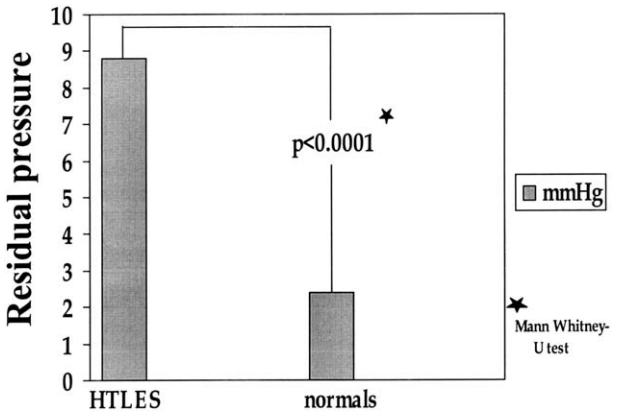


**Fig. 5.** LES residual pressure measured at the point coinciding with the upstroke of the peristaltic wave 5 cm above the LES in HTLES compared to normals.

complaints (Fig. 4). The median duration of the primary symptoms was 3 years (range 2 to 408 months).

The resting LES pressure measurements for the 100 patients with HTLES are presented in Table 2. Very high LES resting pressures were measured at the respiratory inversion point in some patients, and the ninety-fifth percentile value for HTLES group was 49.5 mm Hg. Nutcracker esophagus, defined by the presence of mean distal amplitudes in the distal esophagus greater than 180 mm Hg, was present in 23 patients (23%). Thirty-eight patients had manometric evidence of a hiatal hernia with a double hump.

As shown in Fig. 5, the residual LES relaxation pressure was significantly higher in the patients with HTLES (median 8.9 mm Hg; range 5.6 to 15.1 mm Hg) compared to a cohort of asymptomatic volunteers (median 2.4 mm Hg; range 1.3 to 4.0 mm Hg [$P < 0.0001$]).[9] There was no significant difference in the other relaxation parameters in patients with HTLES compared to the volunteer group (see Table 2).

The mean (halfway) intrabolus pressure measured 5 cm above the LES was significantly higher in patients with HTLES (median 9.1 mm Hg; range 5.4 to 13.3 mm Hg) compared to the intrabolus pressure measured in 53 asymptomatic volunteers (normal values according to Nisim et al.[11]) (median 6.0 mm Hg; range 3.8 to 8.0 mm Hg [$P < 0.0001$]) (see Fig. 6). There was no significant difference in the duration of intrabolus pressure in patients with HTLES compared to the 53 volunteers ($P = 0.24$).[11] The median and (twenty-fifth to seventy-fifth percentile) values for the other intrabolus measurements for the HTLES group are shown in Table 2.

There was no significant difference in any of the manometric measurements other than distal esophageal body contraction amplitudes for the subgroup of 23 patients with a nutcracker esophagus compared to the HTLES patients without a nutcracker esophagus. Even with the inclusion of the patients with nutcracker esophagus in the HTLES group, there was no significant difference between the contraction amplitudes measured at the two distal esophageal body levels in patients with HTLES compared to a cohort of 53 asymptomatic volunteers.[11]

**Table 2.** Manometry measurements in 100 patients with HTLES

| Measurements | HTLES (median) | HTLES (interquartile range) | Normal (median) | *P* value |
|---|---|---|---|---|
| Resting LES | n = 100 | | n = 50 | |
| LES pressure (mmHg) | 31.5 | 28–37.5 | 13.8 | <0.0001 |
| Overall length (cm) | 3.6 | 3–4.2 | 3.6 | 0.27783 |
| Intra-abdominal length (cm) | 1.8 | 1.4–2.5 | 2.2 | 0.15294 |
| LES relaxation | n = 100 | | n = 40 | |
| Residual pressure (mmHg) | 8.9 | 5.6–15.1 | 2.4 | <0.0001 |
| Nadir pressure (mmHg) | 0.7 | −2.1–4 | — | — |
| Duration of relaxation (sec) | 8.1 | 7.7–8.6 | 8.4 | 0.46 |
| Time to residual pressure (sec) | 5.4 | 4.8–5.8 | 5.7 | 0.15 |
| INTRABOLUS | n = 100 | | n = 53 | |
| Mean overall pressure (mmHg) | 8.9 | 5.7–13 | — | — |
| Mean half-way pressure (mmHg) | 9.1 | 5.4–13.3 | 6 | <0.0001 |
| Bolus tail pressure (mmHg) | 14.2 | 9.2–22 | — | — |
| Duration (sec) | 4.6 | 3.6–5.7 | 5 | 0.2368 |

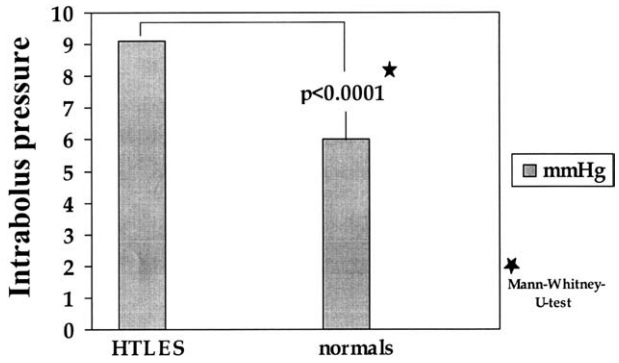


**Fig. 6.** Mean intrabolus pressure measured at the contraction wave 5 cm above the LES in HTLES compared to normals.

There were no statistically significant associations between the preceding manometric measurements and the presence or severity of the five most frequent symptoms (Mann-Whitney U test; data not shown). This lack of a significant association was found even when the patients were divided according to symptom severity scores, for example, between HTLES patients with no or mild dysphagia compared to those with moderate or severe dysphagia. Patients were divided into three groups according to LES pressures (26 to 35 mm Hg, n = 69; 36 to 46 mm Hg, n = 20; >46 mm Hg, n = 11). An analysis (Wilcoxon and Fisher) of the groups was made according to graded (1 to 3) symptoms of the following: heartburn, $P = 0.35$; chest pain, $P = 0.43$; regurgitation, $P = 0.32$; dysphagia, $P = 0.37$; and nausea, $P = 0.26$. The same tests were done with a subdivision of the median LES pressures into two groups (<31.4 mm Hg and >31.4 mm Hg). There was no statistical difference between the groups.

There were also no significant differences between the frequencies of symptoms in the group of 38 HTLES patients with LES relaxation to normal levels (residual pressure <7.5 mm Hg; ninety-fifth percentile of normal) compared to the 62 patients with incomplete relaxation (residual pressure ≥7.5 mm Hg) (heartburn, $P = 0.7912$; chest pain, $P = 0.6796$; regurgitation, $P = 0.4355$; dysphagia, $P = 0.1517$; nausea, $P = 0.9964$). Chest pain was the only symptom that was reported more frequently by patients with an abnormally high bolus pressure ($P = 0.0131$).

Nineteen (26%) of the 73 patients with HTLES who underwent 24-hour pH distal esophagal monitoring had increased acid exposure, as evidenced by an increased composite (DeMeester) score. The median DeMeester score among these patients was 22.7 (range 18.9 to 33.5). The total percentage of time with a pH < 4 was 6.7% (normal range < 4.4%) (Table 3). This abnormal acid exposure took place in the upright and postprandial periods (see Table 3). Most (14 [73%] of 19) of the patients with increased distal esophageal acid exposure on 24-hour pH monitoring presented with a primary symptom of heartburn. The other primary symptoms included regurgitation, chest pain, cough, asthma, and epigastric pain.

Compared to a cohort of 300 patients with an abnormal 24-hour pH score and symptoms but no HTLES (209 males, 91 females), patients with HTLES plus GERD had esophageal exposure to pH < 4 for a significantly lower percentage for the total monitored time (9.2% vs. 6.7%; $P = 0.004$) (Fig. 7) and for the supine time (7% vs. 2.9%; $P = 0.02$) (Fig. 8). The two groups were similar in exposure time to pH < 4 during the upright period and for the total number of single episodes of reflux, or the total number of reflux episodes longer than 5 minutes (data not shown).

## DISCUSSION

The pathophysiology and clinical significance of the HTLES is uncertain.[5,14–18] Previous studies with heterogeneous groups of patients reported that the most predominant symptoms were dysphagia (37% to 100%) and chest pain (33% to 100%).[2–5,14–17] In contrast, we found that patients who had HTLES presented most frequently with the typical reflux symptoms of regurgitation (75%) and heartburn (71%), although dysphagia (71%) and chest pain (49%) were also frequently reported. The lower frequency of chest pain in the current study compared

**Table 3.** Patterns of gastroesophageal reflux in patients with HTLES (% time pH < 4 in 24 hour esophageal pH-study)

| % time pH < 4 | Total time (normal <4.4%) | Upright period (normal <8.4%) | Supine period (normal <3.4%) | Postprandial period (normal <8.2%) |
|---|---|---|---|---|
| Median | 6.7 | 9.1 | 2.9 | 8.8 |
| 5th percentile | 3.6 | 0 | 0 | 0 |
| 95th percentile | 13.3 | 17.9 | 15.2 | 32.3 |

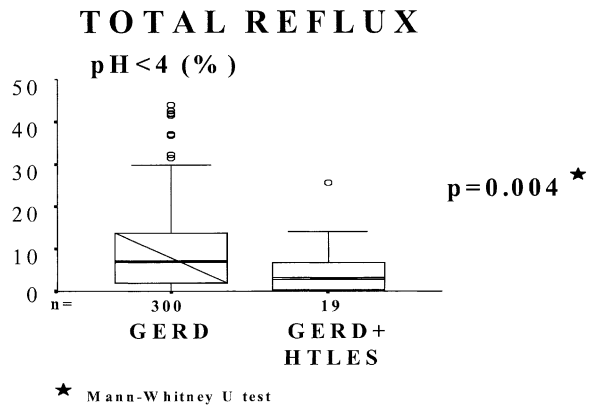


**Fig. 7.** Total reflux (% pH < 4) in HTLES with GERD compared to a cohort of patients with GERD but no HTLES (Stem-and-Leaf Plot for GERD versus GERD + HTLES).

to other studies may reflect a tendency for patients with chest pain to be referred to a gastroenterologist rather than a surgeon. Regarding the primary symptoms alone, heartburn (35%) and dysphagia (23%) were the prevailing complaints, whereas regurgitation was the primary symptom in only 8% and chest pain in 12%.

The patients with both HTLES and abnormal esophageal acid exposure (n = 19) most frequently reported having heartburn (74%), whereas 11% complained of pulmonary symptoms such as cough or asthma. This spectrum of symptoms is similar to that reported by Katzka et al.[17] who found that 50% of patients presented with heartburn and 50% had chest pain. We found no significant association between the symptoms and any manometric measurement. Waterman et al.[5] also found no difference in the LES parameters of the patients with or without dysphagia or chest pain.

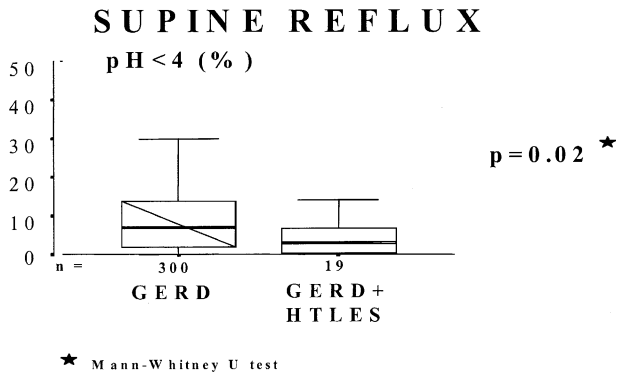


**Fig. 8.** Supine reflux (% pH < 4) in HTLES with GERD compared to a cohort of patients with GERD but no HTLES (Stem-and-Leaf Plot for GERD versus GERD + HTLES).

Although previous studies have reported that LES relaxation is normal (>75% relaxation from the LES resting pressure) in patients with HTLES,[16,19] our assessment of LES dynamics indicates that LES relaxation is frequently abnormal. Most of the patients in our study (62%) had incomplete LES relaxation after wet swallows, with a residual pressure greater than 7.5 mm Hg (ninety-fifth percentile of normal).[9] It may be speculated that the abnormal LES relaxation characteristics explain the patients' complaints, but in our study the symptoms reported by those with normal and abnormal LES relaxation were similar.

We found that the mean "ramp" intrabolus pressure was significantly elevated in patients with HTLES compared to a group of normal individuals. The intrabolus pressure is a waveform on esophageal manometry that precedes the peristaltic upstroke resulting from a swallow. The finding of an increased intrabolus pressure in these patients, who have both high resting LES pressures and incomplete LES relaxation, supports the possibility that the intrabolus pressure is an indicator of esophageal outflow resistance. Few previous studies investigated the intrabolus pressure, its modulation by bolus volume and viscosity, and its association with esophageal outflow obstruction. A study by Ren et al.,[20] in which concurrent esophageal manometry and video fluoroscopy were used, suggested that the pressure distribution within the bolus results from both the force generated by esophageal muscle contractions, which serves to propel the bolus, and from the forces resisting the bolus movement. These investigators concluded that factors producing resistive forces may indirectly affect pressure in the lumen-occluded region via mechanisms that are not hydrodynamically determined, such as altered muscle preload or neurogenic feedback mechanisms.[20] If this concept is correct, the elevated intrabolus pressure in patients with HTLES may be an important indicator of the pressure generated by these resistive forces. Stein et al.[21] suggested that, compared to standard manometry, ambulatory esophageal motility monitoring provides a more precise classification of esophageal motor disorders and more sensitively detects abnormal esophageal motor activity. An unpublished ambulatory manometry study from this department found that significantly increased bolus pressures were present in patients with HTLES when either liquid or solid boluses were ingested.

Contraction amplitudes consistent with a diagnosis of nutcracker esophagus were found in 23% of the patients with HTLES. The patients with elevated esophageal body contraction amplitudes were more likely to have chest pain. A nutcracker esophagus is

common in patients with HTLES, and previous reports documented this finding in up to 56% of patients with HTLES.[3,5,15,18] In our study, manometric measurements, apart from the distal esophageal body contraction amplitudes, were similar in patients with and without nutcracker esophagus. The cause of the high distal esophageal body amplitudes remains uncertain but may result, as proposed by Kaye,[22] from compensation of the smooth musculature adjacent to the hypertensive sphincter.

Several methods have been used to assess the functional significance of HTLES.[5,18] Barium esophagography studies reported by Waterman et al.[5] found either no anatomic abnormality or only a slight narrowing of the gastroesophageal junction. Furthermore, there was no esophageal emptying abnormality with the use of either liquid barium or solid boluses in those studies, leading the authors to conclude that the manometric diagnosis of HTLES was without any significant relevance to bolus progression.[5] In contrast, Freidin et al.[18] identified a delay in bolus transit through the gastroesophageal junction in 25% of their patients with HTLES. Results of upper gastrointestinal endoscopy have been reported to be typically normal in patients with HTLES. Similarly, scintigraphic esophageal emptying studies have found either normal transit or only minimal retention.[3,15–17]

Twenty-six percent of the patients with HTLES who underwent 24-hour pH monitoring in our study had increased esophageal acid exposure. This finding is very similar to that reported by Katzka et al.[17] who considered that transient LES relaxations were likely to account for the apparent paradox of abnormal reflux in patients with this disorder. Somewhat surprisingly, we were not able to demonstrate decreased LES resting residual or nadir pressures in HTLES patients with GERD compared to HTLES patients without GERD. Because only patients with normal esophageal body function were in the study group, reduced esophageal clearance is unlikely to be the cause of the increased acid exposure found in some patients in our study. Similar to Katada et al.,[17] we also found no correlation between the DeMeester score and the residual pressure among the patients with a positive pH test.[3]

We found a significantly lower total and supine percentage of time with a pH $< 4$ in patients with HTLES when compared to a cohort of 300 patients with GERD. Others have similarly shown that patients with both HTLES and GERD have less reflux than those with GERD without HTLES, and patients with HTLES rarely develop advanced grades of esophagitis.[17] Of the 10 patients with HTLES and GERD who underwent endoscopy in the study by Katzka et al.,[17] nine had normal examination results. It is possible that the hypertensive LES may offer protection from increased reflux, especially in the supine position.

The treatment of HTLES remains controversial. Our study suggests that there is an outflow obstruction in HTLES, and this should therefore be the focus of any therapy. Smooth muscle relaxants such as calcium channel blockers or nitroglycerin are the usual first treatments offered to symptomatic patients.[23] The more severe or resistant cases may require pneumatic dilatation, botox injection, or myotomy.[23–25]

Because there is no evidence to suggest that HTLES is caused by gastroesophageal reflux, we assume that the high pressure in the LES and the gastroesophageal reflux should be addressed separately. If both conditions are separate entities, medical management would resolve into a trial of antacid therapy to address the reflux. Katza et al.[17] successfully treated nine patients who had both HTLES and gastroesophageal reflux with antireflux medication. Another three patients in their series did not respond to medication and were referred for fundoplication, again with good results. According to their report, the addition of a myotomy would appear to be unnecessary, and we must assume that the hypertensive LES is also related to the reflux. Patients who do not have gastroesophageal reflux have been treated successfully with calcium channel blockers, but long-term follow-up is lacking.[3,26] A surgical antireflux procedure will control reflux and is an essential addition for patients who undergo myotomy. Champion et al.[27] have already reported on 16 patients with a hypertensive LES who underwent myotomy and posterior fundoplication with good results. A total fundoplication would not be contraindicated because the body motility in these patients is adequate.

REFERENCES

1. Code CF, Schlegel JF, Kelley ML Jr, Olsen AM, Ellis FHJ. Hypertensive gastroesophageal sphincter. Proc Mayo Clin 1960;35:391–399.
2. Bremner CG. The hypertensive lower esophageal sphincter. In: Stipa S, Belsey RHR, Moraldi A, eds. Serono Symposium No. 43. "Medical and Surgical Problems of the Esophagus." London and New York: Academic Press, 1981, pp 241–245.
3. Katada N, Hinder RA, Hinder PR, Lund RJ, Perdikis G, Stalzer RA, McGinn TR. The hypertensive lower esophageal sphincter. Am J Surg 1996;172:439–442.
4. Pedersen SA, Alstrup P. The hypertensive gastroesophageal sphincter. A manometric and clinical study. Scand J Gastroenterol 1972;7:531–534.
5. Waterman DC, Dalton CB, Ott DJ, Castell JA, Bradley LA, Castell DO, Richter JE. Hypertensive lower esophageal sphincter: What does it mean? J Clin Gastroenterol 1989; 1:139–146.

6. Zaninotto G, DeMeester TR, Schwizer W, Johansson KE, Cheng SC. The lower esophageal sphincter in health and disease. Am J Surg 1988;155:104–111.
7. Crookes PF, Ritter MP, Bremner CG, DeMeester TR. Static and dynamic function of the lower esophageal sphincter before and after laparoscopic Nissen fundoplication. J GASTROINTEST SURG 1997;1:499–504.
8. Kahrilas PJ, Dodds WJ, Hogan WJ. Effect of peristaltic dysfunction on esophageal volume clearance. Gastroenterology 1988;94:73–80.
9. Bremner CG, Hamrah P, Hashemi M, et al. Lower esophageal sphincter (LES) relaxation. A standardized method of analysis. Gastroenterology 1999;116:G4196.
10. Bremner CG, DeMeester TR, Bremner RM, Mason RJ, eds. Esophageal Motility Testing Made Easy. St. Louis: Quality Medical Publishing, 2001.
11. Nisim AA, Gastal OL, Johansson J, Campos GM, Hashemi M, Lord RVN, Theisen J, Crookes PF, DeMeester TR, Bremner CG. A manometric indicator of esophageal outflow resistence: Ramp intrabolus pressure. Gastroenterology 1999; 116:S0036.
12. Jamieson JR, Stein HJ, DeMeester TR, Bonavina L, Schwizer W, Hinder RA, Albertucci M. Ambulatory 24-hour esophageal pH monitoring: Normal values, optimal thresholds, specificity, sensitivity, and reproducibility. Am J Gastroenterol 1992;87:1102–1111.
13. Johnson LF, DeMeester TR. Development of the 24-hour intraesophageal pH monitoring composite scoring system. J Clin Gastroenterol 1986;8(Suppl 1):52–58.
14. Graham DY. Hypertensive lower esophageal sphincter: a reappraisal. South Med J 1978;71(Suppl 1):31–37.
15. Sullivan SN. The supersensitive hypertensive lower esophageal sphincter. Precipitation of pain by small doses of intravenous pentagastrin. J Clin Gastroenterol 1986;8:619–623.
16. Bassotti G, Alunni G, Cocchieri M, Pelli MA, Morelli A. Isolated hypertensive lower esophageal sphincter. Clinical and manometric aspects of an uncommon esophageal motor abnormality. J Clin Gastroenterol 1992;14:285–287.
17. Katzka DA, Sidhu M, Castell DO. Hypertensive lower esophageal sphincter pressures and gastroesophageal reflux: An apparent paradox that is not unusual. Am J Gastroenterol 1995; 90:280–284.
18. Freidin N, Traube M, Mittal RK, McCallum RW. The hypertensive lower esophageal sphincter. Manometric and clinical aspects. Dig Dis Sci 1989;34:1063–1067.
19. McBride PJ, Hinder RA, Filipi C, Raiser F, Katada N, Lund RJ. Surgical treatment of spastic conditions of the esophagus. Int Surg 1997;82:113–118.
20. Ren J, Massey BT, Dodds WJ, Kern MK, Brasseur JG, Shaker R, Harrington SS, Hogan WJ, Arndorfer RC. Determinants of intrabolus pressure during esophageal peristaltic bolus transport. Am J Physiol 1993;264:G407–G413.
21. Stein HJ, DeMeester TR, Eypasch EP, Klingman RR. Ambulatory 24-hour esophageal manometry in the evaluation of esophageal motor disorders and noncardiac chest pain. Surgery 1991;110:753–761.
22. Kaye MD. Anomalies of peristalsis in idiopathic diffuse oesophageal spasm. Gut 1981;22:217–222.
23. Richter JE, Dalton CB, Bradley LA, Castell DO. Oral nifedipine in the treatment of noncardiac chest pain in patients with the nutcracker esophagus. Gastroenterology 1987;93:21–28.
24. Jamieson WR, Miyagishima RT, Carr DM, Stordy SN, Sharp FR. Surgical management of primary motor disorders of the esophagus. Am J Surg 1984;148:36–42.
25. Traube M, Lagarde S, McCallum RW. Isolated hypertensive lower esophageal sphincter: Treatment of a resistant case by pneumatic dilatation. J Clin Gastroenterol 1984;6:139–142.
26. Nasrallah SM, Tommaso CL, Singleton RT, Backaus EA. Primary esophageal motility disorders: Clinical response to nifedipine. South Med J 1985;78:312–315.
27. Champion JK, Delisle N, Hunt T. Laparoscopic esophagomyotomy with posterior partial fundoplication for primary esophageal motor disorders. Surg Endosc 2000;14:746–749.

# Effect of Colonic Distention on Ileal Motor Activity With Evidence of Coloileal Reflex

*Ahmed Shafik, M.D., Ph.D., Ali A. Shafik, M.D., M.Ch., Ismail Ahmed, M.D., M.Ch.*

Chyme delivery from the ileum to the colon is controlled by various neurologic and hormonal factors, many of which remain to be identified. In this report we investigated the effect of colonic distention on ileal motility with the aim of identifying the mechanism of chyme delivery from the ileum to the colon. The right colon of 16 healthy volunteers (12 men and 4 women; mean age 36 ± 9 years standard deviation) was distended by a balloon that was filled with saline solution in increments of 20 ml. The pressure response of the terminal ileum to the colonic distention was recorded by a saline-perfused tube. The test was repeated in nine subjects after the colonic segment around the balloon was anesthetized by xylocaine injection into the colonic wall. Twenty and 40 ml colonic distention produced no significant ileal pressure response. Colonic distention with 60 ml produced an increase in colonic pressure ($P < 0.05$), as measured by intraballoon pressure, and a decrease in ileal pressure ($P < 0.05$); a similar response was achieved with 80 ml distention. At 100 ml colonic distention, the balloon was dispelled to the transverse colon. Distention up to 100 ml of the anesthetized colonic segment produced no significant colonic or ileal pressure response. The flow of chyme from the small to the large gut appears to be controlled by a reflex mechanism that we call the "coloileal reflex." Whenever the right colon is distended with a substantial volume of chyme that increases the intraluminal pressure, it is suggested that ileal relaxation occurs, which delays the emptying of chyme from the ileum. (J GASTROINTEST SURG 2003;7:701–705)


KEY WORDS: Chyme, constipation, intestinal transit, colonic motility, ileal motility

The movements of the intestine are under neural, myogenic, and hormonal control.[1] The intestinal innervation is made up of intrinsic and extrinsic components that control the intestinal movements. In addition, the volume and composition of gut contents play a role in variations of motility patterns.[1–3] The extrinsic component comprises long and short extrinsic reflex pathways via the spinal cord and prevertebral ganglia.[4–7] The intrinsic component consists of the myenteric (Auerbach's) and the submucosal (Meissner's) plexuses.[8] These plexuses contain some sensory neurons that receive information regarding the composition of the intestinal content (chemoreceptors) and the degree of expansion of the intestinal wall (mechanoreceptors) from nerve endings near the epithelial layer and in the smooth muscle layer.[5,9–11]

The intestinal motor activity is responsible for the aboral movement of the chyme inside the small intestine until it reaches the colon. The process of chyme delivery to the colon is probably under the control of neurologic and hormonal factors; however, the control mechanisms have thus far remained poorly understood.[12–14] In the current study, we investigated the effect of colonic distention on the motility of the terminal ileum aiming to identify the mechanism of chyme delivery from the ileum to the colon.

## MATERIAL AND METHODS

### Subjects

The study comprised 16 healthy volunteers (12 men and 4 women) who had a mean age of 36.4 ± 9.2 years standard deviation (SD) (range 24 to 43 years). They had had no gastrointestinal complaints in the past and had none at the time of presentation. Physical examination, including neurologic assessment, was normal. Results of laboratory tests were unremarkable, and abdominal ultrasound images were normal. Informed consent was obtained from all subjects, and the study was approved by the Faculty Review Board and Ethics Committee of our institution.

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## Methods

The subjects were instructed to fast for 12 hours before the test, and the bowel was evacuated by saline enema. The right colon was distended by means of a thin polyethylene infinitely compliant balloon, 3 cm in diameter, which was attached to the end of a 10 F tube (London Rubbers Industries Ltd., London, UK). The pressure that was measured within the balloon was considered to be representative of the colonic pressure. A metallic clip was applied to the distal end of the tube for fluoroscopic control.

With the subject lying in the left lateral position and under no medication, the collapsed balloon was introduced per anus into the right colon under endoscopic guidance. The tube was connected to a strain gauge pressure transducer (Statham P 23bb Medtronic, Oxnard, CA). Its location in the colon during the test was controlled fluoroscopically when we noticed a change in the length of the tube section that was lying outside the anal orifice.

The ileal pressure was measured by means of a saline-perfused tube. A 10 F tube, with multiple side ports at its distal closed end, was introduced through the anus, under endoscopic control to lie in the terminal ileum 8 to 10 cm proximal to the ileocecal junction. A metallic clip was attached to the distal end of the tube for fluoroscopic control. The tube was connected to a pneumohydraulic capillary infusion system (Arndorfer Medical Specialties, Greendale, WI), supplied with a pump that delivered saline solution continually via the capillary tube at a rate of 0.6 ml/min. The transducer outputs were registered on a rectilinear recorder (RS-3400, Gould Inc., Cleveland, OH). Occlusion of the recording orifice produced a pressure elevation of greater than 250 cm $H_2O$/sec.

Prior to pressure recording in the colon and ileum, the balloon in the colon and the manometric tube in the ileum were allowed a 20-minute period for gut adaptation. The colonic balloon was then filled with saline solution in increments of 20 ml up to 100 ml and at a rate of 1 to 3 seconds, and the pressure response of the terminal ileum to colonic distention was registered. The pressure in the colonic balloon remained constant during distention. The test was performed in the cecum and in the middle and upper third of the ascending colon. The balloon was deflated when moved to the part to be examined.

## Anesthesia of the Colon

Nine of the 16 subjects consented to undergo testing of the ileal response to distention of the anesthetized colon, whereas seven did not participate in this part of the test. The colon was anesthetized with 10 ml of 2% xylocaine (Astra, Södertälje, Sweden) added to 10 ml of normal saline solution. Through a colonoscope the anesthetic solution was injected by means of a needle into the colonic wall at multiple sites around the location of the balloon. The ileal pressure response to colonic balloon distention in increments of 20 ml was recorded 20 minutes after xylocaine injection and 3 hours later when the effects of anesthesia had waned. On another day, the test was repeated using normal saline solution instead of xylocaine.

The reproducibility of the results was ensured by repeating the recordings and measurements at least twice in the same subject, and then calculating the mean values. The results were analyzed statistically using Student's $t$ test, and values were given as means ± standard deviation (SD). A value of $P < 0.05$ was considered significant. One-way analysis of variance with Dunnett's post test was also performed using GraphPad Prism version 3.00 for Windows (GraphPad Software, Inc., San Diego, CA).

## RESULTS

No adverse side effects were encountered during or after the tests, and all of the volunteers were evaluated. The mean resting colonic pressure was 6.8 ± 1.2 cm $H_2O$ and ileal pressure was 7.2 ± 1.1 cm $H_2O$ (Table 1). On colonic balloon distention with 20 and 40 ml of saline solution, no changes in the colonic or ileal pressures were recorded ($P > 0.05$ and $P > 0.05$, respectively; Fig. 1, *A*; see also Table 1). Colonic distention with 60 ml produced a significant rise in colonic pressure ($P < 0.05$) and a decrease in ileal pressure ($P < 0.05$; see Table 1). Colonic distention with 80 ml produced colonic and ileal pressure responses similar to those of the 60 ml distention, with

**Table 1.** Effect of colonic distention on ileal pressure

| Distending volume (ml) | Pressure (cm $H_2O$) | | | |
|---|---|---|---|---|
| | Colonic | | Ileal | |
| | Mean | Range | Mean | Range |
| 0 (basal) | 6.8 ± 1.2 | 5–9 | 7.2 ± 1.1 | 5–10 |
| 20 | 6.4 ± 1.2 | 5–9 | 6.9 ± 1.1 | 5–10 |
| 40 | 6.7 ± 1.2 | 5–10 | 7.3 ± 1.1 | 5–11 |
| 60 | 18.4 ± 4.6* | 14–22 | 2.3 ± 0.7* | 1.8–3 |
| 80 | 20.5 ± 5.1* | 15–23 | 2.2 ± 0.7* | 1.5–3 |
| 100 | 46.6 ± 7.5* ↑† | 38–58 | 2.1 ± 0.6* ↓† | 1.2–2.8 |

Values presented as mean ± standard deviation.

*$P < 0.05$; Significant using Student's $t$ test when compared with basal value.

†$P < 0.0001$; significant using one-way analysis of variance across values.

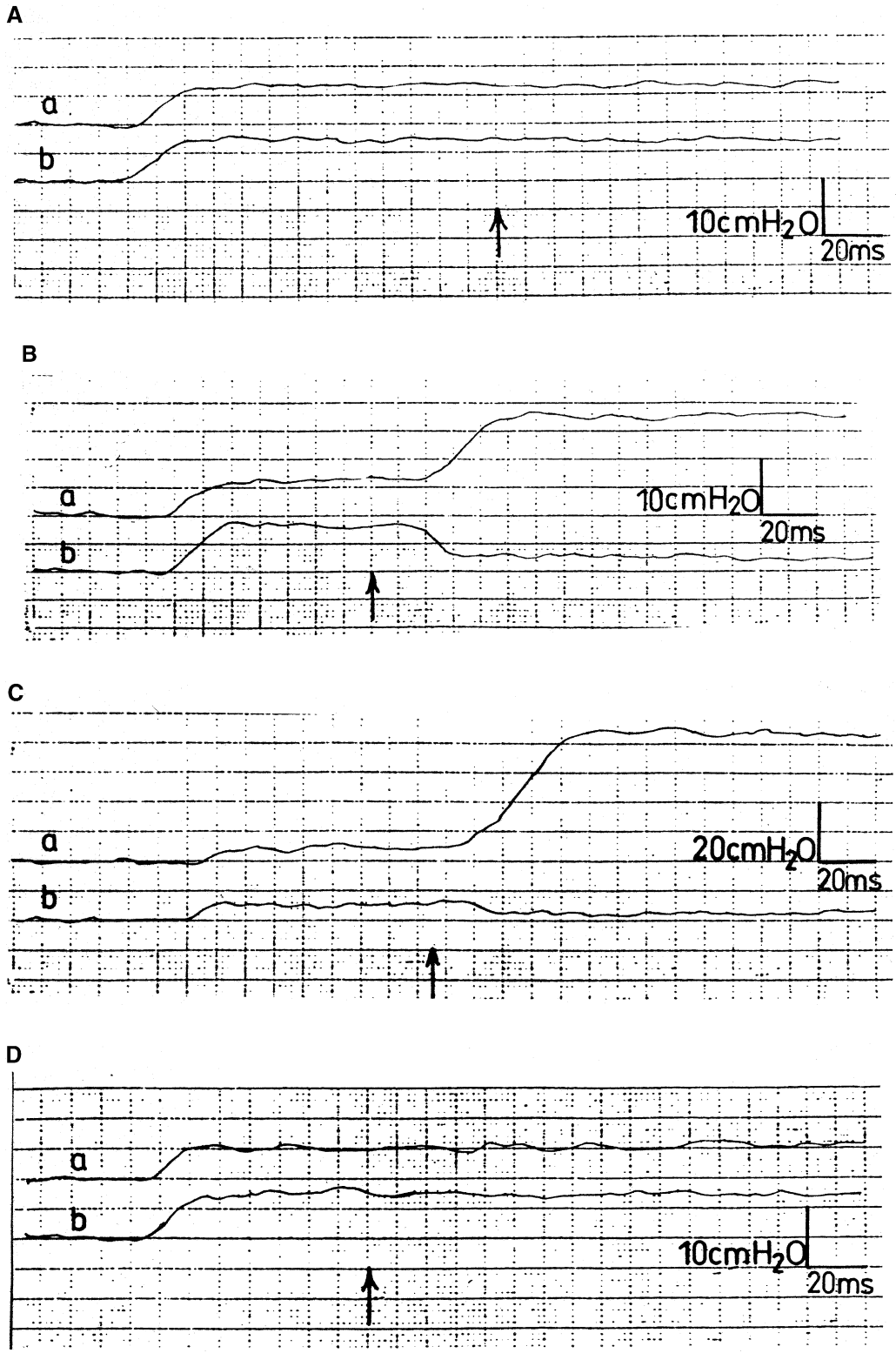


**Fig. 1.** Pressure tracing showing the colonic (*a*) and ileal (*b*) pressure responses to colonic balloon distention with (**A**) 40 ml, (**B**) 80 ml, (**C**) 100 ml, and (**D**) 100 ml of saline solution at 20 minutes after the colon is anesthetized. The increase in pressure at the beginning of the recording represents the resting pressure. ↑ = distention.

no significant difference ($P > 0.05$; see Table 1 and Fig. 1, *B*). The decrease in ileal pressure lasted as long as the colonic balloon remained distended; on deflation of the balloon, the ileal pressure rose to the basal value. On colonic distention with 100 ml, the colonic pressure increased to a mean of 46.6 ± 7.5 cm $H_2O$ ($P < 0.01$), and the balloon was dispelled to the transverse colon (see Table 1). The ileal pressure showed a temporary decrease to a mean of 2.1 ± 0.6 cm $H_2O$ ($P < 0.05$; Fig. 1, *C*) followed by an increase to the basal value.

One-way analysis of variance across the values showed that the increase in the distending volume produced a significant increase ($P < 0.0001$) in the colonic pressure and a significant decrease ($P < 0.0001$) in the ileal pressure (see Table 1). The aforementioned results were recorded with no significant difference whether the test was performed in the cecum or in the middle and upper third of the ascending colon ($P > 0.05$).

### Effect of Colonic Anesthesia

Twenty minutes after the colon had been anesthetized, colonic distention up to 100 ml caused no significant change in the ileal or colonic pressure ($P > 0.05$; Fig. 1, *D*). Three hours later, it caused ileal and colonic pressure changes similar to those before anesthesia ($P > 0.05$ and $P > 0.05$, respectively). Distention of the saline-injected colon produced ileal and colonic pressure responses similar to those before saline infiltration ($P > 0.05$).

The aforementioned results were reproducible with no significant difference when the recordings and measurements were repeated in individual subjects.

## DISCUSSION

The current study may shed some light on the mechanism of transit of the intestinal contents from the small intestine to the colon. The colonic balloon distention with various volumes presumably simulates the filling of the colon with varied amounts of luminal contents delivered from the ileum.

The study has shown that colonic or ileal pressure did not respond to colonic balloon distention with small volumes. This finding probably indicates that the colonic filling with small volumes of chyme does not interfere with the passage of intestinal contents to the colon; the chyme continues to flow to the colon. However, colonic distention with large volumes causing an increase in colonic pressure or wall tension led to a decrease in ileal pressure supposedly signifying ileal relaxation. We suggest that this ileal relaxation functions to retard the flow of intestinal contents from the ileum to the colon, thus delaying transit of distal ileal content in the colon. It delays the emptying of additional chyme from the ileum entering the colon until the latter evacuates by itself. Meanwhile, stasis of chyme in the terminal ileum appears to allow time for absorption of intestinal contents, as has also been mentioned by other investigators.[15,16]

The decreased ileal pressure and presumably related ileal hypotonia were maintained as long as the colonic distention was continued. Meanwhile, the colonic pressure increased on increase of colonic distention, whereas the ileal pressure decrease remained constant. Colonic distention with bigger volumes moved the balloon to the transverse colon; this was followed by normalization of ileal pressure. Emptying of the colon and normalization of ileal pressure would allow the flow of chyme into the colon.

The current findings do not contradict those reported by Cohen et al.,[17] who showed that the high pressure at the "ileocecal junction" decreased with ileal balloon distention and was elevated with colonic balloon distention. This effect allows chyme to pass to the cecum when the ileum is distended with chyme, and increases the pressure within the ileocecal junction on colonic balloon distention to prevent further passage of chyme from the ileum. The results of the current study add to the findings of Cohen et al.; thus, when the colon is distended, the "ileum" relaxes while the "ileocecal junction" pressure increases. Both actions presumably prevent chyme from reaching the distended colon.

The mechanism of colonic distention inducing the decline in ileal pressure needs to be clarified. The enteric nervous plexus contains sensory neurons or mechanoreceptors that receive information regarding the degree of expansion of the intestinal wall.[5,9–11] It appears that the mechanoreceptors in the colonic wall are stimulated by balloon distention. Impulses are probably transmitted intramurally through the enteric nervous plexus with a resulting decrease in ileal pressure.

### The Coloileal Reflex

The current findings demonstrate a hitherto unrecognized relationship between colonic distention and ileal pressure. The ileal pressure response to colonic distention affirms the hypothesis of the possible involvement of a reflex, which we term "coloileal reflex." The constancy of this reflex relationship is evidenced by reproducibility and by its absence on blocking of the intramural neural plexus of the colon, a possible arm of reflex. The coloileal reflex is suggested to be evoked only on colonic distention with large

volumes, thus preventing flooding of the colon and allowing it to evacuate itself. Small-volume colonic distention did not initiate the reflex.

## CONCLUSION

The flow of chyme from the small to the large intestine seems to be partially controlled by the coloileal reflex, which regulates the aboral transit of the ileal contents. Whenever the right colon is distended with large volumes of chyme, ileal relaxation occurs, which delays the emptying of additional chyme from the ileum. The coloileal reflex is believed to be a neurally mediated reflex.

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REFERENCES

1. Sarna SK. Physiology and pathophysiology of colonic motor activity. Dig Dis Sci 1991;36:998–1018.
2. Flourie B, Phillips S, Azpiroz F. Cyclic motility in canine colon: Responses to feeding and perfusion. Dig Dis Sci 1989; 34:1185–1192.
3. Shibata C, Saski I, Matsuno S, Mizumoto A, Itoh Z. Colonic motility in innervated and extrinsically denervated loops in dogs. Gastroenterology 1991;101:1571–1578.
4. Frantzides CT, Sarna SK, Matsumoto T, Lang IM, Condon RE. An intrinsic neural pathway for long intestino-intestinal inhibitory reflexes. Gastroenterology 1987;92:594–603.
5. Costa M, Furness JB. Nervous control of intestinal motility. In Bertaccini IG, ed. Mediators and Drugs in Gastrointestinal Motility. New York: Springer-Verlag, 1982, pp 279–382.
6. Kreulen DL, Szurszewski JH. Reflex pathways in the abdominal prevertebral ganglia: Evidence for a colo-colonic inhibitory reflex. J Physiol 1979;295:21–32.
7. Brugère HB, Ferre JP, Ruckebusch Y. Colonic motility and transit after intermesenteric nerve transection and mesenteric ganglionectomy in dogs. J Gastrointest Motil 1991;3: 107–116.
8. Junqueira LC, Carneiro J, Long JA. Digestive tract. In Junqueira LC, Carneiro J, Long JA, eds. Basic Histology, 5th ed. Los Altos, CA: Lange Medical Publications, 1986, pp 326–353.
9. Radke R, Krammer HJ. Enteric nervous system (ENS) similarities and differences in the gastrointestinal tract, gall bladder and pancreas. Neurogastroenterologia 1996;3:93–105.
10. Krammer HJ, Karahan ST, Rumpel E, Klinger M, Kuhnel W. Immunohistochemical visualization of the enteric nervous system using antibodies against protein gene product (PGP) 9.5. Ann Anat 1993;175:321–325.
11. Goyal RK, Hirand I. The enteric nervous system. N Engl J Med 1996;334:1106–1115.
12. Schemann M, Ehrlein HJ. Postprandial patterns of canine jejunal motility and transit of luminal content. Gastroenterology 1986;90:991–1000.
13. Spiller RC, Trotman IF, Higgins BE. The ileal brake—inhibition of jejunal motility after ileal fat perfusion in man. Gut 1984;25:365–374.
14. Spiller RC, Brown ML, Phillips SF. Decreased fluid tolerance accelerated transit and abnormal motility of the human colon induced by oleic acid. Gastroenterology 1986;91:100–107.
15. Quigley EMM. Motor activity of the distal ileum, ileocecal sphincter and its relation to the region's function. Dig Dis 1988;6:229–241.
16. Rouillon J-M, Azpiroz F, Malagelada J-R. Reflex changes in intestinal tone: Relationship to perception. Am J Physiol 1991;261:G280–G286.
17. Cohen S, Harris LD, Levitan R. Manometric characteristics of the human ileocecal junctional zone. Gastroenterology 1968;54:72–75.

# Patients With Crohn's Disease Are Unaware of the Risks That Smoking Has on Their Disease

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Smoking, both in quantity and duration, increases the risk of recurrent Crohn's disease (CD) and the need for surgical treatment of CD. This study assessed awareness among patients with CD of the risks of smoking on their disease. We distributed self-administered questionnaires to 714 CD patients under follow-up at the University Hospital Birmingham, United Kingdom. We asked the patients eight multiple-choice (*yes/uncertain/no*) questions about the effects of smoking on health and on CD. We also determined relevant patient demographics, smoking history, and medical history. A total of 312 patients completed the questionnaire. Patients acknowledged the dangers of smoking on overall health (91.5%), lung cancer (89.6%), lung disease (90.8%), and cardiovascular disease (85.3%). Employed, educated, and homeowning patients demonstrated significantly more recognition of these smoking risks. Conversely, few patients recognized that smoking increases the risks of development of CD (9.5%) and of reoperation for CD (12.0%). Moreover, few patients recognized that both the quantity of cigarettes smoked (11.4%) and the duration of smoking (17.4%) increase the risk of reoperation. Patients with CD are unaware of the risks that smoking has on their disease, indicating a need for increased patient education with regard to the effects of smoking on CD. (J GASTROINTEST SURG 2003;7:706–711) 

KEY WORDS: Smoking, Crohn's recurrence, awareness of risk

Crohn's disease (CD) is a nonspecific chronic, transmural, inflammatory disease affecting any part of the gastrointestinal tract, particularly the ileocecal region. Recurrence of CD after surgical resection is common. There is good reason to identify ways to prevent recurrence of CD. Only 12% of patients with CD maintain a relapse-free course 10 years after diagnosis.[1] Seventy percent to 90% of patients with CD undergo resection within 10 years of diagnosis.[2,3] Furthermore, the rates of symptomatic postoperative recurrence are approximately 6% of patients at risk per year, 30% to 33% at 5 years, and 44% to 60% at 10 years.[2] Eventually, more than half of the patients treated surgically will require one or more reoperations for recurrence.[3,4] The effectiveness of adjuvant medication in preventing reoperation for recurrence is variable. 5-ASA compounds may reduce the risk of recurrence of ileal CD, but only five studies have demonstrated any such benefit.[5–9]

Many studies have implicated tobacco smoking as a possible exacerbating factor for CD.[10–12] Several studies have concluded that CD patients who smoke are more likely to require earlier and multiple surgical treatments for recurrence.[13–18] In clinical practice, we have found that few CD patients appreciate that smoking may accelerate the course of the disease. Thus we undertook a survey among CD patients in the United Kingdom to determine their awareness that smoking has an exacerbating effect on CD. No previous study has investigated this particular area of patient awareness.

## MATERIAL AND METHODS

### Sample

Our target population consisted of all 714 CD patients followed up in the Department of Surgery,

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University Hospital Birmingham NHS Trust, Birmingham, England. The Department of Surgery maintains a computer database of all patients with a diagnosis of CD. The database provided medical data on disease site, demographics, surgical history, and smoking practices. We distributed a self-administered questionnaire by mass mailing to all patients in the database. We also distributed this questionnaire in person during July and August 2000. Informed consent was obtained from all study subjects. We offered no remuneration to the patients for completing the survey. Both the Human Subjects Ethics Committee of Stanford University and the University of Birmingham Hospital Local Research Committee approved this study.

### Questionnaire

The focus of the questionnaire was a series of eight multiple-choice (*yes/uncertain/no*) questions regarding the effects of smoking on health. Additionally, the questionnaire ascertained demographic information (sex, ethnicity, age, employment status, home ownership, and level of formal education), medical history (number of operations for CD, family history of CD, family history of ulcerative colitis), and history of smoking. We defined a smoker as a person who smokes five or more cigarettes per week. We assessed smoking habits by asking subjects (1) if they had ever smoked, (2) what year they had started, (3) if they had smoked since their first operation for CD (if applicable), (4) how many cigarettes, on average, they smoked per day and per week, (5) how many ounces of pipe tobacco they smoked per week, (6) how many cigars they smoked per week, and (7) if they still smoked, and if not, what year had they stopped.

### Statistical Analysis

After obtaining the number and proportion of *yes*, *uncertain*, and *no* responses for each question, we stratified the distribution of responses according to the following pertinent patient characteristics: age, sex, race/ethnicity, employment status, home ownership, education, number of operations for CD, family history of CD, family history of ulcerative colitis, and smoking status. To determine the influence of these socioeconomic, behavioral, and outcome factors on the answers to the eight questions, we calculated the relative proportions (relative risks) of each stratified category to answer either *yes*, *uncertain*, or *no*. We calculated the confidence intervals for each relative proportion at a 95% confidence level. We grouped smoking history into three categories (current, former, and never), age into four categories (20 to 34 years, 35 to 49 years, 50 to 64 years, and 65+ years), and formal education level into three categories (no formal education, secondary education only, and post-secondary education [university degree, professional qualification, or postgraduate qualification]). Moreover, we condensed ethnicity from six categories (white, Asian, Chinese, African, Afro-Caribbean, and other) into two (white and nonwhite).

## RESULTS

A total of 312 patients completed the questionnaire. The response rate was 43.6%. Demographic, medical, and smoking characteristics for all respondents are presented in Table 1.

The number and proportion of the *yes*, *uncertain*, and *no* responses for the eight questions are presented in Table 2. The majority of the patients recognized that smoking was a health hazard (92%) and was associated with lung cancer (90%), lung disease (90%), and cardiovascular disease (85%). Patients who were employed, those who were homeowners, and those who had attained a post–secondary education

**Table 1.** Demographic, medical, and smoking characteristics for all 312 respondents

| | | |
|---|---|---|
| Age (yr) | Mean (±SD) | 49.2 (±15.27) |
| | Range | 20 to 83 |
| Gender | Men | 116 (37%) |
| | Women | 196 (63%) |
| Race/ethnicity | White | 303 (97%) |
| | Nonwhite | 9 (3%) |
| Employment | Employed | 171 (55%) |
| | Unemployed | 87 (29%) |
| | Retired | 54 (17%) |
| Home owner | Yes | 222 (71%) |
| | No | 87 (28%) |
| Education levels | No secondary education | 100 (32%) |
| | Secondary education only | 133 (43%) |
| | Post-secondary education | 79 (25%) |
| Number of operations for CD | 0 | 24 (8%) |
| | 1 (only) | 105 (33%) |
| | 1+ | 288 (92%) |
| | 2+ | 183 (59%) |
| | 3+ | 100 (32%) |
| | 4+ | 52 (17%) |
| | 5+ | 27 (9%) |
| Family history of | CD | 61 (20%) |
| | Ulcerative colitis | 56 (18%) |
| Smoking status | Current | 99 (32%) |
| | Former | 90 (29%) |
| | Never | 119 (38%) |

**Table 2.** Patient awareness of smoking as a risk factor for morbidity and development and recurrence of Crohn's disease*

| Question | Answer | No. of patients | % of patients† | Smoker‡ | Employed‡ | Home owner‡ | Post-secondary education† | 65+ years/ retired† |
|---|---|---|---|---|---|---|---|---|
| 1. Do you think that smoking is dangerous to one's health? | | | | | | | | |
| | Yes | 282 | 92 | — | 3.3 (1.3–9.1) | 1.2 (1.1–1.4) | 1.1 (1.07–1.2) | — |
| | Uncertain | 19 | 6.2 | — | — | — | — | — |
| | No | 7 | 2.3 | — | — | — | — | — |
| | Missing | 4 | | | | | | |
| 2. Do you think that smoking increases the risk of lung cancer? | | | | | | | | |
| | Yes | 275 | 90 | — | 4.6 (1.8–12.5) | 3.5 (1.6–7.6) | 1.1 (1.05–1.2) | — |
| | Uncertain | 24 | 7.8 | 2.5 (1.1–5.9) | — | — | — | — |
| | No | 8 | 2.6 | — | — | — | — | — |
| | Missing | 5 | | | | | | |
| 3. Do you think that smoking increases the risk of lung disease? | | | | | | | | |
| | Yes | 277 | 91 | — | 3.9 (1.5–4.3) | 2.3 (1.4–5.3) | 1.1 (1.02–1.2) | — |
| | Uncertain | 21 | 6.9 | — | — | — | — | 3.2 (1.4–7.3) |
| | No | 7 | 2.3 | — | — | — | — | — |
| | Missing | 7 | | | | | | |
| 4. Do you think that smoking increases the risk of cardiovascular disease? | | | | | | | | |
| | Yes | 261 | 85 | — | 2.4 (1.3–4.8) | 2.5 (1.4–4.6) | 1.1 (1.02–1.2) | — |
| | Uncertain | 36 | 12 | — | — | — | — | — |
| | No | 9 | 2.9 | — | — | — | — | — |
| | Missing | 6 | | | | | | |
| 5. Do you think that smoking increases the risk of developing Crohn's disease? | | | | | | | | |
| | Yes | 29 | 9.5 | — | — | — | — | — |
| | Uncertain | 207 | 68 | — | — | — | — | — |
| | No | 70 | 23 | — | — | — | — | — |
| | Missing | 6 | | | | | | |
| 6. Do you think that smoking increases the risk of requiring additional operations for Crohn's disease? | | | | | | | | |
| | Yes | 37 | 12 | — | — | — | — | — |
| | Uncertain | 204 | 66 | — | — | — | — | — |
| | No | 66 | 22 | — | — | — | — | — |
| | Missing | 5 | | | | | | |
| 7. Do you think that the number of cigarettes smoked increases the risk of requiring additional operations for Crohn's disease? | | | | | | | | |
| | Yes | 67 | 11 | — | — | — | — | — |
| | Uncertain | 205 | 67 | — | — | — | — | — |
| | No | 35 | 22 | 1.6 (1.06–2.6) | — | — | — | — |
| | Missing | 5 | | | | | | |
| 8. Do you think that the duration of smoking increases the risk of requiring additional operations for Crohn's disease? | | | | | | | | |
| | Yes | 53 | 17 | — | — | — | — | — |
| | Uncertain | 186 | 61 | — | — | — | — | — |
| | No | 66 | 22 | — | — | — | — | — |
| | Missing | 7 | | | | | | |

*Other possible influential factors from Table 1 had no significant impact on patient awareness (other ages: 20–34 years, 35–49 years, 50–64 years); race: white, nonwhite; other education levels: no secondary education, secondary education only; operative experience for Crohn's disease: 0, 1, 2+ operations; family history of Crohn's disease, family history of ulcerative colitis; former smokers; nonsmokers.

†Denominator excludes missing responses.

‡Values are relative proportions and 95% confidence intervals. $P \leq 0.05$ for all values shown ($P > 0.05$ for values not shown).

level demonstrated significantly more recognition of these four risks. Each of these three patient categories had higher relative proportions of *yes* responses to questions 1 to 4, all of which were statistically significant (see Table 2). Smokers had significantly less recognition of the concept that smoking increases the risk of lung cancer. Smokers had a higher relative proportion of *uncertain* answers to question 2, which was statistically significant (see Table 2). Similarly, patients aged 65 and over and retired patients demonstrated significantly less recognition of the concept that smoking increases the risk of lung disease.

Patients aged 65 and over and retired patients (all of whom were 65 and older) also had a higher relative proportion of *uncertain* responses to question 3, which was statistically significant for both (see Table 2).

In contrast, a minority of the patients recognized that smoking increases the risk of developing CD (9.5%), that smoking increases the risk of requiring additional operations for CD (12%), or that the number of cigarettes smoked or the duration of smoking increases the risk of requiring additional operations for CD (11% and 17%, respectively). Most patients chose the response *uncertain* for questions 5 through 8. Smokers demonstrated significantly less recognition of the concept that the number of cigarettes smoked increases the risk of requiring additional operations for CD. Smokers had a higher proportion of *no* answers to question 7, which was statistically significant (see Table 2). None of the other factors we examined had a significant impact on the awareness of the effects of smoking on CD.

## DISCUSSION

Information regarding the risks of smoking on health, lung cancer, lung disease, and cardiovascular disease is widely available throughout the developed world. Our sample of CD patients expressed a culturally receptive acknowledgment of the risks smoking has on health, lung cancer, lung disease, and cardiovascular disease. We assume that Western society, in general, would recognize these risks in a similar fashion as in the case of these CD patients. Thus, on the basis of the distribution of responses to questions 1 to 4, we infer that the patients in our sample did have an understanding of the inherent dangers of smoking that is reflective of the understanding of society in general.

Appropriately, patients of a higher socioeconomic status, as measured by their being employed, owning their own homes, and/or having a higher education, demonstrated an increased awareness of these four particular risks of smoking. We found that all three of these patient characteristics had statistically significant positive associations with one another. This allowed us to group them into one higher socioeconomic status category. We expected socioeconomic status to have an enhancing impact on this particular area of awareness because of the increased access to and availability of information for wealthier and more educated patients. Similar to our expectations, smokers were less likely to agree with the concept that smoking increases the risk of lung cancer. Smokers are also less likely to be home owners, placing them generally at a more disadvantaged socioeconomic level, which may have had some influence on their responses in the questionnaire. Nevertheless, 85.3% of the patients who smoke still responded to question 2 with a *yes* answer, underscoring the general acceptance among society of the dangers of smoking. As the public smoking cessation movement is a relatively new phenomenon, patients aged 65 and over and retired patients demonstrated a lower awareness of (or agreement with) the concept that smoking increases the risk of lung disease. This is an expected generational effect on awareness. Furthermore, we found that older patients were generally less educated. This lack of education may have had some indirect influence in the 65+ year patients' and retired patients' responses in the questionnaire. Nevertheless, 81.3% of patients aged 65 and over, as well as 80.0% of retired patients, still responded to question 3 with a *yes*, again underscoring the general acceptance among society of the dangers of smoking.

Notwithstanding, the patients in our sample did not demonstrate much awareness of the dangers of smoking specifically with regard to Crohn's disease. The high prevalence of an *uncertain* response to questions 5 to 8 demonstrated their uncertainty concerning the effects of smoking on CD. Neither the socioeconomic indexes nor age had an impact in this particular instance. Only patients who were smokers appropriately showed more uncertainty than other patients in their recognition of the notion that the number of cigarettes smoked increases the risk of requiring reoperation. The fact that there were very few factors influencing the understanding of the exacerbating effects of smoking on CD further illustrates the widespread lack of awareness among CD patients of the harmful effects of smoking on their disease.

This evidence of a general lack of awareness of the exacerbating effects of smoking on CD indicates that there is a need for more patient education concerning the harmful effects of smoking on CD. This study stands to motivate the medical community caring for patients with CD to provide more information to patients about the specific dangers of smoking with regard to CD. With more information, patients with CD can make healthier decisions concerning the treatment of their disease and the lifestyle they choose. Furthermore, recommendations to quit smoking, smoking cessation programs, and subsequent patient compliance could reduce the recurrence of CD and, likewise, the need for additional surgical intervention.

We accept the limitations of this survey. The selection bias inherent in a 43.6% response rate compromises the ability to generalize the results from this sample. We did not have either the time or the staff to telephone those patients who did not respond.

Furthermore, many patients were away over the holiday period during which the questionnaires were dispatched. Nevertheless, the distribution of sex, surgical history, and smoking behavior of the sample of enrolled patients resembled that of the target population (Table 3). Sixty-three percent (n = 196) of the sample patients were women, 58% (n = 413) of the target population were women, and 92% (n = 288) of the sample and 89% (n = 633) of the target population had undergone at least one operation for CD. Moreover, 32% (n = 99) of the sample and 37.4% (n = 267) of the target population were smokers. This similarity suggests that the responders, although only 43.6% of the whole, were representative of our target patient population.

Even so, biases may have been present in our target population. The majority of the target population (58%) and the respondents (63%) were women, whereas CD affects men and women equally.[1,3] However, because sex has no significant impact on the patients' answers, the generalizability of the conclusions can be justified. The fact that 97% of the patients claimed to be "white" must also be considered when generalizing the results to other more racially heterogeneous populations. However, the low incidence of CD among nonwhite patients is representative, even in our multiethnic society, as CD usually only affects second- or third-generation Asians (meaning Indians in the United States) to the same extent as white persons. The surgical nature of this patient cohort also may have biased these responses. A large proportion of the sample had had surgical treatment of their CD. However, the operation rate for a single resection almost matched the expected proportions of 70% to 90%.

Biases may also exist as a result of our study design. Any self-administered questionnaire is subject to the errors of recall bias (in the case of dates), lack of patient knowledge (in the case of dates, family history of CD, and family history of ulcerative colitis), and guilty feelings (in the case of smoking habits, education, employment status, and home ownership). Such factors may have produced erroneous reports in the questionnaire, particularly with respect to determining smoking practices, family history of CD, and family history of ulcerative colitis.

The sequence of the questions about awareness of the adverse effects of smoking— that is, having the questions on general health, lung cancer, lung disease, and cardiovascular disease precede the questions pertaining to Crohn's disease—may have influenced some respondents to infer an association with CD in the same way as the previous questions. Even so, the fact that so few patients responded affirmatively to the questions pertaining to CD demonstrates a lack of awareness in this population of the dangers of smoking with regard to CD.

We conclude that although patients with CD are aware of the hazardous effects of smoking on general health, lung cancer, lung disease, and cardiovascular disease, they are unaware of the risks of smoking with regard to the development and recurrence of CD. This study demonstrates the need for more patient education concerning the particular harmful effects of smoking on CD.

**Table 3.** Sex, surgical history, and smoking practices of enrolled patient sample and target population

| Characteristic | Patient sample | Target population |
|---|---|---|
| No. of female patients (%) | 196 (63%) | 413 (58%) |
| No. of patients with at least one operation for CD (%) | 288 (92%) | 633 (89%) |
| No. of smokers (%) | 99 (32%) | 267 (37%) |

REFERENCES

1. Munkholm P, Langholz E, Davidsen M, Binder V. Disease activity courses in a regional cohort of Crohn's disease patients. Scand J Gastroenterol 1995;30:699–706.
2. Bernell O, Lapidus A, Hellers G. Risk factors for surgery and postoperative recurrence in Crohn's disease. Ann Surg 2000;231:38–45.
3. Leiper K, London I, Rhodes JM. Adjuvant post-operative therapy. Baillieres Clin Gastroenterol 1998;12:179–199.
4. Shorb PE. Surgical therapy for Crohn's disease. Gastroenterol Clin North Am 198;18:111–128.
5. IMSG (International Mesalazine Study Group). Coated oral 5-aminosalicylic acid versus placebo in maintaining remission of inactive Crohn's disease. Aliment Pharmacol Ther 1990; 4:55–64.
6. Prantera C, Pallone F, Brunetti G, Cottone M, Miglioli M, for the Italian IBD Study Group. Oral 5-aminosalicylic acid (Asacol) in the maintenance treatment of Crohn's disease. Gastroenterology 1992;103:363–368.
7. Landi B, Anh TN, Cortot A, et al. Endoscopic monitoring of Crohn's disease treatment: A prospective randomized clinical trial. Group D'etudes Therapeutiques Des Affections Inflammatories Digestives. Gastroenterology 1992;102:1647–1653.
8. Caprilli R, Andreoli A, Capurso L, et al. for the Gruppo Italiano per Io Studio del Colon e del Retto (GISCR). Oral mesalazine (5-aminosalicylic acid; Asacol) for the prevention of postoperative recurrence of Crohn's disease. Aliment Pharmacol Ther 1994;8:35–43.
9. McLeod RS, Wolff BG, Steinhart H, et al. Prophylactic mesalamine treatment decreases postoperative recurrence of Crohn's disease. Gastroenterology 1995;109:404–413.
10. Russell MG, Volovics A, Schoon EJ, et al. European Collaborative IBD study group. Inflammatory bowel disease: is there

any relation between smoking status and disease prevention? Inflammatory Bowel Dis 1998;4:182–186.
11. Corrao G, Tragnone A, Caprilli R, et al. Risk of inflammatory bowel disease attributable to smoking, oral contraception and breastfeeding in Italy: A nationwide case-control study. Cooperative Investigators of the Italian Group for the Study of the Colon and the Rectum (GISC). Int J Epidemiol 1998;27: 397–404.
12. Cosnes J, Carbonnel F, Carrat F, et al. Effects of current and former cigarette smoking on the clinical course of Crohn's disease. Aliment Pharmacol Ther 1999;13:1403–1411.
13. Lindberg E, Jarnerot G, Huitfeldt B. Smoking in Crohn's disease: Effect on localization and clinical course. Gut 1992; 33:779–782.
14. Cottone M, Rosselli M, Orlando A. Smoking habits and the recurrence of Crohn's disease. Gastroenterology 1994;106: 643–648.
15. Breuer-Katschinski BD, Hollander N, Goebell H. Effect of cigarette smoking on the course of Crohn's disease. Eur J Gastroenterol Hepatol 1996;8:225–228.
16. Medina C, Vergara M, Casellas F, et al. Influence of the smoking habit in the surgery of inflammatory bowel disease. Rev Esp Enferm Dig 1998;90:771–778.
17. Yamamoto T, Keighley MR. The association of cigarette smoking with a high risk of recurrence after ileocolonic resection for ileocecal Crohn's disease. Surg Today 1999; 29:579–580.
18. Yamamoto T, Keighley MR. Long-term outcome for total colectomy and ileostomy for Crohn's disease. Scand J Gastroenterol 1999;34:280–286.

# *Errata*

The publisher regrets the following two misprints in author names as follows:

In the article entitled, "Laparoscopic Colectomy in Obese and Nonobese Patients," published in the May/June issue of the JOURNAL OF GASTROINTESTINAL SURGERY (2003;7:558–561) the authors should have been listed as Anthony J. Senagore, M.D., M.S., Conor P. Delaney, M.Ch., Ph.D., F.R.C.S.I.(Gen), Khaled Madboulay, M.D., Karen M. Brady, B.S.N., R.N., C., Victor W. Fazio, M.D.

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In the Erratum for the article entitled, "Apoptotic and Proliferative Indexes in Esophageal Cancer: Predictors of Response to Neoadjuvant Therapy," published in the May/June issue of the JOURNAL OF GASTROINTESTINAL SURGERY (2003;7:583), the authors should have been listed as Beardsmore DM, Verbeke CS, Davies CL, Guillou PJ, and Clark G.W.B.

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# *Announcements*

**Southwestern Center for Minimally Invasive Surgery (SCMIS): Laparoscopic Management of CBD Stones,** August 15–16, 2003; The University of Texas Southwestern Medical Center at Dallas. For further information contact: Jennifer Leedy, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9059. Phone: 214-648-3792; fax: 214-648-2317; e-mail: jennifer.leedy@utsouthwestern.edu

**Southwestern Center for Minimally Invasive Surgery (SCMIS): Laparoscopic Bariatric Surgery Mini-Fellowship Program,** August 24–29, 2003; October 26–31, 2003; The University of Texas Southwestern Medical Center at Dallas. Cost: $12,500 (team of 2 physicians and 1 nurse); $6,250 (physician); $1,000 (nurse). For further information contact: Jennifer Leedy, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9059. Phone: 214-648-3792; fax: 214-648-2317; e-mail: jennifer.leedy@utsouthwestern.edu

**Southwestern Center for Minimally Invasive Surgery (SCMIS): Laparoscopic Bariatric Surgery,** September 26–27, 2003; The University of Texas Southwestern Medical Center at Dallas. Cost: physicians ($300, lecture only; $1050, lecture and lab); UTSW and SCMIS Alumni ($250, lecture only; $950, lecture and lab); nurse ($175, lecture only; $375, lecture and lab). For further information contact: Jennifer Leedy, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9059. Phone: 214-648-3792; fax: 214-648-2317; e-mail: jennifer.leedy@utsouthwestern.edu

**Southwestern Center for Minimally Invasive Surgery (SCMIS): Laparoscopic Splenectomy,** November 14–15, 2003; The University of Texas Southwestern Medical Center at Dallas. For further information contact: Jennifer Leedy, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9059. Phone: 214-648-3792; fax: 214-648-2317; e-mail: jennifer.leedy@utsouthwestern.edu